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Prize Lectures and Biographical Notes

EJE Award 2019 – Biography

Mirjam Christ-Crain is full Professor of Endocrinology, Diabetes and Metabolism at the University of Basel and the University Hospital of Basel, Switzerland. She studied medicine in Basel and Vienna and did her MD in the year 2000 at the University of Basel and completed her PhD degree in 2007 at the University of London followed by her habilitation at the University of Basel in 2007. From 2009 to 2015 she had a research professorship of the Swiss National Science Foundation. Her main research interest is on vasopressin-dependent disorders of fluid homeostasis, i.e. diabetes insipidus and hyponatremia. She authored and co-authored more than 200 publications and received several awards for her research. From 2013, she has been the Deputy Chief at the Clinic for Endocrinology, University Hospital Basel and from 2014 she has been the Head of the Department of Clinical Research at the University of Basel.

The European Journal of Endocrinology Prize Lecture

EJE1

New approaches in the differential diagnosis of Diabetes insipidus

Prof Mirjam Christ-Crain
Switzerland.

The differential diagnosis of hypotonic polyuria is a frequent problem in clinical practice. Three fundamentally different types of defects have to be differentiated: central diabetes insipidus characterized by a lack of the antidiuretic hormone arginine vasopressin; nephrogenic diabetes insipidus characterized by renal insensitivity to arginine vasopressin; and primary polydipsia due to primary excess of fluid intake. The differentiation is crucial as treatment differs substantially and incorrect strategies may lead to severe complications. Since decades the indirect water-deprivation-test is the reference standard for this differentiation. However, it is technically cumbersome and highly vulnerable to false diagnosis. A new test with high diagnostic accuracy is urgently needed. Copeptin is the C-terminal segment of the arginine vasopressin prohormone and is an easy to measure and stable arginine vasopressin surrogate. In patients with hypotonic polyuria, high baseline copeptin levels without prior water deprivation unequivocally identified patients with nephrogenic diabetes insipidus. Conversely, in a large prospective diagnostic study the performance of copeptin after hypertonic saline-infusion was directly compared with that achieved by the water-deprivation-test. Stimulated copeptin levels with a cutoff of 4.9 pmol/L had a high diagnostic accuracy to differentiate between patients with central diabetes insipidus and primary polydipsia, clearly superior to the diagnostic accuracy of the classical water deprivation test. More patients preferred the hypertonic saline plus copeptin test to the water deprivation test, mainly because of its shorter duration. Constant surveillance of plasma sodium levels is important and even simpler test methods should be evaluated. In conclusion, copeptin measured after hypertonic saline infusion has the potential to become the new reference standard in the differential diagnosis of hypotonic polyuria.

DOI: 10.1530/endoabs.63.EJE1

ESE Geoffrey Harris Prize 2019 – Biography

Günter K Stalla MD, is Professor of Internal Medicine at the Ludwig-Maximilians University, Munich and medical director of Medicover Neuroendocrinology. For almost 30 years, he has been the head of the Department of Internal Medicine and Clinical Neuroendocrinology in the Max Planck Institute of Psychiatry. He finished his residency at the Medical Clinic IV of the Ludwigs-Maximilians University of Munich. He is auditor for endocrinology, diabetology and andrology at the Bavarian Chamber of Physicians. Günter Stalla has focused his entire career in neuroendocrinology in general and the discovery of pathogenic and therapeutic mechanisms for pituitary diseases in particular. He has more than 400 publications in renowned international journals, including The Lancet, Cell, and Nature Medicine, and supervised clinical trials for the development of new treatment concepts for endocrine diseases. Believing in the importance of education and training, he has been a supervisor and mentor of more than 50 MD and PhD students and early career researchers, several of whom moved on to curve excellent career paths in academia and industry. Prof. Stalla has been founding member and chair of the Neuroendocrinology Section of the German Society of Endocrinology (DGE), former board member and media spokesperson of the DGE and is now the President elect of the DGE. He has served as President and President past of the European NeuroEndocrine Association. He has organized several successful national and international meetings.

The Geoffrey Harris Prize Lecture

GH1

Translational research in pituitary disease

Mr Günter K Stalla
Germany.

The pituitary gland has always held a special allure; so small and yet so complex pathophysiology and clinical presentation. I heard the call of its sirens in the late 70's just after finishing my medical examination and it was the realization of how little we know about pituitary disorders that prompted me to specialize in endocrinology in view of working in neuroendocrinology. In 1990, I got the great fortune to head an endocrine outpatient unit and a research laboratory, which enabled me to embark on a life-long quest on pituitary disorders in general and pituitary tumours in particular, in a truly translational manner. During the years, we identified factors that are deregulated during pituitary tumorigenesis and brought forward novel therapeutics, without forgetting that there is more in our patients than their tumour. Their comorbidities are as complex as the tumour that causes them and cause deep scars that affect their physical wellbeing and quality of life. Almost 30 years later, we undoubtedly know a lot more about the triggering molecular events, but when it comes to patient management, we still rely on improved versions of traditional therapeutics. There is still a long way to go and only with cooperation and rigorous training of the next generation of experts, we can hope one day to defeat this multifaceted devastating disease.

DOI: 10.1530/endoabs.63.GH1

European Hormone Medal 2019 – Biography

Jens Bollerslev is head of the Section of Specialized Endocrinology at Oslo University Hospital, and Professor of Endocrinology at the University of Oslo, Norway. He has been a member of the Executive Board of the European Society of Endocrinology (ESE), former chair of the ESE Education Committee (2014–17), chair of the ESE committee for Post Graduate Courses (2016–19) and is currently chair of the newly established ESE PARAT project. Moreover, he was a member of the ESE Clinical Committee and was involved in the development of ESE Clinical Guidelines. He serves on the Editorial Board of the Journal of Clinical Endocrinology & Metabolism as well as Endocrine. His special interest is within clinical and translational endocrinology, and in particular in classical endocrine diseases, such as Acromegaly and Cushing's, often studying bone as target tissues for clinical activity. A major interest has been devoted to metabolic bone disorders, other than postmenopausal osteoporosis, as illustrated by his work for The Scandinavian Investigation of Primary Hyperparathyroidism. He has a deep interest in the control of bone remodeling as seen in the classical endocrine and inherited metabolic diseases (like Human Osteopetrosis and High Bone Mass Phenotypes), and also in relation to solid organ transplantation. As such, he has published more than 280 papers in international, peer reviewed journals and has been a mentor of more than 20 doctoral thesis projects.

European Hormone Medal Lecture

EHM1

Monogenic Bone Disorders as a Model for Novel Treatment of Osteoporosis

Prof Jens Bollerslev
Norway.

Bone remodeling is a fine tuned process optimizing bone biomechanical properties. Peak bone mass is reached in early adult life, where after bone mass declines in both sexes leading to an increasing risk for low energy fractures. The understanding of bone remodeling has led to pharmacologic treatment of osteoporosis, being different antiresorptive modalities or anabolic treatment with PTH - or analogues. Inherited osteosclerotic bone disorders have been diagnosed since the introduction of radiography. Interestingly, some disorders were prone to pathological fractures, some not. The most severe forms were typically found to be autosomal recessive, whereas mild types were dominantly inherited. Early systematic studies of different osteosclerotic disorders indicated defective bone resorption as a common radiogrammetric and histomorphometric finding, whereas bone formation seemed to be relatively normal. The high bone mass phenotype was described in the Nineties based on family studies of index cases with high BMD. Further genetic studies revealed gain of function mutations in the LRP5 gene in several different family forms, pointing to the *Wnt* signaling pathway as pivotal for bone remodeling. The opposite picture, the Osteoporosis Pseudo-Glioma Syndrome was at the same time found to be caused by a loss of function mutation in *LRP5*. The regulation of the *Wnt* signaling pathway was discovered to be even more complicated by studies of van Buchem's disease and Sclereosteosis in the early Zero'es, discovering Sclerostin produced by the osteocytes as yet another important player in the bone remodeling mosaic. Defective Sclerostin leads to a constitutive activation of *Wnt* with bone formation activation, followed indirectly by inhibition of bone resorption – a new dual concept by Nature. Monoclonal antibodies towards Sclerostin (Romososumab) are by now close to the clinic (approved by FDA) as a new treatment modality for osteoporosis. Fracture prevention seems promising, whereas potential cardiovascular side effects are investigated.

DOI: 10.1530/endoabs.63.EHM1

Clinical Endocrinology Trust Award 2019 – Biography

Susan M. Webb was born and qualified from Medical School in Barcelona, Spain, and completed training at St. Bartholomew's Hospital, London and in San Antonio, Texas. She is a Senior Consultant Endocrinologist at the Hospital Sant Pau, and Professor of Medicine at the Universitat Autònoma de Barcelona. She runs the Neuroendocrine Clinic and the Pituitary Disease network of excellence research group (CIBERER unit 747), interested in the long-term consequences of having suffered pituitary diseases and evaluation of health-related quality of life. She coordinates the European Registry on Cushing's Syndrome (ERCUSYN) initially funded by the EU, has been President of the Spanish Society for Endocrinology and Nutrition, Secretary of ENEA, and until 2018 member of the ESE ExCo; she has served on the editorial boards of JCEM, Pituitary, Endocrine, among others. She has been a member of the European Union Committee of Experts on Rare Diseases (EUCERD), and is currently Scientific Assistant Director of CIBERER (Spanish network of excellence for rare diseases) and President of the Rare Disease Advisory Committee of the Catalan health system Catsalut. She has supervised some 20 PhD theses and has (co)-authored over 350 publications (original papers, invited reviews, and book chapters).

Clinical Endocrinology Trust Lecture

CET1

How can patients' perception of outcome be improved after controlling pituitary disease?

Prof Susan M Webb
Spain.

As endocrinologists, we consider a patient with a pituitary disease is controlled if hormone parameters are normalized and tumour growth is stabilized. However, the patients' perception of health is related to whether they can continue performing their daily life, both personal and professional; this is often not the case due to pain, physical or psychological limitations or social/family issues related to their disease. This is more relevant nowadays that pituitary dysfunction can be controlled in most cases, either after surgery or with medical therapy. In the last 2 decades, the long-term impact of prior exposure to hypercortisolism, excess GH/IGF-I or hypopituitarism on patients' health perceptions have become apparent. More cardiovascular, skeletal and neuropsychological morbidity persist after endocrine 'cure'; the latter include worse memory, cognition, executive function, emotional coping, which often lead to more anxiety, depression and psychological distress, with an important impact on perceived quality of life. Patients' perceptions may be overseen or ignored by health professionals, unless specifically mentioned; in this respect, the personal experiences of 'cured' patients, especially those in some way related to the health system or patient associations are very illustrative. It is recommendable to make patients aware of these problems, by devoted multi-disciplinary teams with an understanding of these persistent issues, so they can adapt to these limitations.This understanding, together with a positive approach to day-to-day life, and comprehension and support from family and friends, contribute to accept this new situation, impacting positively on patients' health perception and long-term prognosis.

DOI: 10.1530/endoabs.63.CET1

Plenary Lectures

Designing Cities and Homes as Exercise Machines: Helping Endocrinologists to Fight Metabolic Disease

PL1

Designing cities and homes as exercise machines: helping endocrinologists to fight metabolic disease

Avi Friedman
Canada.

The obesity epidemic has affected many nations. In Canada, by some estimates, more than 6 million Canadian adults age 20 to 64 are overweight and nearly 3 million are obese. The common tendency is to blame people's dietary choices and sedentary habits. Yet, it can also be argued that poor urban planning practices have largely contributed to a lack of active lifestyles. Low-density suburban sprawl, long commutes, diminishing land for green area and the elimination of sidewalks from local streets are some aspects that have led to reduced physical activity, among residents of all ages. Reversing course and regarding the community and the home as exercise machines need to be a top priority of urban planners and public health officials. Public transit, commercial hubs walking distance away, jogging tracks, bike paths and play spaces should become mandatory features of new residential development. In his presentation, Dr. Avi Friedman, Professor of Architecture at McGill University, recipient of the World Habitat Award and a practicing architect, will illustrate the decline of community planning for healthy living and outline measures that can be reintroduced to foster active lifestyles.

DOI: 10.1530/endoabs.63.PL1

Genetic Epidemiology of Puberty Timing and Reproductive Lifespan (*Endorsed by the European Journal of Endocrinology*)

PL2

Genetic epidemiology of puberty timing and reproductive lifespan

Ken Ong
UK.

Background
The timing of puberty varies widely between individual children. Those in the extreme early or late groups present commonly to endocrine clinics. Furthermore, in population studies the continuum in puberty timing is associated with long-term health outcomes, such as obesity, Type 2 diabetes, sex steroid-sensitive cancers and also with the timing of menopause and reproductive lifespan. This timing is highly heritable. Genome-wide association studies (GWAS), which genotype hundreds of thousands of common genetic variants located across the entire genome, have identified many specific genetic determinants of pubertal timing and these findings have informed the mechanisms that link earlier pubertal timing to increased risks of disease.
Methods & Findings
Through ReproGEN and other large international GWAS consortia, we have identified hundreds of genomic loci with highly robust associations with puberty timing in both sexes, and with menopause timing in women. These studies have shone new light into the biological regulation of the reproductive axis. For puberty timing, many loci implicate genes that regulate the hypothalamo-pituitary-gonadal axis, energy homeostasis and weight gain, and other unanticipated pathways such as genomic imprinting. For menopause timing, DNA damage sensing and repair is the predominant overall mechanism, but there are notable contributions by some hypothalamo-pituitary-gonadal axis genes.
Discussion
This talk will provide an update on GWAS for puberty and menopause timing and will highlight the clinical implications of the findings.

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Pancreatic Beta-cell Ageing: Novel Mechanisms and Consequences in the Management of Diabetes

PL3

Pancreatic beta-cell ageing: Novel mechanisms and consequences in the management of diabetes

Susan Bonner-Weir
USA.

Pancreatic beta-cells maintain the body's glucose levels within a very narrow range. In the face of insulin resistance and obesity, most people do not become diabetic due to the ability of the endocrine pancreas to have compensatory growth. Any limitation on replacement or shortening of lifespan could have dire consequences for glucose homeostasis. Type 2 diabetes develops only when b-cells fail to compensate for increased demand from insulin resistance. While Type 2 diabetes (T2D) increases with age with the majority of patients being above the fifth decade of life, the specific contribution of beta cell aging and senescence to diabetes has had limited study. Yet the deficiency in proliferative response to increased demand may arise partly from the accumulation of senescent beta-cells. Cellular senescence is a state in which cells cease to divide but remain metabolically active with an altered phenotype. Cells in general, and presumably beta cells, senesce in response to stressors and aging, resulting in changes in structure and function that may include irreversible growth arrest and alterations in gene expression. With age, an accumulation of dysfunctional senescent beta-cells likely contributes to impaired glucose tolerance and diabetes. From our studies we have shown that there are differently aged beta cells in the adult pancreas. Even in young (3–4 month old) mice, a population of beta-cells express known aging markers (senescence-associated acidic beta-galactosidase activity (b-Gal), *p16Ink4a* and p53BP1) and that this population increased with age. Aged beta-cells had impaired function, characterized by higher basal insulin secretion and a lower recruitment to glucose challenges; senescent beta cell secrete a number of cytokines and chemokines, known as senescence-associated secretory profile (SASP) that have detrimental effects on neighboring cells. Importantly acute insulin resistance, induced by the insulin receptor antagonist S961 or high fat diet, resulted in expression of aging markers suggesting that insulin resistance as a driver of accelerated beta-cell aging. Additionally even mild hyperglycemia induces a markedly changed beta cell phenotype and dysfunction. We will address the relationship between beta-cell aging, the development of diabetes and if there are strategies to decrease the load of aged beta-cells in order to improve cellular identity, function and overall metabolic parameters.

DOI: 10.1530/endoabs.63.PL3

Exercise Training in the Management of Type 2 Diabetes

PL4

Exercise training in the management of type 2 diabetes

Juleen Zierath
Sweden.

Type 2 diabetes mellitus is a life threatening metabolic disease reaching epidemic proportions. Although the molecular basis for this pathology is incompletely understood, genetic and environmental factors, probably in a synergistic manner, contribute to the risk of developing type 2 diabetes. The burden of type 2 diabetes and related co-morbidities on society is enormous, and growing, given that there is no cure in sight. Type 2 diabetes shares many features of 'accelerated aging' including insulin resistance, defective oxidative metabolism/mitochondrial function and loss of muscle mass. Strikingly, long-term participation in vigorous exercise programs mitigates secondary aging and reduces disability and mortality. This association advances the notion that exercise promotes 'healthy aging', reduces the impact of metabolic disease, and improves the quality of life. At the molecular level, exercise results in a rapid, but transient change in the epigenome by modifying DNA methylation of the promoters of key genes regulating mitochondrial function and biogenesis in skeletal muscle. Recent evidence suggests that intimate links between epigenetic regulation and the circadian clock exist that are likely to contribute to the plasticity of insulin sensitive organs to exercise and nutrition. Therefore, we are currently addressing whether synchronizing exercise and nutrient interventions to the molecular circadian clock will maximize the health promoting benefits of exercise to enhance insulin sensitivity and mitochondrial biogenesis. This lecture will present new evidence highlighting exercise-responsive treatment targets and optimal exercise intervention strategies to mitigate secondary aging and prevent metabolic disease.

DOI: 10.1530/endoabs.63.PL4

Paracrine Regulation of the Adrenal Cortex

PL5

Paracrine regulation of the adrenal cortex

Dr Hervé Lefebvre
France.

Numerous *in vitro* studies have shown that the secretory activity of the human adrenal cortex is activated by a wide variety of neuropeptides and conventional neurotransmitters released in the vicinity of adrenocortical cells by chromaffin cells, endothelial cells, adipocytes, cells of the immune system and nerve endings. The role of these paracrine factors in the physiological control of the adrenocortical function remains unclear, especially for cortisol production which is principally dependent on ACTH secretion. However, it appears likely that intraadrenal bioactive signals are involved in the regulation of aldosterone secretion which is partly independent of the renin-angiotensin system. In particular, increasing evidence indicates that aldosterone production is stimulated by neural inputs, leptin and serotonin (5-HT) released by subcapsular mast cells. Interestingly, the occurrence of paracrine regulatory processes has also been reported in adrenocortical hyperplasias and tumors responsible for aldosterone or cortisol excess. These mechanisms roughly involve the same actors as those operating in the normal adrenal but exhibit alterations at various levels which tend to reinforce their potency to increase steroid production. The main defects in the intraadrenal control systems noticed so far include hyperplasia of cells producing the paracrine factors and illicit expression of the latter and their receptors. This new pathophysiological concept is nicely illustrated by mast cell hyperplasia in aldosterone-producing adenomas (APAs) and upregulation of the 5-HT signaling pathway or ectopic synthesis of ACTH in adrenocortical cells in bilateral adrenal hyperplasias responsible for cortisol excess. Upregulated paracrine factors and their receptors are likely to play a significant role in adrenocortical hyperplasia/tumor expansion and associated steroid hypersecretion together with somatic mutations affecting the calcium signaling pathway in APAs or the cAMP/protein kinase A pathway in cortisol-producing adenomas. They also represent new targets for the pharmacological treatment of primary adrenal steroid excess.

DOI: 10.1530/endoabs.63.PL5

Graves Orbitopathy

PL6

Graves Orbitopathy

George Kahaly
Germany.

Graves' orbitopathy (GO) is a rare complex auto-immune disorder which causes substantial morbidity. It can result in orbital disfigurement, double vision and even visual loss. Consequently it has a substantial negative effect on quality of life, mental health and socioeconomic status. The vast majority of patients have Graves' disease (GD), an inflammatory auto-immune condition which is characterized by thyrotropin receptor auto-antibodies (TSHR-Ab). Ocular inflammation at baseline, smoking, TSHR-Ab titre and duration of thyroid dysfunction being the four key risk factors for developing GO in GD. Most of the signs and symptoms of GO can be explained by the expansion of the orbital contents. The orbital fibroblast is the target of a spectrum of autoimmune responses which collectively promote proliferation, excess adipogenesis (formation of new fat cells by differentiation of preadipocytes) and over-production of extra-cellular matrix (ECM). The ECM comprises glycosamino-glycans such as chondroitin sulphate and hyaluronic acid, which is not sulphated but is able to absorb up to 1000 times its weight in water. Steroids are the mainstay of treatment in GO. While this may be a non-specific effect of reducing inflammation and depleting leucocytes, a direct action on the adipocytes including the inhibition of 'browning' processes in orbital fat cells is discussed. Other strategies such as radiotherapy have had their role in combination therapy called into question. Recurrence may occur once steroids are withdrawn. Furthermore, in most cases, normal orbital anatomy is not restored, and skilled rehabilitative surgery is required to reduce disfigurement, double vision and occasionally, to preserve vision. In the last decade, the pathophysiology of GO has also been revised with identification of new potential therapeutic targets. Recent clinical trials have shown that considerable benefit may be derived from the addition of anti-proliferative agents (e.g. mycophenolate sodium) in preventing deterioration after steroid cessation. In addition, targeted biologic therapies have shown promise, including teprotumumab (anti-IGFR) which appears to substantially reduce proptosis, rituximab (anti-CD20) which reduces inflammation and tocilizumab (anti-IL6) which potentially benefits both of these parameters. This review therefore outlines the optimal management of GO and summarises the recent research developments in this area.

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Control of Integrative Physiology by the Melanocortin Circuitry

PL7

Control of integrative physiology by the melanocortin circuitry

Jens Claus Brüning
Germany.

Proopiomelanocortin (POMC)- and agouti related peptide (AgRP)-expressing neurons in the arcuate nucleus of the hypothalamus (ARH) are critical regulators of food intake and energy homeostasis. They rapidly integrate the energy state of the organism through sensing fuel availability via hormones, nutrient components and even rapidly upon sensory food perception. Importantly, they not only regulate feeding responses, but numerous autonomic responses including glucose and lipid metabolism, inflammation and blood pressure. More recently, we could demonstrate that sensory food cue-dependent regulation of POMC neurons primes the hepatic endoplasmic reticulum (ER) stress response to prime liver metabolism for the postpramndial state. The presentation will focus on the regulation of these neurons in control of integrative physiology, the identification of distinct neuronal circuitries targeted by these cells and finally on the broad range implications resulting from dysregulation of these circuits as a consequence of altered maternal metabolism.

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Symposia

Thyroid in Cancer

S1.1

What is the value of molecular markers in nodules?

Laura Fugazzola
Italy.

Cytological evaluation establishes the diagnosis of a benign or malignant nodule in 70–80% of all cases, but the remaining cases lack the features needed for a definitive diagnosis. Molecular tests have been developed to assist in determining if a nodule with indeterminate cytology is benign or malignant. The first studies focused on the analysis of the most common thyroid cancer (TC) mutation, BRAFV600E. However, since many TCs are driven by other mutations, testing for BRAF alone does not provide sufficiently high negative predictive value (NPV) to avoid surgery for nodules lacking this gene mutation. The sensitivity of molecular testing was improved through the introduction of gene panels, which became available for clinical use in the late 2000s. In addition to BRAF, they tested for several other common genes mutated in TC, and these typically rule-in tests panels detected genetic alterations present in ~70% of cases. The next step in the evolution of molecular testing has involved the use of NGS. The ThyroSeq panels are NGS panels with a high sensitivity and are able to quantitatively assess the proportion of cells carrying a given mutation. In 2012 a 'rule out' test was introduced, namely the Afirma test, which does not rely on detecting gene mutations but is based on the analysis of expression changes in 167 genes. The Afirma test evaluates the gene expression profiles, reports the result as either 'benign' or 'suspicious', and has a high NPV. The main disadvantage of these tests is the high cost, which makes them rarely used in Europe. In order to generate a reliable but cheaper test, we set up a custom Mass Array platform (PTC-MA), which allows the simultaneous detection of the 13 hotspot mutations and seven fusion genes more frequently found in TC, in a time and cost-effective manner.

DOI: 10.1530/endoabs.63.S1.1

S1.2

Iodine refractoriness in thyroid cells

Chris McCabe
UK.

The ability of thyroid cells to specifically uptake radioiodine is frequently compromised in the neoplastic setting, particularly in older patients with poorly differentiated thyroid cancer and larger metastases, resulting in a 10-year survival rate of less than 10%. The mechanisms which govern cellular iodide uptake via the sodium iodide symporter (NIS) have been elucidated with increasing molecular clarity over the past 35 years. NIS is regulated in a tissue-specific manner, and its correct functioning is sensitive to an incredibly wide array of regulatory events, from the genetic to the epigenetic, via miRNAs and lncRNAs, as well as transcription factors, hormones and growth factors, and is particularly at the mercy of activated kinase pathways. New mechanisms regulating NIS activity continue to be identified, shining fresh light on the ways in which thyroid cells become refractory to iodide uptake, particularly in aggressive thyroid cancer. This considerable experimental endeavour is currently driving ongoing clinical trials aimed at overcoming iodine refractoriness, with the consensus view that single agent approaches may not be sufficient to boost NIS function for effective therapy. To this end, new insight into how NIS is intracellularly trafficked and targeted to the plasma membrane is emerging, which may transform our understanding of how to ultimately address iodine refractoriness. Thus combinatorial approaches targeting key components of NIS repression and mislocalisation may finally be able to overcome the iodine refractoriness which is a hallmark of dedifferentiated thyroid cancer, opening the possibility of effective treatment to patients who currently cannot uptake sufficient radioiodine for tumour cell ablation.

DOI: 10.1530/endoabs.63.S1.2

S1.3

New paradigms in the treatment of low risk thyroid cancer

Martin Schlumberger
France.

Abstract Unavailable.

Trends in Puberty

S2.1

Exploring the Epigenetic landscape of puberty

Alejandro Lomniczi
USA.

During the infantile-pubertal transition, a diversity of behavioral, physiological, morphological and molecular changes are required in order to attain fertility. An essential step in this process is the reactivation of the pituitary-gonadal axis by increased hypothalamic secretion of Gonadotropin-Releasing Hormone (GnRH). This drives the adenohypophysis to increase the pulsatile release of luteinizing hormone (LH) with diurnal periodicity, the first endocrine sign of pubertal development. The current dogma postulates that diminishing transsynaptic inhibition jointly with increased excitatory inputs is responsible for the reactivation of GnRH release. With the advent of new high throughput genomic technologies today we can interrogate the developing hypothalamus for genome-wide changes in mRNA expression as well as epigenetic modifications associated with gene regulatory/promoter regions. Over the last several years, a plethora of new transcriptional complexes, some of which with epigenetic capabilities have been found to be involved in the hypothalamic control of pubertal development. Here, we will review the contribution of several families of epigenetic writers, readers, and erasers in the shift from a repressive to an activated chromatin state at promoter and enhancer regions of the Kiss1 gene during the infantile-pubertal transition. This relatively new mode of epigenetic regulation opens up to the exciting possibility that the reactivation of the GnRH pulse generator lays in the genetic/epigenetic architecture of the Kiss neuron. In addition, we will discuss the tantalizing possibility that epigenetics serves as a relay of environmental signals known for many years to modulate pubertal development.

DOI: 10.1530/endoabs.63.S2.1

S2.2

Endocrine disrupters in puberty

Anne-Simone Parent
Belgium.

Onset of puberty strongly depends on organizational processes taking place during the fetal and early postnatal life. Therefore, exposure to environmental pollutants such as Endocrine disrupting chemicals during critical periods of development can result in delayed/advanced puberty and long-term reproductive consequences. Human evidence of altered pubertal timing after exposure to endocrine disrupting chemicals is equivocal. However, the age distribution of pubertal signs points to a skewed distribution towards earliness for initial pubertal stages and towards lateness for final pubertal stages. Such distortion of distribution is a recent phenomenon and suggests environmental influences including the possible role of nutrition, stress and endocrine disruptors. Some rodent and ovine studies indicate a possible role of fetal and neonatal exposure to EDCs, along the concept of early origin of health and disease. Such effects involve neuroendocrine mechanisms at the level of the hypothalamus where homeostasis of reproduction is programmed and regulated. We have shown that neonatal exposure to the ubiquitous endocrine disruptor Bisphenol A (BPA) leads to opposing dose-dependent effects on the neuroendocrine control of puberty in the female rat. In particular, a very low and environmentally relevant dose of BPA delayed neuroendocrine reproductive maturation through increased inhibitory GABAergic neurotransmission. More recently, we studied the effect of a mixture of endocrine disrupting chemicals on female sexual development during three generations. Female rats (F0 generation) were orally exposed to a mixture of 14 anti-androgenic and estrogenic EDCs or corn oil for 2 weeks before and throughout gestation and until weaning. While F2 and F3 females showed delayed vaginal opening, decreased percentage of regular estrous cycles and decreased GnRH interpulse interval, no such changes were detected in F1 animals. These reproductive phenotypes were associated with alterations in both transcriptional and histone posttranslational modifications of hypothalamic genes involved in reproductive competence. F1 females that were exposed *in utero* to the EDC mixture, showed a reduction in thyroxin hydroxylase mRNA expression and impaired maternal behavior. Overall, our data shows that gestational and lactational exposure to an environmentally relevant EDC mixture transgenerationally affects sexual development throughout epigenetic reprogramming of the hypothalamus. Such effects could be mediated by alterations of maternal behavior caused by exposure of the first generation to the EDC mixture.

DOI: 10.1530/endoabs.63.S2.2

S2.3

The genetic basis of pubertal timing

Sasha Howard
UK.

Whilst the timing of pubertal onset varies within and between different populations, it is a highly heritable trait. The timing of sexual maturation is highly correlated within families and in twin studies, suggesting strong genetic determinants. However, despite this strong heritability, our knowledge of the genetic control of puberty remains limited. Disturbances of puberty (precocious, delayed or arrested) encompass an important group of pathologies. Firstly, they are common, affecting up to 4% of adolescents. In addition, abnormal timing of pubertal development is associated with adverse health and psychosocial outcomes. This has importance both for the individual, but also has a potential major impact on public health, especially in view of the secular trend towards an earlier age of puberty onset. Self-limited delayed puberty (DP) and familial central precocious puberty (CPP) are common inherited conditions defined by disordered pubertal timing, each with an established genetic basis. Self-limited DP, also known as constitutional delay of growth and puberty, is a highly heritable condition, which segregates in an autosomal dominant pattern (with or without complete penetrance) in the majority of families. Like self-limited DP, CPP often has a strong familial basis. Segregation analysis points to an autosomal dominant inheritance pattern with incomplete sex dependent penetrance. Two key imprinted genes have been identified as causal in pedigrees of CPP: *MKRN3*, and *DLK1*. *MKRN3* is thought to contribute to the puberty 'brake' restraining the hypothalamic-pituitary-gonadal axis via inhibition of GnRH release. Recent discoveries have begun to address the question of genetic regulation in self-limited DP. Using next generation sequencing (NGS) to explore a large DP patient cohort, mutations in the *IGSF10* gene were in 10% of probands. Following this discovery, mutations in several further genes involved in the gonadotropin-regulating hormone (GnRH) pathway have been identified in families with self-limited DP: *EAP1*, *HS6ST1* and *LGR4*. These results provide a new mechanism for delayed puberty: through defects in genes controlling the development of the GnRH neuroendocrine network. Importantly, for the majority of DP patients these are not defects in those genes that are known to produce complete GnRH deficiency in conditions such as hypogonadotropic hypogonadism. Moreover, genetic overlap has been identified between regulators of the timing of puberty in the general population identified from genome wide association studies, and both self-limited DP and CPP, including genes involved in energy metabolism.

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Circadian Clocks: From Pathophysiology to Chronomedicine

S3.1

Circadian control of glucocorticoid function

David Ray
UK.

The glucocorticoid receptor (GR) is a nuclear receptor, a major drug target, and the end point of the hypothalamic-pituitary-adrenal axis. Glucocorticoids (GC) are essential for life, but in excess cause disordered energy metabolism, including increased weight gain, adiposity and hepatosteatosis; all programmes modulated by the circadian clock. Secretion of GC is regulated by the circadian clock, but could their actions be also? Here, using mouse as a model, we found that while the anti-inflammatory GC actions were maintained irrespective of dosing time, the liver was significantly more GC sensitive during the day. The time of day variation in GC action was underpinned by a physical interaction of GR with circadian transcription factor REVERBa, and co-binding with liver specific HNF transcription factors on chromatin. REVERBa promoted efficient GR recruitment to chromatin during the day, acting in part by maintaining histone acetylation, with REVERBa dependent GC-responses providing segregation of carbohydrate and lipid metabolism. Importantly, deletion of *Reverba* inverted circadian liver GC sensitivity, and protected mice from hepatosteatosis induced by chronic GC administration. Our results reveal a mechanism by which the circadian clock acts through REVERBa in liver on elements bound by HNF4A/HNF6 to direct GR action on energy metabolism.

DOI: 10.1530/endoabs.63.S3.1

S3.2

Fixing the broken clock in adrenal disorders

Andrea Isidori
Italy.

Context
Glucocorticoids (GC) mediate some of the adverse health-related consequences of circadian misalignment, such occurs in shift workers who have an increased cardio-metabolic, immune and cancer risk. Investigating the effect of circadian cortisol exposure in patients with GC excess and defect is crucial. In a therapeutic perspective large attention has been given to the total daily GC exposure, much less to the timing-of-the-day relative exposure. Clock genes are essential components of the machinery controlling circadian functions and are synchronized by GCs. Until recently, clock genes have not been investigated in patients with Adrenal Insufficiency (AI) or Cushing's syndrome (CS), despite they represent a disease model of endogenous clock misalignment.
Objective
We evaluated the effect of the timing of GC exposure on circadian gene expression in peripheral blood mononuclear cells (PBMCs) of patients with AI or CS enrolled in the DREAM[1] and TheHOURS (The circadian rhythm in cusHing syndrOme in active phase and dUring RemiSsion) trials.
Results
Compared with healthy controls, we found dysregulated many clock-related genes, with a distinctive profile in the AI and CS groups. Several metabolic and inflammatory signalling pathways were found altered in patients exposed to high evening/night GC levels or multiple peaks and trough during the day. Disease-specific effects were found in the profile of circulating PBMCs. More, PBMCs fluctuations during the day was not entirely abolished, but shifted or altered in patter and intensity. Medical interventions were partially able to restore the expression on clock-related genes, intracellular signalling and profiles of circulating PBMCs.
Conclusions
Pharmacological strategies designed to consider circadian timing of drug/hormone delivery, and circadian regulation of drug metabolism and of target gene/protein expression may be beneficial in the treatment of many chronic HPA-axis disorders.
Reference
1. Isidori AM *et al*. *Lancet Diabetes Endocrinol*. 2018; 6(3):173 & Venneri MA *et al*. *JCEM 2018*; 103(8):2998.

DOI: 10.1530/endoabs.63.S3.2

S3.3

Understanding the molecular basis of seasonal changes in behavior

Takashi Yoshimura
Japan.

Appropriate timing of various seasonal processes, such as reproduction, migration and hibernation, is crucial to the survival of animals living in temperate regions. Although this phenomenon has been studied for decades, the underlying mechanisms of seasonal changes in behavior are not well understood. Medaka fish (*Oryzias latipes*) are an excellent model for studying seasonal adaptation, as they are active and exhibit clear phototaxis in conditions simulating summer, but are inactive and fail to exhibit phototaxis in conditions simulating winter. Mate preference tests using virtual fish created with computer graphics demonstrate that medaka are more attracted to orange-red-colored model fish in summer than in winter. Transcriptome analysis of the eye reveals dynamic seasonal changes in the expression of genes encoding photopigments and their downstream signaling components, suggesting that plasticity in phototransduction is crucial for seasonal changes in color perception. We have also performed transcriptome analysis using medaka hypothalamus and pituitary gland and found that an uncharacterized long non-coding RNA (lncRNA) is strongly regulated by photoperiod. Since knockout medaka of this lncRNA show different responses to stress, we propose that photoperiodic regulation of this lncRNA modulates seasonal changes in behavior. Although humans are not typically considered seasonal, some evidence suggests that seasonal variation in physiology and behavior do exist. Seasonal affective disorder patients, experiencing recurrent winter episodes of depressed mood, show electroretinogram changes in winter with lower sensitivity compared with healthy subjects. I will discuss how we can better understand seasonal changes in behavior using unique animal models.

DOI: 10.1530/endoabs.63.S3.3

Immunology and Endocrinology (*Endorsed by Endocrine Connections*)

S4.1

Basic: immunotherapy and endocrine disease

Mario Caturegli
USA.

Abstract Unavailable.

S4.2

Clinical: Immunotherapy and endocrine disease

Maria Stelmachowska-Banaś
Poland.

Immunotherapy with immune checkpoint inhibitors has become an effective treatment of many malignancies resistant to conventional chemotherapies. Immune checkpoints are molecules on the surface of immune cells involved in the regulation of the immune response and immune checkpoint inhibitors are monoclonal antibodies directed against certain immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1) and its ligand (PD-L1), resulting in T-cell activation and antitumor activity. However, immune checkpoints also play a crucial role in maintaining immunological self-tolerance and preventing autoimmune disorders. Interfering with this mechanism can cause immune-related adverse events (irAEs) presenting as autoimmune disorders affecting numerous organs in the body. Endocrinopathies are among the most common irAEs associated with immune checkpoint inhibitors and most of them include thyroid dysfunction (typically associated with anti-PD-1 antibodies) and hypophysitis (typically associated with anti-CTLA-4 antibodies probably as a result of ectopic expression of CTLA-4 antigens on the cells of a human hypophysis). Insulin-deficient diabetes mellitus and primary adrenal insufficiency are rare endocrine toxicities associated with immune checkpoint inhibitors, but can be life-threatening if not promptly recognized and treated. Some endocrinopathies as thyrotoxicosis are transient, may resolve spontaneously and require only monitoring or symptom control but others, such as central adrenal insufficiency and primary hypothyroidism, are persistent and require proper life-long hormonal replacement. Combination of anti-CTLA-4 and anti-PD-1 treatment is usually associated with the highest incidence and severity of immune checkpoint inhibitors endocrinopathies. Given the increasing use of immune checkpoint inhibitors, cooperation between oncologists and endocrinologists is crucial in the management of patients with immunotherapy-induced endocrinopathies. Making an appropriate diagnosis and adequate hormonal relacement may improve the prognosis of oncological patients in whom immunotherapy-induced endocrinopathy have occurred.

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S4.3

Transitional: The diagnostic value of autoimmune antibodies in endocrine disorders

Olle Kämpe
Sweden.

Abstract Unavailable.

Microbiota as New Treatment for Diabetes and Metabolic Disease

S5.1

Human gut microbiome: hopes, threats and promises

Hubert VIDAL
France.

The gut microbiota is now the subject of considerable investigation and our knowledge of its composition and understanding of functions are rapidly growing.Gut microbiota has profound impact on host physiology and it is now well-established that dysbiosis is associated with altered glycemic control and type 2 diabetes development. Targeting microbiota appears therefore as a promising strategy for the treatment of diabetic patients. Using probiotics in order to modulate blood glucose has been considered for a long time. However, the low efficacy of currently available probiotics highlights the lack of well-defined and standardized methodology to identify and select bacterial strains with real anti-diabetic properties. A better understanding of the mechanisms by which gut microbiota impacts host physiology is needed to identify such probiotic strains. In this presentation, we will discuss some innovative strategies to identify bona fide probiotic strains with anti-diabetic potential.

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S5.2

Fecal transplantation: Myth or reality

Max Nieuwdorp
The Netherlands.

Alterations in (small) intestinal microbiota are associated with aberrant insulin secretion. We previously showed that fecal transplantation (infusing intestinal microbiota from lean donors) in insulin resistant subjects has beneficial effects on the recipients' microbiota composition and glucose metabolism via altering fecal SCFA producers levels (Vrieze, Gastroenterology 2012). Followup studies suggest that this beneficial effect can be divided in responders and non responders based on SCFA producing microbiota engraftment and beneficial metabolites (Kootte, Cell Metabolism 2017). In line, unpublished data from our group suggest that FMT in new onset type 1 diabetes patients also can drive beneficial effects on residual betacell function (de Groot/Roep/Nieuwdorp, manuscript in preparation). To our surprise however, oral butyrate supplementation had no beneficial effect on glucose metabolism in both type 1 and type 2 diabetes subjects (de Groot/Roep/Nieuwdorp, submitted; Bouter/Nieuwdorp, Clin Transl Gastro 2018). Combined our data thus suggest that specific missing intestinal (SCFA producing) strains might be developed as therapeutics for treatment in both type 1 and type 2 diabetes.

DOI: 10.1530/endoabs.63.S5.2

S5.3

Targeted Microbiome Intervention for handling insulin resistance

Matthias Laudes
Germany.

Abstract Unavailable.

A Better Life with Thyroid Hormone (*Endorsed by the European Journal of Endocrinology*)

S6.1

Prediction of the thyroid axis set-point

Marco Medici
The Netherlands.

In the last few years studies have shown that subtle variations in thyroid function, including subclinical thyroid dysfunction, and even variation in thyroid function within the normal range, are associated with morbidity and mortality. It is estimated that 40–65% of the inter-individual variation in serum TSH and FT4 levels is determined by genetic factors. To identify these factors, various linkage and candidate gene studies have been performed in the past, which have identified only a few genes. In the last decade, genome-wide association studies identified >100 genetic variants, while whole exome and whole genome sequencing studies are expected to further clarify the genetic basis of thyroid function in the near future. The identification of these genes has paved the way for various lines of research. Examples of follow-up *in vitro* characterization studies of these genes include the identification of SLC17A4 as a novel thyroid hormone transporter and AADAT as a novel thyroid hormone metabolizing enzyme. Furthermore, mendelian randomization studies are expected to clarify whether the observed associations between minor variations in thyroid function and clinical endpoints are causal or not, which is key when considering treatment for these mild variations in thyroid function. Finally, these genetic markers have been associated with normal range thyroid function as well as thyroid dysfunction, thereby possibly serving as predictive markers for the individual thyroid setpoint and for thyroid disease.

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S6.2

Subclinical hypothyroidism in children

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Italy.

Subclinical hypothyroidism (SH) is a biochemical condition defined by increased TSH serum concentration above the normal range associated with normal concentrations of T4 and Free T4. In children SH is often a benign and remitting condition, for which risk of progression to overt hypothyroidism depends on the underlying cause (i.e. autoimmune SH is associated with an increased risk whereas non–autoimmune with a low risk of progression to overt hypothyroidism). The major concern regarding SH is to establish whether this condition should always be considered an expression of mild thyroid dysfunction. Growth and neurocognitive outcome in children do not appear to be affected by SH, however recent data suggest that mild SH may be associated with subtle pro-atherogenic abnormalities. The benefits of levothyroxine therapy are far from clear, therefore the optimum management of children with SH remains a matter of debate and depends on the etiology and degree of TSH elevation and should be individually tailored.

DOI: 10.1530/endoabs.63.S6.2

S6.3

Subclinical hypothyroidism in the elderly

Salman Razvi
UK.

Background
Both overt hypothyroidism as well as subclinical hypothyroidism is frequently encountered in older individuals. It is increasingly being recognised that treatment of subclinical hypothyroidism may not be beneficial, particularly in an older person. These findings are particularly relevant at a time when treatment with thyroid hormones is increasing and more than 10–15% of people aged over 80 years are prescribed levothyroxine therapy.
Main body
The prevalence of hypothyroidism increases with age. However, the upper limit of the TSH reference range also rises with age. Furthermore, there is evidence to suggest that minor TSH elevations are not associated with important outcomes such as symptoms, impaired quality of life, cognition, cardiovascular events and mortality in older individuals. There is also evidence that treatment of mild subclinical hypothyroidism may not benefit quality of life and/or symptoms in older people. It is unknown whether treatment targets should be reset depending on the age of the patient. It is likely that some older patients with non-specific symptoms and incidental mild subclinical hypothyroidism may be treated with thyroid hormones and could potentially be harmed as a result or, at best, have no beneficial impact.
Conclusions
Evidence suggests that threshold for treating mild subclinical hypothyroidism in older people should be high. In addition, it is reasonable to aim for a higher TSH target in treated older hypothyroid patients, as their thyroid hormone requirements are lower. Therefore, it is important that age-appropriate TSH reference ranges should be considered in the diagnostic pathway of identifying hypothyroidism. Appropriately designed randomised controlled trials are required to confirm risk/benefit and cost-effectiveness of treatment of subclinical hypothyroidism in older people. Until the results of such RCTs are available to guide clinical management international guidelines should be followed that advocate a conservative policy in the management of mild subclinical hypothyroidism in older individuals.

DOI: 10.1530/endoabs.63.S6.3

Endocrine Disrupting Chemicals (*Endorsed by Endocrine Connections*)

S7.1

Mixtures measured in human, disrupt thyroid hormone signaling and behavior in Xenopus laevis

Jean-Baptiste Fini
France.

Endocrine disrupting chemicals (EDCs) harm human health both as single molecules and as mixtures. Most research on EDCs is done on individual chemicals whereas we are exposed to mixtures of numerous and possibly interacting molecules. This discrepancy presents a dilemma for risk assessment and legislation. Thyroid hormones are essential for normal brain development where they influence, through specific embryonic and post-natal periods all the steps of brain development. In adults, TH roles are essential to brain function and to general metabolism (thermogenesis, fat burning, etc.). As number of compounds produced by chemical industries increased by 300 fold since the 70's, and many reports in the scientific literature show that many of these chemicals are potential Endocrine disruptors (EDCs) we questioned the thyroid hormone disrupting effect of common chemicals. We hypothesized that this axis could be a key target for disruption and hence alter normal brain development. To test this hypothesis, we used a thyroid disruptor screening assay, the Xenopus Embryonic Thyroid Assay (XETA), RT-qPCR on brain tissue, and behavior analysis. We used to independent strategies with different mixtures from human data. First we recreated m a mixture of 15 compounds commonly found in Human beings and tested them at the concentration meassured in amniotic fluid and study the effects on thyroid hormone signaling and adverse effects on our tadpole model. Second, a novel approach, developed within the European project, EDC-MixRisk, was to classify adverse mixtures of chemicals found in population based on epidemiological studies and test their EDC potential with both *in vivo* and *in vitro* assays. Samples from about 2,000 pregnant women were examined and retrospective analysis on offspring identified a chemical mixture for which embryonic exposure was associated with language delay, an indication for neurodevelopmental delay. Results on the two kind of mixtures show significant modification of TH availability (XETA assay) at the actual mixture concentration found in fluids of pregnant women. Second, mRNA levels of key genes involved the TH-signaling pathway showed significant alteration of TH-dependent genes at the accrual exposure level. Finally, mixtures were found to alter tadpoles'mobility behavior. Taken together, these results show advantages of using different strategies and necessity to take into consideration mixture in both experimental studies and risk assessment.

DOI: 10.1530/endoabs.S7.1

S7.2

Actions of endocrine disrupting chemicals on pancreatic beta cells and risk of diabetes mellitus

Angel Nadal
Spain.

Type 2 diabetes (T2D), results from a deficiency in insulin action on peripheral tissues together with a lack of compensatory insulin production and release by pancreatic beta cells. The etiology of T2D involves both, genetic predisposition and environmental factors. Bisphenol-A (BPA) is a widespread endocrine disrupting chemical that modify pancreatic beta cell function and induce insulin resistance in rodents after treatment during different timing of exposure, including pregnancy. This is a sensitive period of susceptibility for both mothers and offspring. Epidemiological studies associate BPA levels in urine with T2D development in adult humans. Adult male mouse treatment with low doses of BPA induces insulin resistance and hyperinsulinemia. Experiments using isolated beta cells as well as whole islet of Langerhans, suggest that BPA acts directly in beta cells to increase insulin content and release. Insulin content regulation by BPA is an estrogen receptor alpha (ERα) dependent process. In addition, BPA regulates beta cell electrical activity via a pathway which involves estrogen receptors β (ERβ). Electrophysiological measurements showed a decrease in sodium, calcium and total potassium currents in BPA-treated islets which is in line with BPA effects on gene expression. BPA-induced changes were abrogated in beta cells derived from $ER\beta^{-/-}$ mice, suggesting that ERβ mediates BPA effects on ion channel expression and function in pancreatic beta cells.

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S7.3

Prenatal obesogen exposure leads to a transgenerational thrifty phenotype in mice

Bruce Blumberg
USA.

Obesity is commonly ascribed to an imbalance between caloric intake and energy expenditure, but a growing body of evidence underscores the contributions of other factors in the obesity epidemic. We found that exposure of F0 animals to TBT throughout pregnancy and lactation predisposed male F4 descendants of TBT-treated animals to obesity when challenged with a higher fat diet. The TBT group showed impaired ability to mobilize fat during fasting and elevated serum leptin levels. Limited fat mobilization and elevated leptin levels suggest that fat accumulation results, in part, from leptin resistance. Integrated methylome and transcriptome analysis from fat and liver of F4 animals revealed that ancestral TBT exposure led to changes in global DNA methylation consistent with architectural changes in chromatin structure. Our results show that ancestral, in utero exposure to TBT alters chromatin structure to modulate expression of genes important for fat storage and mobilization. We propose that altered chromatin structure is a novel method for transgenerational transmission of the effects of obesogen exposure.

DOI: 10.1530/endoabs.63.S7.3

Genderdysphoria – Delayed Puberty

S8.1

Psychoendocrinology of gender dysphoria

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Italy.

Usually, gender identity (GI) and biological sex are physiologically consistent, but this is not the case when individuals have a GI disorder/dysforia (GD) and thus require hormonal and/or surgical feminization/masculinization to reduce the discrepancy between the sense of self and sexual characteristics. The role of the Endocrinologist expert in Sexual Medicine and, in particular, in GD is crucial and pivotal. They (the transgenders), in fact, are a heterogeneous population for age of first referral to a specialist, type and amount of adjustment required, and for clinical situations. The GI is the perception that the subject has of his/her belonging to a gender, regardless of biological sex. Hence, the diagnosis of GD can only be self-reported, and 'cross-sex' hormonal treatment (HT) plays a key role in the process of transition: anatomical and psychological changes, when properly prescribed in the above-mentioned cases can significantly improve the psycho-social quality of life and indirectly confirm the diagnosis. HT itself represents, in fact, the confirmation of GI to the subject. Quality of life improvement thanks to HT reduces any psychiatric co-morbidity often associated with GD. By using an open-source morphing program (gtkmorph) based on the X-Morph algorithm we found that Male-to-Female (MtF) GD subjects and heterosexual females showed the same pattern of mating strategies measured as face preferences: a clear preference for less dimorphic (more feminized) faces for both short- and long-term relationships. Conversely, both heterosexual and homosexual men selected significantly much more dimorphic faces, showing a preference for hyperfeminized and hypermasculinized faces, respectively. These data showed that the facial preferences of MtF GD individuals mirror those of the sex congruent with their gender identity, providing a new evidence on the psychoendocrinology of GD.

DOI: 10.1530/endoabs.63.S8.1

S8.2

Management of puberty in transgender adolescents

Martine Cools
Belgium.

Context
Childhood gender dysphoria, when not attenuating after the onset of puberty, is very likely to persist. The aim of puberty suppressing therapy in gender dysphoric adolescents is increasingly shifting from 'buying time to reflect on the diagnosis' towards 'avoiding the development of secondary sexual characteristics while awaiting eligibility for cross-sex hormones'. Various treatment regimens are available to suppress or decrease the effects of endogenous gonadal hormones.
Methods
We will review the literature and research data from our group to investigate the effects of various puberty suppressing medications (GnRH analogues, pro- and anti-androgenic progestins) on the developing body. Effects on growth, bone mass development and body composition will be discussed, as well as treatment schedules and effects of cross-sex hormones. Unsolved questions and directions for future research will be indicated.
Results
GnRHa can prevent but not reverse the development of secondary sexual characteristics. Progestins are a cheap alternative and induce discrete body changes towards the desired gender, which may be beneficial especially in adolescents diagnosed at more advanced pubertal stages. Final height is suboptimal for many trans boys and girls. GnRHa should be started as early as possible to prevent the early growth-limiting effects of estrogens in trans boys. Bone health is mainly compromised in trans girls, irrespective of treatment choice, and is at least in part related to other than sex steroid effects.
Conclusion
Puberty suppressing and cross-sex hormone therapies can be safely used in transgender adolescents although very little data exist on the long-term use of GnRHa. The respective place of the various alternative medications for puberty suppression needs to be determined. Modifications to the existing schemes for puberty induction are needed in this specific population to ensure optimal outcomes. Transgender youth represent an excellent model to study the development of sexually dimorphic traits during puberty.

DOI: 10.1530/endoabs.63.S8.2

S8.3

Gender reassignment surgery in dysphoria

Nicolas Morel-Journel
France.

Abstract Unavailable.

Controversies in Adrenal Disease

S9.1

Metanephrines: Plasma or Urine

Graeme Eisenhofer
Germany.

Measurements of plasma or urinary metanephrines are recommended for diagnosis of pheochromocytoma and paraganglioma (PPGL). Differences of opinion exist concerning what test offers optimal diagnostic accuracy and whether supine sampling is required for the plasma test. Whether urinary free metanephrines offer advantages over deconjugated metabolites and the relative utilities of additional measurements of methoxytyramine are also unclear. This presentation covers 25 years of experience with PPGL, including a recent prospective study of 2,056 patients with suspected PPGL, among who 236 had tumors confirmed. Patients at high risk for PPGL were screened due to an incidentaloma, hereditary risk or past history of PPGL, whereas those at low risk were tested because of signs and symptoms of apparent catecholamine excess. With seated sampling the plasma test suffers from compromised specificity rendering diagnostic performance no better than urinary tests. With supine sampling the plasma test offers higher diagnostic sensitivity than urinary free and deconjugated metabolites at identical specificities for plasma and urinary free metabolites, but lower specificities for deconjugated metabolites. Addition of methoxytyramine is useful for the plasma panel, but offers negligible value for urinary panels. Superiority of plasma over urinary tests is most apparent for patients at high risk of PPGL, whereas diagnostic performance differs little for those at low risk. The superior diagnostic performance of the plasma than both urinary panels for patients at high risk of PPGL indicates preference for this test at specialist centers where such patients may be best managed, but only with appropriate pre-analytics. At other centers where it is not possible to sample blood in the supine position or where testing is largely carried out because of signs and symptoms it may be preferable to use urinary measurements. In this case traditional measurements of deconjugated metanephrines should be abandoned in favor of the free metabolites.

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S9.2

The dos and don'ts of genetic testing in phaeochromocytoma

Mercedes Robledo
Spain.

Phaeochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumours with marked genetic heterogeneity, being the most inherited human tumour described so far. Around 40% of patients will be a carrier of a germline mutation in any of the know PPGL genes, and thus, for years most of studies have been performed on germline DNA. Findings from genetic testing in tumour DNA has dramatically changed the scenario. Nowadays, it is as relevant to make the screening on the germline DNA as to discard somatic mutations in those negative patients for the former analysis. From a daily basis genetic testing lab, there are important implications of having a genetic diagnosis in every single PPGL patient regardless the age of diagnosis or metastatic status, especially when the results would influence the management of the patient, or relatives at risk of being a mutation carrier. Where Next Generation Sequencing platforms are available, it is not only determinant the source of DNA sample to study, but also the availability of clinical information that will be used in the variant's interpretation step. This is a challenging task not only for laboratories that very often must apply a plethora of functional assays to demonstrate pathogenicity, but also for professionals responsible of genetic counseling and patient management. Another factor that should not be overlooked is the importance of selecting appropriately the tumour material to work with. This critical step should be done by pathologists in order to avoid masked mutations and therefore, false negative results. An increase in the knowledge of the molecular mechanisms involved in PPGL initiation, progression, and metastasis is fundamental for optimizing clinical management of this complex disease. It make sense that genetic information could be useful for selecting therapeutic options, as in the most of PPGLs it is detected a germline or somatic mutation in a gene or molecular pathway that can be therapeutically targeted by at least one antitumor agent clinically available for another disease.

DOI: 10.1530/endoabs.63.S9.2

S9.3

Is there a role for subtotal adrenalectomy

Radu Mihai
UK.

Historically, bilateral subtotal adrenalectomy was first attempted in patients with failed pituitary surgery for Cushing syndrome. Currently the operation is discussed predominantly in the context of familial phaeochromocytomas in an attempt to preserve sufficient cortical function and avoid life-long steroid dependence. The patients have to be informed of the significance of their particular genetic mutation, the impact of the size of tumours on the intraoperative feasibility of cortex-sparring, the risk of ipsilateral recurrence and the (limited) ability to ensure adequate stress-related steroid response. Technically the operation is made possible by the extensive venous drainage of the gland, such that dividing the main adrenal vein does not preclude preservation of viable and functional adrenal remnant. The advantages of the retroperitoneoscopic versus the laparoscopic approach will be discussed. Such patients should be referred to units/surgeons with established experience with adrenal surgery and this can only be achieved through centralization of these rare cases in dedicated medical institutions. Current issues regarding training and delivery of adrenal surgery will be mentioned.

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Cancer Drug-induced Osteoporosis (*Endorsed by Endocrine Connections*)

S10.1

Mechanisms of skeletal metastasis

Martina Rauner
Germany.

Skeletal lesions are a frequent complication of breast and prostate cancer. At present, 60–80% of patients with breast or prostate cancer develop bone metastases, which frequently result in skeletal-related events, including pathological fractures, pain, and neurological syndromes that require surgery or radiotherapy, and reduce quality of life. Autocrine and paracrine factors modulate various aspects of bone metastasis, including tumor proliferation, epithelial-to-mesenchymal transition, sensitization of skeletal sites to tumor homing, instruction of the microenvironment to support tumor persistence, and initiation of a vicious cycle that further promotes tumor growth and survival. In the vicious cycle, tumor cells, in particular breast cancer cells, produce osteoclast-stimulating cytokines and growth factors, either directly or by enhancing their production by mesenchymal stromal cells. This process results in excessive bone destruction that is typical of osteolytic bone metastases. However, it also releases large amounts of locally stored growth factors from the bone matrix that serve as survival factors for tumor cells. More recently, osteogenic pathways have been implicated in the development of bone metastasis. Normal bone formation depends on osteogenic differentiation of mesenchymal stromal cells towards osteoblasts and later to osteocytes. Tumors such as breast cancer secrete e.g. the Wnt inhibitor DKK-1, which suppresses osteoblast differentiation and inhibits bone formation and repair. By contrast, prostate cancer cells produce growth factors, which act as local stimulators of osteoblast functions, contribute to the osteomimicry phenotype of prostate cancer, and lead to excessive, but unorganized, newly formed bone, the hallmarks of osteosclerotic bone metastases. Taken together, prostate and breast cancer use specific molecular setups to induce their hallmark-type of bone lesion. Understanding the underlying mechanisms will help develop targeted therapies to treat bone metastasis.

DOI: 10.1530/endoabs.63.S10.1

S10.2

Aromatase inhibitors and bone

Carola Zillikens
The Netherlands.

Abstract Unavailable.

S10.3

TSH suppressive therapy and bone

Claudio Marcocci
Italy.

Thyroid hormones stimulates bone turnover. Increased blood levels of thyroid hormones are associated with a negative balance at individual bone remodeling unit and bone loss. It is well know that hyperthyroidism is a common cause of secondary osteoporosis and increased risk of fragility fractures. Mild hyperthyroidism (suppressed TSH and normal free thyroid hormones), as observed in autonomous thyroid nodules or following administration of TSH-suppressive doses of thyroid hormones (TSH-ST), may be associated with bone loss and fragility fractures, particularly in postmenopausal women. Low/undetectable TSH may also contribute to the deleterious effects of TSH-ST on bone, as suggested by animal studies showing that TSH inhibits osteoclastogenesis, promotes apoptosis of mature osteoblasts and stimulate osteoblast differentiation and the association of bone mineral density and TSH in postmenopausal women. The guidelines suggest measuring bone mineral density (BMD) in assessing skeletal health women under TSH-ST, but recent data suggest that BMD measured by DXA may not be a reliable marker of bone fragility in this context. In this regard an increased rate of vertebral fractures has been reported in postmenopausal women receiving TSH-ST independently of BMD (normal, osteopenia and osteoporosis), suggesting a potential role of structural abnormalities. As a matter of fact, recent studies in postmenopausal women under long-term TSH-ST have shown a deterioration of trabecular bone score (TBS) in the absence of a decline in vertebral BDM measured by DXA, but a significant association of TBS with volumetric BMD as assessed by central quantitative computed tomography.

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S11.2

Environmental endocrine disruptors and testicular germ cell cancer

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France.

Testicular germ cell cancer is the most frequent cancer of the young men with an increasing incidence all over the world. Pathogenesis and reasons of this increase remain unknown but epidemiological and clinical data have suggested that like genital malformations and sperm impairment, it could include developmental and environmental factors, including fetal exposure to environmental endocrine disruptors (EEDs). Several groups including ours have shown that TGCC is estrogen dependent especially seminoma the most frequent histological type. By studying *in vitro* human seminoma cell lines, it was possible to identify two different kind of effects of estrogens and xenoestrogens through at least two different estrogen receptors. Estradiol (pM and nM) and diethylstilbestrol induced a suppressive genomic effect by binding to ERβ, the only classical nuclear receptor expressed in normal and malignant germ cells. However, estradiol, estradiol linked to bovine serum albumin (E2-BSA) which does not cross the membrane, bisphenol A and atrazine, induced a proliferative effect through the non classical membrane G protein related estrogen receptor GPER/GPR30, by a rapid non genomic activation of transduction pathways including several G protein-dependent kinases. Bisphenol A acted at very low doses (pM and nM) similar to the concentrations which were found in human male cord blood, illustrating a very high affinity for GPR30 explaining the paradoxal inverse U shaped dose response curve. GPR30 was found to be overexpressed in seminomas partly due to the presence of a particular genetic polymorphism and ERβ was decreased when compared with normal testicular tissue possibly linked to epigenetic modifications which can be induced in rodent by fetal exposure to EEDs. Carcinogenetic effect of EEDs by impairing germ stem cells development is supported by TGCC estrogen dependency. However, more longitudinal prospective epidemiological studies and molecular epigenetic screening are necessary to clearly demonstrate this developmental relationship.

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EDCs & Reproduction

S11.1

Impact of pesticide postnatal exposure on oocyte quality and clinical outcomes of patient undergoing IVf programme

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In reproductive pathology, the impact of endocrine disruptor's on fertility potential declining is well documented; women exposed to pesticides have a risk to affect oocyte maturation and competency because Oocyte quality is a key limiting factor in female fertility which is firstly reflected by morphology feature. Centrally located cytoplasm granulation (CLCG) is one of cytoplasmic dysmoprhisms exhibited by oocytes which could be linked to pesticide exposure with relative risk to decrease ICSI outcomes. During our IVF programme we included 633 women undergoing intracytoplasmic spermatozoa injection (ICSI) program between 2009 and 2011 living in Picardy region-France with pesticide exposure. The whole lot was divided into two groups based on CLCG prevalence of oocytes (LCLCG; $n=83$: Low prevalence of CLCG under 25%; and HCLCG; $n=68$: High prevalence of CLCG over 75%). The embryological and clinical outcomes were analysed for both groups calculating the difference between them. As result, couples with HCLCG compared to LCLCG showed a decrease in embryo cleavage, ongoing pregnancy and live birth rates (82%, 14% and 13% vs 99%, 32% and 30%, respectively) while early miscarriage rate was increased (47% vs 11%) with OR (3.1 [95%CI]). Due to high pesticide exposure (over 3000 g/ha), there is higher risk to engender disturbed oocytes cohort with high prevalence of CLCG over 75%.

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S11.3

Mitigating against endocrine disruption in pregnancy

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Denmark.

Three decades ago wildlife findings of intersex, malformations and sex ratio changes in marine species, birds and mammals could be associated to environmental pollution. Public concern arose as to whether this was also a threat to humans as many countries experience an increase i.e. in the prevalence of infertility and obesity. Humans are continuously exposed to small doses of hundreds of EDCs throughout life and we know very little about their combined effects. Over the past 10–15 years more and more plausible links are being established between chemical exposures to a large range of new and old, persistent and non-persistent, chemicals and male as well as female reproductive health, i.e. dioxins, PCBs, flame retardants, perfluorinated chemicals, pesticides, phthalates, parabens, phenols and UV filters. Especially foetal exposure during pregnancy has been linked to adverse health effects in the offspring as this period is a vulnerable developmental window. After initial scepticism, many academic societies have endorsed the concept of endocrine disruption through environmental chemicals and modern lifestyle. Their support helps on many fronts: promoting research in the field, raising funds, engaging producers of customer products in better labelling and development of safer alternatives, increasing public awareness as well as prompting governmental agencies into action. Population cohort biomonitoring studies show that regulatory bans of chemicals in consumer products, i.e. certain phthalates, indeed lower individual exposure and thereby the individual 'cocktail load'. In parallel, it is paramount to ensure that any novel chemical is well-tested for endocrine disrupting effects before being approved for unlimited use.

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Craniopharyngioma; A challenging Tumour to Treat and a Difficult Aftermath

S12.1

The view of the surgeon: When, how much and when to refrain from surgery?

Stephanie Puget
France.

Abstract Unavailable.

S12.2

New potential treatment alternatives in patients with papillary craniopharyngioma

Tareq Juratli
USA.

Craniopharyngiomas are surgically challenging brain tumors. Postoperatively, quality of life is often significantly impaired due to neurological and endocrinological complications. Currently, FDA approved systemic treatments are not available for patients in whom craniopharyngiomas recur after surgery and radiation. Papillary craniopharyngiomas are characterized by the presence of $BRAF^{V600E}$ mutations. In this presentation, the authors generate an overview of all currently available information on targeted therapy in patients with $BRAF^{V600E}$ mutant papillary craniopharyngiomas with BRAF and/or MEK inhibitors. To date, all cases showed dramatic responses to targeted treatment with BRAF (and MEK) inhibitors. Although our data are highly informative for guiding patient treatment, uncertainty remains with regards to the optimal timing, the specific agents (single agent or dual therapy) to be used and the duration of treatment. The ongoing multicenter phase II Alliance A071601 trial (NCT03224767) of vemurafenib and cobimetinib for patients with biopsy-proven residual or recurrent papillary craniopharyngiomas should provide additional information to help inform patient management.

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S12.3

How to manage the long-term consequences of hypothalamic damages

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Sweden.

When a craniopharyngioma (CP) causes hypothalamus (HT) damage this will result in hypothalamic obesity (HO), cognitive dysfunction and increased stroke mortality. Suggested treatment when the HT is affected by a CP is subtotal resection and in some cases followed by cranial radiotherapy (CRT). In the preoperative phase, a multidisciplinary team may suggest HT sparing surgery with subtotal tumour removal. If in spite of all efforts the HT is damaged, there will be an immediate increase in hunger craving resulting in a devastating weight increase. The strongest increase in weight is within the first 12 mo and the proposal is that neurally mediated high insulin is the primary factor in the development of HO. Within weeks, an MRI gives information of the extent of HT damage and also of the remaining HT volume. The HT volume may give the cardiovascular prognosis. Immediate efforts of dieticians and cardiovascular drugs with GLP-1 agonist, and central stimulating drugs need to be administered. Later in the follow up diffusion tensor imaging (DTI), a noninvasive technique of the white matter of the brain, may predict cognitive dysfunction. White matter lesions (WML), seen on T2 MRI, are pathological changes caused by obstruction of small cerebral vessels resulting in hypo-perfusion and are predictive of stroke. CP patients, who have a reduced HT volume and were treated with CRT have increased WML volume. Assessment of HT volume, DTI, WML should be considered in the postoperative phase and follow up care of patients with CP as this may create an opportunity for early preventive treatment of cognitive dysfunction, CV disease and stroke risk. These different assessments can also be used in a broader perspective for all tumours that involves the HT.

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Central Control of Metabolism: Brain Rules All

S13.1

Sensors of survival: Pleiotropic function and the regulation of hunger circuits

J Nicholas Betley
USA.

The brain regulates food intake by processing sensory cues and peripheral physiological signals. Recently, we have gained an increased understanding of the neural networks that regulate food intake. However, understanding how nutrients and post-ingestive signals regulate the activity of hunger-sensitive neurons remains an important question. To understand the neural control of food intake, we monitor the activity of hunger-sensitive neural populations in the awake behaving animal. Our recent work has demonstrated that nutrients, independent of the sensory experience of food, have the ability to change the activity of both hypothalamic and midbrain neurons that influence food intake. Further, vagal gut-brain signaling is necessary to rapidly transmit this information. We have identified satiation hormones that are likely responsible for activating the vagal signaling and have discovered that they work synergistically. Finally, we find coordinated and bidirectional modulation of hypothalamic and midbrain circuits by food rewards. Taken together, these studies begin to unpack how networks of neurons in the brain influence food intake.

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S13.2

Role of mitochondria/cell bioenergetics in CNS regulation of energy balance

Marc Claret
Spain.

Pro-opiomelanocortin (POMC) neurons in the arcuate nucleus (ARC) of the hypothalamus are critical regulators of appetite, energy expenditure and glucose metabolism. POMC neurons are able to sense circulating hormones and nutrients informing about the energy status of the organism. However, the molecular mechanisms underlying nutrient-sensing in POMC neurons remain incompletely understood. Mitochondria are key organelles implicated in cellular nutrient/energy management and are able to bioenergetically adjust to different metabolic situations. A remarkable feature of mitochondria is their capacity to change their morphology through coordinated fusion and fission events, a mechanism that links nutrient availability with bioenergetic adaptations. Mitochondrial fusion is a process that requires the GTPases mitofusin (Mfn) 1, Mfn2 and OPA1. We hypothesized that mitochondrial fusion in hypothalamic POMC neurons may represent primary nutrient/energy-sensing processes implicated in the hypothalamic regulation of energy balance and metabolism. To test this hypothesis, we have generated mice lacking the main fusogenic proteins specifically in POMC neurons and conducted detailed phenotyping and molecular studies. Our data demonstrate divergent metabolic outcomes depending on the deleted fusion protein, which are mediated by different tissues and molecular processes. These results suggest that mitochondrial dynamics in POMC neurons is a critical mechanism implicated in the maintenance of systemic energy balance and glucose homeostasis.

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S13.3

Genetics of appetite regulation: Can an old dog teach us new tricks?

Giles Yeo
UK.

It is clear that the cause of obesity is a result of eating more than you burn. What is more complex to answer is why some people eat more than others? Over the past 20 years, insights from human and mouse genetics have illuminated multiple pathways within the brain that play a key role in the control of food intake. We now know that the brain leptin-melanocortin pathway is central to mammalian food intake control, with genetic disruption resulting in extreme obesity. These, however, remain rare, with the major burden of disease carried by those of us with 'common obesity'. In recent years, genome-wide association studies have revealed more than 100 different candidate genes linked to BMI, with most, including many components of the melanocortin pathway, acting in the CNS and influencing food intake. So while severe disruption of the melanocortin pathway results in severe obesity, subtle variations in these same genes influence where you might sit in the normal distribution of BMI. As we now enter this 'post-genomics' world, can this new information influence our treatment and management of obese patients?

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Innovations in NETs

S14.1

Innovative imaging of benign insulinomas – the end of sampling

Emanuel Christ
Switzerland.

Background
Benign insulinomas are the most prevalent cause of endogenous hyperinsulinaemic hypoglycaemia (EHH) in adults and due to their small size difficult to localise. Until now, the most sensitive test to localize the area of the potential insulinoma was the intra-arterial calcium stimulation test, an invasive procedure with its associated risk. In contrast to the other neuroendocrine tumors, benign insulinomas do not exhibit upregulated somatostatin receptors sutype 2 (sst2) but present with an increase in GLP-1 receptors (GLP-1R). GLP-1Rs can be targeted with GLP-1 analogues such as exendin-4. We aimed at prospectively comparing the accuracy of ^{111}In-DOTA-exendin-4 SPECT/CT, ^{68}Ga-DOTA-exendin-4 PET/CT, standardised 3-Tesla contrast-enhanced MRI (ceMRI), and non-standardised baseline imaging (ceCT/ceMRI) in patients with EHH.
Methods
We prospectively enrolled $>$ 80 patients with neuroglycopenic symptoms due to EHH and no evidence for metastatic disease on conventional imaging using ^{111}In-DOTA-exendin-4 SPECT/CT, ^{68}Ga-DOTA-exendin-4 PET/CT and compared the sensitivity of the GLP-1R imaging to conventional imaging procedures (ceMRI and ceCT). The reference standard was surgery with histology and normalisation of blood glucose levels.
Findings
Patients were referred from whole Switzerland, Europa and USA. Baseline not standardised conventional imaging identified suspicious lesions in ca. 40% of the patients. Accuracy for PET/CT, SPECT/CT and standardised MRI, was 93·9%, 67·5% and 67·6%, respectively. GLP-1R imaging was useful in EHH in the context of benign sporadic insulinomas, in adult nesidioblastosis (^{68}Ga-DOTA-exendin-4 PET/CT) and in patients with multiple endocrine neoplasia type 1 with multiple pancreatic lesions on conventional imaging. The size of the detected lesions was 4–25 mm.
Conclusion
GLP-1R PET/CT performed significantly better than SPECT/CT and conventional imaging and should be the diagnostic tool of choice in patients where localization fails with conventional imaging. Intra-arterial calcium stimulation test may only be indicated when GLP-1R PET/CT fails to localize the suspected lesion.

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S14.2

A role for radionuclide therapy for high-grade NETs

Halfdan Sorbye
Norway.

Background
Peptide receptor radionuclide therapy (PRRT) is an established treatment of metastatic low-grade and intermediate-grade neuroendocrine tumors (G1-G2). However, its possible benefit in high-grade gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN G3: NET G3 and NEC) has been unknown.
Methods
Data from 3 recent retrospective studies (Thang *et al*. 2018, Zhang *et al*. 2018, Carlsen *et al*. 2019) on efficacy and toxicity of PRRT in patients with GEP NEN G3 were assessed. All patients had a high uptake on somatostatin receptor imaging and most had progressive disease.
Results
The 3 studies (one multicenter) included in total 249 patients, mainly pancreatic primaries (60–69%). Treatment was mainly given as 2nd or 3rd line therapy. Response rates were 31–44%. Disease control rate (DCR) was 69–78%. Grade 3-4 hematological or renal toxicity occurred in 1%, 16% and 17% of patients. Progression free survival (PFS) and overall survival (OS) was higher in patients with Ki-67 21–55% vs Ki-67 $>$55%: PFS 11–16 m vs 4–6 months and OS 22–46 m vs 7–9 months. In the multicenter study, patients with well differentiated tumors (NET G3, $n=60$) had a better PFS and OS compared to poorly differentiated carcinomas (NEC, $n=62$): PFS 19 vs 8 months ($P<0.001$) and OS 44 vs 19 months ($P<0.001$).
Conclusion
Three retrospective cohorts of patients with GEP NEN G3 treated with PRRT demonstrates quite similar results with promising response rates, disease control rates, PFS and OS in patients with mainly progressive disease. Based on these results, PRRT may be considered for patients with high-grade GEP NEN G3 (NET G3 and NEC).

DOI: 10.1530/endoabs.63.S14.2

S14.3

Fishing for NETs

Giovanni Vitale
Italy.

Neuroendocrine tumors (NETs) are a class of rare and heterogeneous neoplasms derived from the neuroendocrine system. Animal models are indispensable tools for investigating the pathogenesis, mechanisms for tumour invasion and metastasis and new therapeutic approaches for cancer. Unfortunately, only few models are available for NETs, probably due to the rarity and heterogeneity of this group of neoplasms. The tropical teleost zebrafish (Danio rerio) is a popular vertebrate model system that offers unique advantages for the study of a variety of biological processes. The small size and low cost of maintenance, together with the high prolific nature, the external fertilization and the rapid development of its transparent embryos have led to the first emergence of the zebrafish as reliable and suitable embryological model. Moreover, due to the proved conservation in genetic programs and physiology between fish and mammals, zebrafish has become a powerful model for studying human diseases, including cancer. This presentation provides an overview of the state of the art of zebrafish model in the cancer research with a main focus on NETs, highlighting future developments in this field.

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European Young Endocrine Scientists (EYES)

S15.1

European Young Endocrine Scientists (EYES) – Organ cross-talk in endocrine disease

Peter Aldiss
UK.

'European Young Endocrine Scientists' (EYES), founded in 2011, is a committee under the patronage of the European Society of Endocrinology (ESE). Our primary goal is to increase the mutual exchange of ideas and knowledge between early career researchers (ECR's) across Europe, in both basic and clinical endocrinology. EYES enables ECR's from all ESE member societies to actively contribute to the society's activities and help them fully develop into the next generation of endocrinologists. We provide a platform for ECR's in endocrinology to make them feel welcome at ESE and to familiarize themselves with the society's conferences. This years' session will once again give outstanding ECR's a platform to present their research with a focus on the role

of organ cross-talk in disease. With exciting talks on the role of glucocorticoids in the expansion of bone marrow fat and the winner of best oral communication at the annual EYES meeting this session is not to be missed! We invite all early career basic and clinical endocrinologists to attend and join us here and at the EYES networking event at ECE 2019.

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S15.2

Investigating glucocorticoid excess as mediators of bone marrow adiposity expansion during caloric restriction

Andrea Lovdel
UK.

Background
Bone marrow adipose tissue (BMAT) comprises >10% of total adipose mass in healthy humans and further increases during caloric restriction (CR). However, BMAT function during CR and other conditions remains poorly understood. Circulating glucocorticoids also increase during CR, and glucocorticoid therapy increases BMAT; thus, ***we hypothesise that glucocorticoid excess mediates BMAT expansion during CR***. Many effects of endogenous glucocorticoid excess are mediated by 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1), which catalyses intracellular regeneration of active 11-hydroxy glucocorticoid from inert 11-keto forms.
Objectives
Determine 1) if CR increases glucocorticoid activity within adipose tissue and bones; and 2) if ablation of 11β-HSD1 blocks CR-induced BMAT expansion.
Methods
Male and female C57BL/6J mice lacking 11β-HSD1 (KO) or littermate controls were fed *ad libitum* (AL) or 70% of AL intake (CR) from 9–15 weeks of age. Each week, body mass and composition were measured and blood collected. Plasma corticosterone and 11-dehydrocorticosterone were measured by ELISA or liquid chromatography-tandem mass spectrometry. Bone loss and BMAT were measured by micro-computed tomography.
Results
1) In control and KO mice, CR decreased body and lean mass. Body fat decreased in males only. CR increased circulating corticosterone levels in both sexes and genotypes. Circulating 11-dehydrocorticosterone concentration was significantly greater in AL and CR KO mice than in controls. 2) CR increased expression of the glucocorticoid target gene *Fkbp5* in white adipose tissue and bone. CR-induced BMAT expansion occurred in females of both genotypes and in control males, but not in KO male mice. CR induced cortical bone loss in females only and this was unaffected by genotype.
Conclusions
CR increases glucocorticoid action within bones and induces cortical bone loss. Knockout of 11β-HSD1 prevents CR-induced BMAT expansion in male, but not female, mice. These findings highlight glucocorticoids as potential mediators of sexually-dimorphic BMAT formation during CR.

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S15.3

Best young abstract submission

Abstract Unavailable.

S15.4

The role and cross-talk between incretin hormones and occurrence of non-alcoholic steatohepatitis

Benjamin Bouillet
France.

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease and has an estimated prevalence of 25–30% worldwide, rising to 90% in morbidly obese patients and to 60% in patients with type 2 diabetes (T2D). The mortality related to NAFLD, attributed to hepatic and extra-hepatic diseases, continues to increase. Moreover, T2D is an aggravating factor for NAFLD, as it increases the risk of developing non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis and hepatocellular carcinoma. Nevertheless, there is currently no specific pharmacologic treatment for NAFDL and its only validated treatment is weight loss. A number of studies of animal models and human trials have provided evidence of a beneficial effect of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on liver fat content and NASH. These data suggest that this treatment could represent a new alternative for NAFLD management. The studies evaluating the effects of GLP-1RAs on NAFLD will be described and discussed. The mechanisms underlying these effects will be analyzed. Indeed, the effects of GLP-1RAs on weight reduction and lipid metabolism seem to be the two main mechanisms explaining the decrease in liver fat content with this treatment. However, larger studies of longer duration with complete histological outcomes are needed to determine the precise effect of GLP-1RAs in NASH improvement and to assess the efficacy of GLP-1RAs according to the presence or not of type 2 diabetes.

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S15.5

Lysophosphatidic acid in pathogenesis of *HNF1B*-MODY syndrome

Beata Małachowska
Poland.

Background
HNF1B-MODY is a rare autosomal dominant monogenic form of diabetes coexisting with kidney abnormalities.
Objectives
Identification of altered serum metabolites among *HNF1B*-MODY patients and investigating its function in syndrome pathogenesis.
Methods
We recruited patients with *HNF1B*-MODY ($N=10$), *HNF1A*-MODY ($N=10$), polycystic kidney disease: non-dialyzed and dialyzed ($N=8$ and $N=13$ respectively) and healthy controls ($N=12$). Serum samples were fingerprinted by LC/MS. Observed metabolic changes were validated. A HepG2 cell line was used in order to study *in vitro* the cellular effect of selected serum metabolite stimulation.
Results
From serum metabolomics fingerprinting we identified eight metabolites that had convergent fold change for comparison of *HNF1B*-MODY versus all other groups. Three of them were lysophosphatidic acid species (LPAs: 18:1, 18:2, 20:4) that proved to be the best biomarkers for *HNF1B*-MODY (Area under ROC curve 1.00 (95%CI 0.91–1.00); 1.00 (95%CI 0.91–1.00); 0.92 (95%CI 0.80–0.98) respectively). On a second set of samples we confirmed elevated levels of LPA among *HNF1B*-MODY patients ($P=0.0063$). The main enzyme producing serum LPA – autotaxin – was down-regulated in sera of *HNF1A*- vs *HNF1B*-MODY patients ($P=0.0173$) but did not differ between *HNF1B* and other groups (all P values >0.84). Upon LPA stimulation of human hepatocytes with silenced *HNF1B* the downregulation of autotaxin expression was observed. In the absence of functional Hnf1b, the stimulatory effect of LPA on the Wnt pathway was disrupted and reversed, with LPA stimulation leading to a decrease of phospho-GSK-3a/b protein ($P=0.0169$).
Conclusions
An important lipid mediatory compound – LPA was found to be elevated in serum of patients with *HNF1B*-MODY. LPA can be involved with pathogenesis of *HNF1B*-MODY syndrome via the disruption of LPA-mediated regulation of Wnt pathway.
The study was funded by the PRELUDIUM grant (2016/21/N/NZ5/01448) of the National Science Center, Poland and by JDRF-ISPAD Research Fellowship Award 2017.

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S15.6

Closing remarks and invitation to the EYES social

Thomas Cuny
France.

Abstract Unavailable.

Thyroid in Pregnancy

S16.1

Thyroid autoimmunity and (in)fertility

David Unuane
Belgium.

Thyroid autoimmunity (TAI) is the most frequent autoimmune disorder in women of childbearing age and increases the risk of thyroid dysfunction. TAI has been shown to be more common in women seeking counselling for infertility. The underlying causal mechanism that may account for any possible detrimental effect of TAI on fertility aspects remains hypothetical. In general, increased levels of anti-thyroid peroxidase abs (TPO-abs) have been defined as the most sensitive marker of TAI and linked to the risk of (sub) clinical hypothyroidism. As a consequence most studies investigating the prevalence of TAI in infertile women or any relation between TAI and pregnancy outcomes are based on the presence of TPO-abs alone and do not take into account thyroglobulin autoantibodies (Tg-abs). Assisted reproductive technology (ART) is often proposed as a treatment option for couples confronted with fertility problems. TAI has been linked to adverse pregnancy outcome with an increased risk of miscarriage and preterm delivery in spontaneous pregnancy as well as in pregnancy after ART. Since the late 1990s several studies have been published on the impact of TAI and pre-conception TSH thresholds on the outcome after ART. The outcome of these studies however are conflicting. Therefore, todays guidelines on the management of TAI in the particular case of ART are based on limited evidence. In the present presentation we will give an overview on the association of TAI and female infertility. We will discuss the possible underlying mechanisms that may connect TAI to fertility issues. Furthermore, the current evidence on the impact of TAI and pre-conception TSH thresholds on outcome after ART will be highlighted. Based on this evidence we will have a critical look at today's guidelines on this issue.

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S16.2

Thyroid disease and pregnancy outcomes

Fereidoun Azizi
Iran.

Abstract Unavailable.

S16.3

Mild maternal thyroid dysfunction during pregnancy and offspring neurodevelopment

Deborah Levie
The Netherlands.

In humans, brain developmental processes start already around week 5 of gestation and continue throughout pregnancy and postnatal life. The migration, differentiation, proliferation, and myelination of neurons are thyroid hormone dependent processes, as shown in animal studies. The fetal thyroid gland is not functionally mature before week 18–20 of gestation. During this period the fetus acquires thyroid hormone for the most part via placental transfer from the mother. This implies that there is an important time frame during which thyroid hormone dependent processes of brain development are completely dependent on the placental transfer of maternal thyroid hormones. A lack of thyroid hormone exposure to the fetal brain during its developmental stages in utero can lead to severe neurological phenotypes, such as cretinism, which is caused by iodine deficiency. While there is abundant evidence for an association of low maternal FT4 (hypothyroidism and/or hypothyroxinemia) during gestation with poorer fetal neurocognitive outcomes, evidence for an association of maternal subclinical hypothyroidism (elevated TSH but normal FT4) during pregnancy with offspring neurodevelopmental outcomes is scarce. In this talk the latest clinical studies on mild thyroid dysfunction and offspring neurodevelopmental outcomes will be discussed, including studies that have investigated critical time windows for exposure to inadequate thyroid hormone availability. Identifying critical time windows are important for improved understanding of thyroid physiology, translation of animal studies to human physiology, to facilitate the design of future randomized controlled studies on the benefits of treatment (i.e. subclinical hypothyroidism or hypothyroxinema) and aid clinicians in optimizing risk assessment strategies. In this talk I will also go over some of the challenges and next steps in these type of studies.

DOI: 10.1530/endoabs.63.S16.3

Where do Pituitary Tumours Come From?

S17.1

Specification of pituitary cell fates

Jacques Drouin
Canada.

The pituitary derives from an invagination of the oral ectoderm, Rathke's pouch, where pituitary progenitors are specified during early development. These progenitors are marked by expression of Sox2 and their entry into differentiation involves a switch from Sox2 to expression of other transcription factors implementing each of the lineage-specific differentiation programs. This switch is also accompanied by a switch in cell cycle control mechanisms that may be disrupted in pituitary tumors. Determination and maintenance of each pituitary lineage is dependent on a small number of the lineage-specific transcription factors. Whereas the mechanism for specification of the pituitary fate compared to oral ectoderm is still unknown, recent work has identified Pax7 as the pioneer transcription factor that specifies the intermediate lobe melanotrope fate. Pax7 achieves this through epigenetic mechanisms that 'open' about 2500 enhancers genom- wide. The interplay between the specification pioneer factor Pax7 and the POMC lineage determination factor Tpit will be discussed. The diversity of pituitary tumors reflect the composition of the normal gland with some tumors presenting with relatively well differentiated features and hormone secretion whereas others, the non-functioning adenomas, may reflect some progenitor or precursor states.

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S17.2

Pertubations in novel signalling pathways

Cynthia Andoniadou
UK.

Abstract Unavailable.

S17.3

'From Lab to Clinic – Can we translate into effective therapeutics'

Peter Kamenický
France.

The first line treatment of somatotroph adenomas is pituitary surgery, that aims at removing the tumor, but which is frequently incomplete, as invasion into cavernous sinuses often limits the surgical resection. Multimodal medical treatment, which is burdensome, very expensive and has variable therapeutic efficacy, is currently required in more than 60% of the patients. New therapeutic approaches are therefore necessary for controlling hormone secretion, tumor development and (invasive) growth. Besides activating *GNAS* gene mutations, promoting tumor development in ~30% of cases, the molecular pathogenesis of somatotroph adenomas is rather poorly understood. We have recently described a distinct molecular subclass of *GNAS* mutation-negative somatotropinomas, clinically revealed by a paradoxical increase of GH to oral glucose load related

to pituitary glucose-dependent insulinotropic polypeptide receptor (GIPR) expression. This ectopic *GIPR* expression occurred through hypomorphic transcriptional activation and is likely driven by *GIPR* gene micro-amplifications and/or DNA methylation abnormalities. These findings provide useful molecular profiling that refines the somatotroph tumor classification. However, to what extent the ectopic GIPR is functionally involved tumor growth and GH hypersecretion? A hallmark of GIP-dependent Cushing syndrome is the low fasting plasma cortisol concentration that increases following GIP release after meals. In patients with acromegaly with ectopic GIPR in their somatotropinomas, fasting GH concentrations are not suppressed. The impact of prolonged fasting is difficult to address because of ethical issues. Recently, a specific naturally occurring GIP antagonist GIP (3–30) NH2 has been investigated in humans. Targeting the ectopic GIPR by this antagonist could be an interesting novel therapeutic strategy in some acromegalic patients. However, the important intra-tumor heterogeneity of pituitary adenomas with GIPR expressed only in some cell clones challenges the therapeutic efficacy of this approach.

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Congenital Hypogonadotropic Hypogonadism: New Insights into GnRH Regulation

S18.1

The transcription factor Gli3 plays a pivotal role in controlling the development of the terminal nerve and GnRH-1 neuronal migration

Paolo E Forni
USA.

Normosmic idiopathic hypogonadotropic hypogonadism (nIHH) and Kallmann syndrome (KS) represent two rare phenotypic presentations of humans with hypogonadotropic hypogonadism secondary to GnRH deficiency. KS/nIHH is genetically heterogeneous and is characterized by incomplete penetrance and variable expressivity. Some genetic variants may play the role of modifier alleles or act as 'second hits', providing an explanation of this phenotypic variability. In addition to the reproductive phenotypes, nIHH and KS subjects also commonly exhibit craniofacial defects. In humans, mutations in *GLI3,* encoding a transcriptional regulator of sonic hedgehog (Shh) signaling, causes a spectrum of craniofacial defects including a short nose with flat nasal bridge and cleft palate. *Gli3 loss-of-function affects the development of the olfactory system*: By examining the development of the vomeronasal sensory neurons, terminal nerve and GnRH-1 neurons, in a Gli3 mouse mutant model [Gli3 extra-toe (Xt)], we found: 1) a large reduction in the number of vomeronasal sensory neurons, 2) defective development and routing of the terminal nerve fibers, and 3) nearly complete absence of GnRH-1 neuronal migration to the brain. Notably, only a delay in GnRH-1 neuronal migration was observed in $Gli3^{Xt/WT}$heterozygous embryos with no obvious differences after birth. Analyzing whole exome data from a large cohort of nIHH/KS probands, we also identified several rare *GLI3* variants in humans. Luciferase assays and subcellular localization confirmed complete loss-of-function for one novel *GLI3* mutation which was seen in an KS individual who also displayed polydactyly. As a some of the patients carrying rare missense *GLI*3 variants also harbored heterozygous mutations in other KS/nIHH candidate genes we propose that human *GLI3* mutations could play an important modifier role and contribute to the oligogenic nature of KS/nIHH.

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S18.2

Flipping the GnRH switch with microRNAs

Andrea Messina
Switzerland.

A sparse population of a few hundred primarily hypothalamic neurons forms the hub of a complex neuroglial network that controls reproduction in mammals by secreting the 'master molecule', gonadotropin-releasing hormone (GnRH). Both the Kisspeptin input on GnRH neurons and timely changes in GnRH expression are necessary for the onset of puberty. However, the exact molecular mechanisms underlying this process remain elusive. Here, we report that a dramatic inversion in microRNA expression profile within postnatal GnRH neurons acts as an epigenetic switch that triggers the prepubertal increase in GnRH expression and controls the ability of GnRH neurons to sense Kisspeptin input, for a correct initiation of puberty. The disabling of this microRNA-mediated switch leads to hypogonadotropic hypogonadism and infertility in mice. The underlying mechanism involves a complex and multilayered network of transcriptional activators and repressors reciprocally controlled by several microRNA species, including miR-200 and miR-155. These microRNAs tune the balance between inductive and repressive signals to trigger a rise in hypothalamic GnRH expression and to control the expression of Kisspeptin receptor. Anomalies in this microRNA-embedded genetic network, which appears essential for the neuroendocrine control of reproduction by controlling both Kisspeptin sensitivity and GnRH production, could thus underlie dysfunctions of human puberty and fertility when a genetic cause is not apparent.

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S18.3

Congenital hypogonadotropic hypogonadism: clinical perspectives

Jacques Young
France.

Abstract Unavailable.

Adrenal Insufficiency

S19.1

New insights into autoimmune adrenal insuffisiency

Esytein Husebye
Norway.

Autoimmune adrenal insufficiency (AAI) is a classic organ-specific autoimmune disease caused by immune-mediated destruction of steroidogenic cells in the adrenal cortex. Autoreactive T cells and autoantibodies targeting the steroidogenic cytochrome P450 enzyme 21-hydroxylase (21OH) are present in the majority of patients. AAI can appear isolated or as part of two forms of autoimmune polyendocrine syndromes, the rare monogeneic autoimmune polyendocrine syndrome type 1 (APS-1) and the common autoimmune polyendocrine syndrome type 2 (APS-2), the latter affecting more than half of the AAI population. A study of the Swedish twin registry has revealed that the probandwise concordance for monozygotic twins was 0.71 (95% CI 0.40-0.90) and the heritability 0.97 (95% CI 0.88-99), which is at least as high as for celiac disease. Several genes are implicated in disease risk, first and foremost the major histocompatibility complex (MHC). Other associated genes include BACH2 (BTB and CNC Homology 1, Basic Leucine Zipper Transcription factor 2) and AIRE (autoimmune regulator). Disease risk is associated with an accumulated number of risk variants in the individual patient. Lymphocytic infiltrations of the adrenal cortex of deceased AAI patients have been described. We now demonstrate the presence of both T- and B cells during active autoimmune adrenalitis. The majority of the T cells are CD8+ cytotoxic T cells, although CD4+T and CD20+B cells as well, particularly in distinct foci of dense lymphocytic infiltrations. T cells with reactivity towards distinct and conserved portions the 21OH protein have been reported in peripheral blood and is probably present in abundance in these foci. Autoimmune adrenalitis is a slowly evolving process in most cases, leading to clinical symptoms and biochemical aberrations only in the latter stages of the disease. Although the majority are thought to loose all adrenocortical function, a subset of patients seem to retain both glucocorticoid and mineralocorticoid function even decades after being diagnosed with AAI. This indicates that there is an opportunity for immunomodulary and regenerative therapy in AAI.

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S19.2

Long-term results of modified release glucocorticoids in adrenal insufficiency – are they really better?

Gudmundur Johannsson
Sweden.

Before the availability of glucocorticoids as drugs, the majority of patients with primary adrenal insufficiency (AI) died within 2 years of diagnosis. Today patients with AI receive life-long replacement therapy with glucocorticoids with the assumption that life expectancy is normal. Recent studies have, however, shown excess mortality in patients with both primary and secondary AI mainly due to cardiovascular diseases and infections. Patients with AI also have increased rate of diabetes, hypertension and hospital admission rates due to infections. It is likely that non-physiological exposure of glucocorticoids both in term of dose and time exposure profile contributes to this poor outcome together with inadequate intercurrent illness rescue therapy. Modified release hydrocortisone has been developed to improve outcome among patients with AI, by improving the circadian exposure of hydrocortisone. Prospective trials have shown indications that the metabolic outcome is improved and frequency of infections may be reduced in comparison with the same daily dose of conventional hydrocortisone. Treatment with modified release hydrocortisone may also improve and normalise immune function and peripheral expression of clock genes. Limited data exist on the long-term safety of these new treatments from prospective studies. Available data from a 5 year prospective study suggest a good safety profile, but the question remains whether long-term outcome is improved in comparison with conventional glucocorticoid replacement therapy. New options have emerged for the treatment of glucocorticoid deficiency in AI. Outcome from prospective short-term studies has shown promising results. Limited data on long-term treatment outcome with modified hydrocortisone support their safety.

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S19.3

Optimising care delivery in congenital adrenal hyperplasia

Nils Krone
UK.

Congenital adrenal hyperplasia represents a group of autosomal recessive disorders in steroidogenesis causing deficient cortisol biosynthesis. The incidence of congenital adrenal hyperplasia (CAH) in the general population of Western countries is approximately 1 in 10,000 to 1 in 15,000 life births with about 95% of cases caused by 21-hydroxylase deficiency. After the introduction of replacement therapy with glucocorticoids and mineralocorticoids in the 1950s, congenital adrenal hyperplasia is no longer a life-limiting condition. However, CAH has become a chronic life-long condition, with associated comorbidities and long-term health implications. Long-term consequences of CAH and current treatment regimens include unfavourable outcomes involving all organ systems. Comprehensive long-term data on mortality are not available. An important emerging task for paediatric health care provision in CAH is the prevention of long-term health problems. Pharmacotherapy with current approaches remains challenging, with keeping the balance between glucocorticoid overexposure and androgen excess. Over the life-span type and dose of glucocorticoid can change. The relative mineralocorticoid dose per body surface area declines with increasing age. Replacement doses are monitored by clinical and biochemical parameters, with suppression of steroid hormones commonly indicating overtreatment. Several novel experimental pharmacotherapies with the aim to reduce glucocorticoid exposure and to mimic physiological glucocorticoid secretion are under development. The approach to treatment and monitoring remains highly variable and the effects on long-term outcomes remain elusive. This presentation will provide an update on current developments covering care provision, novel adrenal-specific biomarkers with the potential to improve monitoring and experimental approaches. All of these ongoing approaches have will in theory improve CAH management; however, the evidence for improved long-term outcomes is lacking.

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News on Nutrition: When to Eat What

S20.1

Precision nutrition for managing obesity – does it work?

Carlos Celis-Morales
UK.

Background
The epidemic of obesity, together with its associated health burden, continues to spread globally. It is estimated that approximately 2.1 billion adults worldwide are now classified as overweight or obese. Thus, there is an urgent need to develop more effective strategies for preventing and managing obesity. Most population strategies to reduce the rising prevalence of non-communicable diseases (NCDs) have used a 'one size fits all' public health recommendations, e.g. 'eat at least five portions of fruit and vegetables daily'. However, the global burden of NCDs continues to rise, emphasising the need for more effective prevention strategies.
Results
Recent findings from randomised controlled trials have suggested new personalised approaches for the prevention and treatment of obesity, as an alternative to the current strategy of 'one-size-fits-all' approach. Personalised Nutrition (PN), also called Precision Nutrition, has been developed to deliver Personalised interventions designed according to key characteristics of the individual participants (including but not limited to socio-demographics, biomarkers, phenotypic, microbiome and genetic characteristics). The more tailored the intervention, the more sophisticated and potentially expensive it will be to acquire, analyse and act upon those participant characteristics. However, with interventions becoming increasingly plausible on a large scale, thanks to smartphone technology and internet accessibility, some have begun to view PN as a novel way to deliver the right dietary intervention to the wider population. This talk will explore existing evidence, including the Food4Me study, one of the largest personalised trials conducted to date and provide an insight into the real benefits of personalised interventions for obesity management and prevention. Moreover, I will discuss how genetics and novel biomarkers, could be used to improve the design and effectiveness of future personalised interventions and whether existing evidence justifies the use of more sophisticated interventions, to tackle the current obesity epidemic.
Conclusions
Is personalised or Precision Nutrition the way forward?

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S20.2

Is limiting the timing of food intake a viable nutritional approach?

Denise Robertson
UK.

Food restriction and weight-management strategies have been at the forefront of most efficient strategies to prevent and reduce the risk of type 2 diabetes and cardiovascular disease (CVD). However, when people find themselves in an increasingly obesogenic environment it becomes challenging to achieve and maintain successful behavioral changes. Fasting protocols such as intermittent energy restriction (IER) and time-restricted feeding (TRF), or restricting food consumption to specific period during the day or week, have received considerable interest as approaches for weight-management and reducing risk for metabolic diseases. In these strategies, food consumption is altered to produce frequent, repeated periods of short-term fasting, or severe energy restriction. For example, the 5:2 dietary pattern, involving 2 fast days/week (with normal eating on the remaining 5 days) has been shown to be particularly successful. Our previous work in humans has shown significant effects on weight-reduction in addition to lowering blood glucose and lipids, both key risk factors for type diabetes and CVD. TRF is an example of a timed dietary approach, which also falls under the 'intermittent fasting' umbrella, involving limiting intake to a period of several hours (usually ≤ 12 hours), which thereby extends the length of the daily fasting interval. There is some suggestion that the length of fasting duration may exert an additive benefit, presumably by elongating the time spent in a catabolic state. Both IER and TRF appear to demonstrate a metabolic advantage above a simple reduction in energy intake although much of the data is still in rodent models.

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S20.3

PREDIMED Plus trial - energy-restricted Mediterranean diet plus exercise and metabolic health

Emilio Ros
Spain.

The PREDIMED trial showed that long-term adherence to an ad libitum Mediterranean diet (MeDiet) supplemented with extra-virgin olive oil (EVOO) or

mixed nuts reduced incident cardiovascular disease (CVD) in older subjects at high risk. No clinical trials have been conducted to demonstrate whether weight loss sustained over time with an energy-restricted healthy diet plus increased physical activity (PA) reduces CVD risk. We designed the PREDIMED-PLUS study, a 6-year, multicentre, randomized clinical trial for the primary prevention of CVD with an energy-restricted MeDiet plus behavioural support and advice to increase PA, aimed at losing weight in comparison with a control, energy-unrestricted MeDiet without counsel on PA (*www.isrctn.com/ISRCTN89898870*). Participants are 6874 older individuals (aged 55–75 y) with overweight/obesity and the metabolic syndrome and they receive gifts of EVOO and nuts to promote the MeDiet irrespective of group assignment. The final goal regarding adiposity is to obtain a between-group average absolute difference in weight loss and waist circumference reduction $>5\%$. The results of the pilot study concerning the first 610 randomized participants completing intervention for 12 months showed that diet and PA changes were in the expected direction, with significant improvements in the intervention group compared with the control group. After 12 months, participants in the intervention group lost an average of 3.2 kg vs. 0.7 kg in the control group ($P<0.001$). Weight loss $\geq 5\%$ occurred in 33.7% of participants in the intervention group vs. 11.9% in the control group ($P<0.001$). Compared to participants in the control group, those in the intervention group had greater improvements in classical cardiovascular risk factors, except for blood pressure and LDL-cholesterol levels, and greater reductions in insulin resistance, hemoglobin A1c, and circulating levels of leptin, IL-18 and MCP-1 ($P<0.05$, all). In conclusion, among overweight/obese adults with metabolic syndrome, an intervention using energy-restricted MeDiet, PA and behavioral support for 12 months resulted in clinically meaningful weight loss and improvements in intermediate cardiovascular risk factors.

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Rare Bone Disorders

S21.1

Animal models of bone fragility

Antonella Forlino
Italy.

Osteogenesis imperfecta (OI), the most common among the rare hereditary skeletal dysplasias, is a juvenile form of osteoporosis ranging from mild to perinatal lethal forms. Classical OI is a dominant disease affecting the *COL1A1* and *COL1A2* genes encoding for the α chains of type I collagen, the most abundant protein of the bone extracellular matrix (ECM). In the last decade new causative genes associated to dominant, recessive and X-linked transmission of the disease and encoding for proteins involved in type I collagen biosynthesis, processing and secretion as well as in osteoblasts differentiation and activity have been described. How mutations in these genes cause the bone fragility phenotype still require further investigation, but already shed new light on bone biology. The molecular basis of OI was historically attributed to the presence of abnormal collagen in the ECM. Nevertheless, mutant collagen is partially retained in the ER and its misfolding and intracellular accumulation had been observed in OI patients' cells and animal models of classical and new OI forms. A deep understanding of the matrix and intracellular molecular mechanism of the disease as well as the development of new therapeutic approaches for OI and other bone fragility disorders benefit of the use of appropriated animal models. A review of the achievement obtained by the generation and characterization of murine models for dominant and recessive OI forms will be provided. The more recent development and use of teleost models, that provide new tools for osteochondrodysplasia investigation, will be discussed.

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S21.2

New perspectives on the treatment of skeletal dysplasia

Valérie Cormier-Daire
France.

Abstract Unavailable.

S21.3

Osteogenesis imperfecta throughout life

Kassim Javaid
UK.

Abstract Unavailable.

The Pituitary as Metabolic Sensor (*Endorsed by Endocrine Connections*)

S22.1

Kiss1 as integrator of endocrine and metabolic function in the hypothalamic-pituitary axis

Victor Navarro
USA.

Reproduction is a very energy costly function for the organism and, therefore, very tightly regulated by central and peripheral cues that ultimately determine the proper pattern of kisspeptin and GnRH release. Among these, metabolic cues play a critical role in the control of reproductive function, through the interplay of satiety and hunger signals. Further, the interaction between reproductive and metabolic functions is bidirectional, as kisspeptin has also emerged as a novel satiety factor. However, despite the critical role of these neuronal networks for the survival of the individual, the precise mechanisms underlying the control of reproduction and food intake remain incompletely understood. Recent studies from our lab have extended the characterization of this bidirectional regulatory process and identified, on one hand, a novel leptin-responsive population of PACAP neurons in the ventral premammillary nucleus that targets Kiss1 neurons to regulate reproduction—as part of the metabolic control of reproduction. On the other hand, we have documented an active role of Kiss1 neurons in the metabolic (anorexigenic) action of melanocortins through MC4R—as part of the reproductive control of metabolism. Overall, understanding the neuronal pathways and mechanisms underlying this bidirectional interaction of metabolism and reproduction is critical for the development of new approaches to treat metabolic and reproductive disorders with a central origin.

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S22.2

How treatments with endocrine & metabolic drugs influence pituitary cell function?

Giovanni Tulipano
Italy.

A variety of endocrine and metabolic signals regulate pituitary cell function acting through the hypothalamus-pituitary neuroendocrine axes or directly at the pituitary level. The underlying intracellular transduction mechanisms in pituitary cells are still debated. AMP-activated protein kinase (AMPK) functions as a cellular sensor of low energy stores in all mammalian cells and promotes adaptive changes in response to calorie restriction. It is also regarded as a target for therapy of proliferative disorders. Various hormones and drugs can promote tissue-specific activation or inhibition of AMPK by enhancing or inhibiting AMPK phosphorylation, respectively. In the last ten years, evidence has accumulated that pituitary AMPK plays a role in the interplay between the activity of neuroendocrine axes and metabolic functions. AMPK was shown to be a potential point of integration of energy homeostasis with reproduction at the level of pituitary [1]. Moreover, AMPK activation contributes to regulate the normal rat somatotroph cell function in-vitro. More recently, the hypoglycaemic agent metformin was shown to negatively modulate the basal hormone release from non-human primate somatotroph-, gonadotroph- and corticotroph cells in-vitro and to affect the expression of key receptors involved in the regulation of the distinct cell subtype function [2]. Metformin targets different sites of cellular bioenergetics and is an indirect activator of AMPK. To this end, metformin enhances AMPK phosphorylation at threonine-172 in rat pituitary tumor cells. As to pituitary proliferative disorders, the direct AMPK activator AICAR reduces the growth of rat pituitary tumor cells. Actually, primary cell cultures from

GH-secreting human pituitary adenomas were less sensitive to AICAR than rat cell lines. Our research group and other groups [3] have also investigated a possible role of metformin in the treatment of GH-secreting and prolactin-secreting tumors. Metformin can affect cell metabolism and cell signalling, and ultimately cell growth and function in-vitro when used at millimolar concentrations. Both AMPK-dependent and independent mechanisms are involved. The in-vitro effects of metformin may also help highlighting differences in metabolic requirements between pituitary adenomatous cells and normal cells.

References
1. Tosca L *et al.* (2011). Biol Reprod, 84:351–362.
2. Vazquez-Borrego MC *et al.* (2018). Cell Physiol Biochem, 49:1444-59.
3. An J *et al.* (2017). Oncotarget, 8: 37538-49.

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S22.3

Bidirectional interrelationship between growth hormone and metabolism

Raul M Luque
Spain.

Growth hormone (GH)-producing pituitary cells (somatotropes) comprise a fundamental regulator for a plethora of relevant physiological functions, including somatic growth and whole-body metabolism, by controlling the function of different endocrine/non-endocrine targets. Synthesis and release of GH has been classically thought to be primarily regulated by central, dual neuroendocrine signals: i.e. GH-releasing hormone and somatostatin. However, it is progressively becoming evident that multiple metabolic factors, from insulin and IGF-I to adipokines, ghrelin, obestatin, melatonin, cortistatin, neuronostatin, kisspeptin, etc., produced by GH-sensitive metabolic tissues (e.g. pancreas, liver, fat, stomach, etc.) can feedback directly to the pituitary to exert capital adjusts on GH synthesis and release. In this manner, somatotrope cells serve as metabolic sensors of the organism to integrate central and peripheral signals in order to fine-tune whole-body homeostasis, although it is clear that pituitary cell regulation is species-, age- and sex-dependent. The purpose of this presentation is to provide a comprehensive, general overview of our current knowledge on: 1) Central and peripheral metabolic regulators that directly control somatotrope cell function, and their associated intracellular mechanisms, as elucidated by using primary pituitary cell cultures from different species as well as *in vivo* mouse model treated with different metabolic factors; and 2) the metabolic consequences of changing circulating GH levels, by using multiple mouse models with elevated or reduced circulating GH levels [i.e. transgenic animal models with extreme altered levels of GH (giants vs. dwarf), as well as models with alterations in GH levels within the physiologic range (Adult-onset, isolated, GH deficient/AOiGHD, somatostatin/cortistatin-deficient, somatotrope specific insulin-R/IFGI-R deficient mice, etc.]. Additionally, it is now also becoming apparent that different agents used to improve altered metabolic conditions (e.g. biguanides and statins in diabetes and obesity) might also target somatotropes to exert, at least part, some of their beneficial metabolic actions. Thus, overall, the data gathered over the last years reinforce the contention that a clear, bidirectional and (patho)physiologically relevant, interrelationship is in place between GH and metabolism under both normal and altered metabolic conditions, where somatotrope cells act as true homeostatic sensors of the organism, controlling whole body homeostasis and metabolism by integrating central and peripheral signals.

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PCOS: Can We Personalise Treatment?

S23.1

Gut and brain axis

María Insenser
Spain.

Microbiota plays a major role in health and disease in humans. Sex hormones influence the diversity and composition of the gut microbiota. Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder in women of reproductive age (6–20%). PCOS is characterized by the association of androgen excess with oligomenorrhea, anovulatory infertility, and increased metabolic risk factors. The study of the interaction between gut microbiota and sex hormones in PCOS could be key to developing future personalized microbiota-based therapies. The mechanism underlying the association of sexual steroids and gut microbiota composition remains unclear. Very little evidence has been published regarding the implication of microbiota in women with PCOS. However, some studies have found a lower diversity and differential microbiota composition between women with and without PCOS, as well as correlations with clinical parameters of PCOS. Studies of PCOS animal models confirm that hyperandrogenism is capable of modifying the diversity of the gut microbiota community, and this may be a potential mechanism in the pathogenesis of PCOS. The current limitation of our knowledge about molecular mechanisms linking specific bacteria and PCOS highlights the need of interventional studies. Modulation and manipulation of gut microbiome will boost the efficacy of treatments to prevent the deleterious effect of hyperandrogenism on these women and improving their care.

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S23.2

Implicating androgen excess in metabolic disease in PCOS

Michael O'Reilly
UK.

Insulin resistance and androgen excess, alongside anovulatory infertility, are the cardinal clinical and biochemical features of polycystic ovary syndrome (PCOS). Circulating androgen burden and metabolic dysfunction in PCOS are closely correlated, but an independent contribution of androgens *perse*to metabolic and other complications of PCOS remains poorly characterised. My work focuses on delineating the distinct impact of androgens on metabolic function, with a particular focus on adipose tissue and insulin resistance. Adipose tissue is capable of androgen activation, and has a complex network of activating and inactivating enzymes. One of these enzymes, aldoketoreductase type 1 C3 (AKR1C3), activates the androgen precursor androstenedione to more potent testosterone. AKR1C3 expression is upregulated in subcutaneous adipose tissue from women with PCOS compared to BMI-matched controls. Using adipose tissue microdialysis, we have shown that PCOS women have significantly increased adipose concentrations of the active androgens testosterone and dihydrotestosterone compared to controls. Furthermore, using *in vivo* and *in vitro*studies, we have demonstrated direct effects of intra-adipose androgens on adipocyte lipid biology, with increased *de novo* lipogenesis and suppression of lipolysis promoting adipocyte hypertrophy. In other aspects of the presentation, I will discuss the relative contribution of the 11-oxygenated androgen synthesis pathway to circulating androgen burden and metabolic dysfunction in PCOS, which traditionally has been understudied in PCOS and other disorders of androgen excess. Data from a number of population-based studies will also be presented, which we have used to delineate the independent effects of androgen excess on metabolic disorders such as diabetes and non-alcoholic fatty liver disease, as well as on conditions as obstructive sleep apnoea. Lastly, I will present our recent data providing a mechanistic link between androgen excess and idiopathic intracranial hypertension in women, a distinct neuro-metabolic complication.

DOI: 10.1530/endoabs.63.S23.2

S23.3

Treatment options in cardiometabolic pcos phenotype

Mojca Jensterle
Slovenia.

Background
Cardiometabolic polycystic ovary syndrome (PCOS) phenotype is predominantly characterized by obesity. It is clearly associated with impaired metabolic and reproductive health, whereas implications on cardiac health are mostly limited with the exploration of cardiovascular risk factors without actual cardiovascular endpoints. There is a relative lack of systematic prospective studies investigating long-term effects of different treatment options that include phenotype specific outcomes.

Aim
We will cover different treatment interventions available for cardiometabolic PCOS phenotype. The treatment goals will include weight reduction, improvements of metabolic health, decrease of cardiovascular risk and increase in the fertility potential.
Results
Multicomponent lifestyle modification (LSM) is crucial intervention for this phenotype. Metformin in addition to LSM should be considered for managemnent of weight and metabolic outcomes. In clinical practice, LSM and metformin are often insufficient, by means of decreasing weight, preventing conversion rate from normal glucose tolerance to prediabetes and to type 2 diabetes and improving reproductive outcomes. Potential new modifiable risk factors should be addressed in this high-risk population. Some limited data from preclinical and clinical studies support an adjunct management with agents mediating through glucagon-like peptide-1 (GLP-1) axis, including GLP-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. GLP-1 receptor agonists have shown a beneficial effect on weight loss, some cardiometabolic risk factors and some reproductive outcomes. In severly affected individuals, bariatric surgery can be effective in achieving significant weight loss, reduction of cardiovascular risk and might result in a striking PCOS resolution rate.
Conclusions
Management of patients with cardiometabolic PCOS phenotype should aim to reduce weight, improve metabolic derangemnets, decrease risk for cardiovascular diseases and increase fertility potential. There exist some unsolved questions that implicate an exciting new research field with potential wider clinical implications. All this will be put in perspective in this talk.

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What's New in the Adrenal Cortex? (*Endorsed by the European Journal of Endocrinology*)

S24.1

Adrenocortical tumors: new genes, new understanding, new therapy

Mr Guillaume Assie
France.

For the last ten years, genomic approaches have led to important discoveries in adrenocortical tumors, unraveling mechanisms of tumorigenesis and autonomous hormone secretion. Autonomous aldosterone secretion in primary aldosteronism is now seen as induced by abnormal intra-cellular calcium signaling in glomerulosa cells, related to somatic mutations. The most common affects KCNJ5, coding for a membrane channel. A clinical trial with macrolides - impacting this channel- is ongoing. These mutations also impact primary aldosteronism nosography. Firstly, many 'aldosterone producing adenomas' correspond to diffuse adrenal diseases rather than focal alterations. Secondly, there seems to be a continuum between adrenal cortex aging and primary aldosteronism. These novelties should impact the screening and therapeutic strategies. Somatic mutations are found in one third of adrenocortical adenomas. Clinical impact is currently limited. Diffuse primitive adrenal cortex alterations are heterogenous. Discovering ectopic adrenal expression of hormone receptors permitted pharmacological treatment of a few patients with macronodular hyperplasia. Germline mutations of *PRKAR1A* and ARMC5, respectively associated to primary pigmented nodular adrenocortical dysplasia and to multinodular primary macronodular hyperplasia, helped to better classify these lesions. These mutations also improved our mechanistic understanding. Clinical impact is major for mutations carriers and their relatives, enabling early and efficient treatment of potentially deadly conditions. In adrenocortical carcinoma, recurrent somatic mutations mostly affect Wnt/beta-catenin (*CTNNB1* and ZNRF3) and cell-cycle (*TP53*). Therapeutic targeting of these mutations is limited. Few cases with high mutation burden or microsatellite instability - potentially related to germline *MUTHY* or Mismatch repair genes mutations respectively-, may orient towards immune checkpoint inhibitors. Finally, genomic screening of these carcinomas identified two main molecular classes, associated with major differences in outcome. Early prognostic stratification may impact the decision of adjuvant therapy after complete surgery. Taken together, genomic accelerated adrenal research pace, with clinical implications now coming to bedside. Clinical evaluation is now needed.

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S24.2

Primary hyperaldosteronism: does our treatment work?

Dr Tracy Ann Williams
Germany.

Primary aldosteronism (PA) has a prevalence of 5–15% in the general population with hypertension and patients with PA display an increased frequency of target organ damage and cardiovascular damage than patients with hypertension with matched cardiovascular risk profiles. The unilateral and bilateral forms of PA are treated differently usually surgically (unilateral PA) or by antagonism of the receptor for aldosterone (bilateral PA). Medically-treated patients with PA have an increased risk of cardiovascular events which is likely related to insufficient mineralocorticoid receptor blockade. Surgically treated patients with unilateral PA can be potentially cured but a wide between-centre variability has been demonstrated. An expert-based consensus established standard criteria to assess clinical and biochemical outcomes after unilateral adrenalectomy (the Primary Aldosteronism Surgical Outcome [PASO] consensus). Application of these criteria to an international cohort demonstrated that less than half of patients are clinically cured (37%, range 17–62) and showed that younger and female individuals are more likely to achieve clinical remission. The identification of baseline factors associated with post-surgical outcomes were used to develop an online score employing 6 presurgical variables for the prediction of clinical remission *versus* patients with likely persistant hypertension after surgery (the PASO predictor). Analysis of adrenal specimens from patients with PA showed that adrenals from patients with persistent aldosteronism after surgery more frequently display signs of hyperplasia and no obvious aldosterone-producing adenoma than those from patients surgically cured of aldosteronism. These approaches are relevant to the clinical setting for the differentiation of patients who are likely to be clinically and biochemically cured after surgery from those who will need continuous surveillance after surgery due to persistent hypertension and primary aldosteronism.

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S24.3

Autonomous cortisol secretion has cardiovascular consequences

Prof Iacopo Chiodini
Italy.

Background
Patients with adrenal incidentaloma (AI) and autonomous cortisol secretion (ACS) show a high prevalence of cardiovascular risk factors and an increased prevalence and incidence of cardiovascular events. Furthermore, some recent data suggest that in these patients, the cardiovascular mortality is also increased. Unfortunately, to date, the diagnosis of ACS is still a matter of debate, and, therefore, it is still not possible to reliably predict the effect of the recovery from ACS in the individual patient. As a consequence, addressing the treatment of choice (i.e. surgical or conservative) is still a challenge in many AI patients.
Material and Methods
We performed a systematic search of medical databases (PubMed, Cochrane Register and EMBASE) until January 31th 2019 using the following key-words: subclinical hypercortisolism, cardiovascular risk, cardiovascular mortality, adrenal incidentaloma and autonomous cortisol secretiom.
Results
The available data show that in AI patients with ACS the surgical removal of the adrenal mass causing ACS can lead to the improvement of hypertension and diabetes, but in many patients with possible ACS the effect of surgery is still largely unknown. No data are available on the effect of the recovery from ACS on the cardiovascular events. Finally, recent evidence suggest that cortisol secretion, peripheral activation and sensitivity could be associated with the presence of hypertension, diabetes and fragility fractures. Therefore, the development of safe and well-tolerated drugs aimed to control cortisol secretion and/or peripheral activation and to modulate glucocorticoid sensitivity will be among the goals of the future research.
Conclusions
Randomized studies are needed to investigate the possibility of predicting the usefulness of surgery by using the available indexes of cortisol secretion in the individual AI patient. The different sensitivity to glucocorticoids and cortisol peripheral activation capacity might influence the choice of the treatment in the individual subject.

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Late Breaking Session

S25.1

Liver Stress kinases – crossroad between obesity and liver cancer (Source paper: Nature 2019)

Guadalupe Sabio
Spain.

Abstract Unavailable.

S25.2

Levothyroxine in preconception women with thyroid peroxidase antibodies

Rima Smith
UK.

Background
Thyroid peroxidase antibodies are associated with increased risk of miscarriage and preterm birth, even when thyroid function is normal. Small trials indicate levothyroxine could reduce such adverse outcomes.
Methods
We conducted a double-blind, placebo-controlled trial to investigate whether levothyroxine treatment would increase live birth rates among euthyroid women with thyroid peroxidase antibodies and a history of miscarriage or infertility. We randomly assigned women to receive 50 mcg daily of levothyroxine or placebo, commenced preconception and continued until the end of pregnancy. The primary outcome was live birth ^{3}34 weeks gestation.
Results
We tested 19,585 women for thyroid peroxidase antibodies and thyroid function across 49 hospitals in the United Kingdom. A total of 952 women were randomly assigned to receive either levothyroxine (476) or placebo (476). The follow-up rate for the primary outcome was 98.7% (940/952). A pregnancy was achieved in 266/470 (56.6%) in the levothyroxine group and 274/470 (58.3%) in the placebo group. The live birth rate in the levothyroxine group was 37.4% (176/470) versus 37.9% (178/470) in the placebo group (relative risk, 0.97; 95% confidence interval [CI], 0.83 to 1.14, $P=0.74$; absolute risk difference, -0.4%; 95% CI, -6.6% to 5.8%). There were no significant differences in other pregnancy outcomes, including the rates of pregnancy loss, preterm birth, or in neonatal outcomes. Serious adverse events occurred in 6% of women in the levothyroxine group and 4% in the placebo group ($P=0.14$).
Conclusion
Treatment with levothyroxine in euthyroid women with thyroid peroxidase antibodies did not increase the rate of live births.

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S25.3

Maternal smoking and high BMI disrupt thyroid gland development

Panagiotis Filis
UK.

Around half of expectant mothers worldwide are overweight or obese and 20% smoke. Exposure to such factors during fetal life is linked to diseases including obesity, cardiovascular disease, and behavioural disorders. Because thyroid hormones control fetal metabolism, cardiac output and brain development, altered fetal thyroid signalling can contribute to future disease. We examined the impact of maternal smoking and overweight/obese (body mass index, BMI, ≥ 25) on the thyroid system in 2nd trimester human fetal tissues from normally progressing, electively-terminated pregnancies. We measured circulating thyroid hormones (THs), thyroid-stimulating hormone (TSH), and thyroid hormone-binding proteins, scored thyroid histology and examined the expression of developmentally-relevant proteins and transcripts in the human fetus and quantified TH transporter and signalling proteins and transcripts in placental plasma membrane preparations and fetal livers extracts. The fetal thyroid system is sexually dimorphic: male thyroids appeared more immature, lacking developmentally increased PAX8. The developmental increase of thyroid sodium-iodide importer NIS and a developmental decrease of the major placental TH transporter LAT1, in male fetuses only, suggest reduced reliance on maternal TH supply and increased fetal TH synthesis. Further, higher circulating triiodothyronine (T3) levels and reduced liver *DIO3* transcript in males indicate decreased peripheral degradation of T3. Maternal smoke exposure increased the developmental trajectory of fetal circulating thyroxine and altered the developmental trajectory of TSH, reversed the negative T4:TSH correlation and decreased PAX8 staining in female fetuses. Fetal thyroids from high BMI mothers were heavier, had reduced PAX8 staining and, in female fetuses, thyroids appeared more immature. Circulating TSH was higher in female fetuses from high BMI mothers. In conclusion, we showed that physiologically the fetal thyroid system is highly sexually dimorphic and responds to maternal smoking and high maternal BMI in a sex-specific manner. Our findings imply that management of the fetal thyroid function in children at risk may minimize predisposition to disease.

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Impact of Thyroid Disease on...

S26.1

Role of thyroid hormones in the pathogenesis and treatment of psychiatric disorders

Bernard Lerer
Israel.

A link between thyroid function and psychiatric illness, particularly major depressive disorder (MDD) is well established. Hypothyroidism has been shown to render patients more susceptible to MDD and less responsive to antidepressant drugs. Triiodothyronine (T3) has been shown to enhance antidepressant response in euthyroid patients who have not responded to standard antidepressant treatment. Furthermore, concurrent treatment with T3 may enhance and possibly accelerate treatment response when administered from the onset of treatment concurrently with antidepressant medication. In mouse studies we have shown that antidepressant effects of T3 as a sole treatment are dose dependent and linked to enhanced serotonin release mediated via effects of chronic administration on 5-HT-1A and 1-B autoreceptors. We have further shown that combined treatment with T3 and an antidepressant enhances hippocampal neurogenesis to a greater extent than antidepressant alone. Since long-term administration of T3 to euthyroid patients is not clinically feasible, we have sought avenues to enhance brain T3 levels by alternate routes. One direction we have explored is specific inhibition of deiodinase 3 (DIO3) by means of novel small molecules synthesized by the use of a DIO3 mimic. Preliminary findings in mice suggest that brain T3 levels may be enhanced by these novel compounds and antidepressant effects may be demonstrable on screening tests. Further studies are in progress.

DOI: 10.1530/endoabs.63.S26.1

S26.2

Bone

Graham Williams
UK.

Abstract Unavailable.

S26.3

Thyroid hormones in the cardiac physiopathology

Maria Luiza Barreto-Chaves

Our group studies the influence of different endocrine factors on cardiovascular function. Ang II is the main vasopeptide of Renin-Angiotensin System (RAS) and exerts its potent biological effects through AT1 and AT2 receptors. In heart, Ang II induces cardiomyocyte hypertrophy and fibroblast hyperplasia through TGF-β1

recruitment. On the other hand, cardiovascular system is very sensitive to the action of the Thyroid Hormones (THs). One major cardiovascular manifestation of THs excess is cardiac hypertrophy. There is a long time our group contributes with different studies demonstrating the interaction between these endocrine systems (RAS and THs). Then, some manifestations that disrupt this interaction may help to explain the variability of cardiovascular manifestations observed, for example, in hypo and hyperthyroidism. In recent years, cardiac hypertrophy and remodeling have increasingly been documented as a consequence of activation of immunologic machinery, where recurrent or sustained inflammatory response plays a causal role in the development of hypertrophy and its transition to heart failure. We have identified novel pathways regulated by THs, which are related to the immune-inflammatory context and may potentially play important roles in the hyperthyroid heart. In this context and consistent with our findings, crosstalk between THs and the RAS suggests that the RAS may be an important mediator of some cardiovascular manifestations of THs. To address this question we have used *in vivo* and *in vitro* experimental models providing a suitable system to monitor changes in the structure and cardiovascular function induced by endocrine factors. Different methodologies have been employed and morphologic, morphometric, biochemical and functional parameters have been used to study molecular and cellular mechanisms associated to cardiovascular biology and in special to this endocrine interaction (RAS and THs).

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What's New in Reproductive Endocrinology?

S27.1

Dissecting androgens in Polycystic Ovary Syndrome (PCOS)

Kirsty Walters
Australia.

Polycystic ovary syndrome (PCOS) is a common hormonal disorder characterised by reproductive hormone dysregulation involving luteinising hormone (LH) hypersecretion and hyperandrogenism, as well as reduced fertility, due to ovulatory disturbance. In addition, women with PCOS are also predisposed to metabolic disturbances such as obesity, insulin resistance, and dyslipidemia, with an increased risk of cardiovascular disease and type 2 diabetes. Currently, as the origins of PCOS remain unknown, mechanism-based treatments are not feasible and management relies on the treatment of symptoms only. However, if the underlying mechanisms involved in the development of PCOS were uncovered then this would pave the way for the development of new interventions for PCOS. Hyperandrogenism is the most consistent PCOS characteristic, and as androgens mediate their actions via the androgen receptor, we have combined a hyperandrogenised PCOS mouse model with global and neuron, granulosa cell or adipose-specific androgen receptor knockout mice to unravel the role of androgens in PCOS. These studies have revealed that androgen actions can mediate the development of PCOS, and have highlighted the importance of non-ovarian (neuroendocrine and adipose) androgen receptor-mediated androgen actions in the origins of PCOS. In particular, we have identified that a specific loss of androgen receptor signalling in the brain protects hyperandrogenised PCOS mice against the development of key reproductive and metabolic PCOS characteristics. These findings support excess androgen receptor-mediated actions in the brain as a key mechanism underpinning the development of PCOS. Hence, our data strongly supports targeting androgen actions in the brain in the development of targeted pharmacological approaches. Collectively these findings provide new insights into how evidence-based interventions may be developed in the future to treat PCOS.

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S27.2

Large scale genetic studies in male infertility

Frank Tüttelmann
Germany.

Infertility affects 10–15% of couples. In about half of them, a descriptive cause can be established in the male partner, mostly reduced sperm output, of which azoospermia, the complete lack of spermatozoa in the ejaculate, is the most severe form. Non-obstructive azoospermia (NOA) comprises several subforms of spermatogenic failure, such as meiotic arrest (MeiA) and Sertoli-Cell-Only syndrome (SCOS). Most of these phenotypes are suspected to be of genetic origin. However, aside from chromosomal aberrations and Y-chromosomal AZF deletions, monogenic causes are poorly understood. Still, a number of candidate genes have been proposed to be associated with NOA, but for the majority functional analyses and validation in independent studies are lacking. Like in many other diseases, genome-wide analyses comprising arrays to detect Copy Number Variants (CNVs) and whole-exome sequencing (WES) to detect nucleotide variation are now utilised in several large scale studies to promote validation of proposed candidate genes and identification of novel genes. Candidate genes for NOA and male infertility will be reviewed and put into perspective of novel findings from the recent WES results. The importance of functional assessment especially of missense variants causing amino acid substitutions will be highlighted. Indeed, we could recently increase causal genetic diagnoses in non-obstructive azoospermic men from ~20% to ~30% by WES together with in silico/in vitro analyses. Identifying the causal mutations in an infertile men has direct implications on treatment, especially decisions on performing a testicular biopsy and counselling about risks for offspring.

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S27.3

Menopause and cardiovascular risk

Irene Lambrinoudaki
Greece.

The transition to menopause is characterised by a decrease in circulating estradiol, relative androgen excess and a decrease in sex hormone-binding globulin concentrations. These hormonal changes are frequently accompanied by an increase in body weight, central obesity, dyslipidemia, insulin resistance and an increase in blood pressure. Aging, comorbidities, depression and inactivity further contribute to the increase in cardiovascular risk after the menopause. Beyond traditional cardiovascular risk, female – specific risk factors consist of a history of preeclampsia or gestational diabetes, a history of PCOS and the presence of severe menopausal symptoms. The risk of ischemic heart disease and stroke increases steeply after the menopause, becomes equal to that of men after the age of 60 and is higher than the risk of men after the age of 75. Cardiovascular mortality in Europe is higher in women compared to men, as women are less aware of their risk and less likely to seek medical help. Life style adaptations including healthy eating patterns, physical activity, maintaining a normal body weight and quitting of smoking are the cornerstone of prevention. Menopausal hormone therapy (MHT), if commenced within the first 10 years after menopause, has a favourable effect on the cardiovascular system, as it promotes vascular compliance, prevents central adiposity and restores lipid and glucose metabolism. MHT, if properly customized, is effective and safe for the majority of women. Transdermal estrogens are the best option for women with risk factors for thrombosis, like obesity or a family history of venous thromboembolism. A metabolically neutral progestogen, like micronized progesterone, dydrogesterone or transdermal norethisterone should be chosen for women with dyslipidemia or impaired glucose metabolism.

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Vitamin D - Non-skeletal Effects in RCT

S28.1

Vitamin D for healthy ageing

Heike Bischoff-Ferrari
Switzerland.

Abstract Unavailable.

S28.2

Vitamin D and type 1 diabetes

Suvi M Virtanen
Finland.

The rapidly increasing incidence of T1D worldwide and studies among migrants have shown that environmental factors play an important role in the pathogenesis of T1D. Identification of these risk-modulating factors would offer an excellent

opportunity to develop effective strategies for prevention of T1D. Vitamin D is one of the main candidates for protection from type 1 diabetes, although prospective epidemiological studies on the effect of vitamin D exposure during pregnancy, infancy and childhood have given inconsistent results. Vitamin D regulates the immune system and autoimmunity, which could be of relevance in the pathogenesis of type 1 diabetes. According to a prospective Norwegian study, high vitamin D status (25-OH vitamin D concentration) during the last trimester was inversely associated with the risk of type 1 diabetes in the offspring, whereas in a comparable Finnish study, vitamin D status during the first trimester was not associated with the disease risk. Recently, maternal vitamin D receptor (VDR) variants were found to be associated with a child's risk of type 1 diabetes independently of the child's genotype suggesting early programming of type 1 diabetes in the fetus. In north Finland 1965 birth cohort, vitamin D supplementation during infancy were inversely associated with type 1 diabetes development, whereas occurrence of rickets was directly associated with the disease. It is noteworthy that vitamin D supplementation recommendations were high at that time in Finland (50 μg/day). Recently findings from international TEDDY Study showed that childhood vitamin D status was protectively associated with islet autoimmunity and that association was modified by one SNIP of VDR. Interactions between genes and vitamin D intake/status on the development of islet autoimmunity and type 1 diabetes may explain the inconsistent findings. Vitamin D metabolism genes are associated with development of islet autoimmunity and type 1 diabetes as well as with vitamin D status.

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S28.3

How and when to measure vitamin D?

Jean Claude Souberbielle
France.

The 25-hydroxyvitamin D (25OHD) serum concentration is the marker of vitamin D status. It is measured by immunoanalysis, mostly on automated platforms, or by separative methods such as HPLC or LC/MS-MS. An important inter-method variability has been evidenced some years ago. This has however improved recently thanks to the availability of an international standard and of a reference method (RM), and to the implementation of the Vitamin D Standardization Program (VDSP). Some problems remain however, specially in conditions where the concentration of the vitamin D-binding protein is greatly modified, such as in late pregnancy, or when the altered composition of the serum induces a «matrix» effect, such as in chronic kidney disease (CKD). The RM is a LC/MS-MS method which uses a complicated sample preparation and an isotope dilution step. It is not designed for use in routine, and a frequent mistake is to consider that LC/MS-MS is (always) the RM. Indeed, while the results of the LC/MS-MS assays are usually better correlated with those of the RM than those of most immunoassays, a significant, and sometimes huge, bias exists between the results of many LC/MS-MS assays and the RM. The VDSP has validated a certification protocol to ascertain that a 25OHD assay is strictly comparable to the RM. An important question is «to which patients should we measure 25OHD ?». Clearly, the answer is to some extent a matter of opinion as evidenced by the very different recommendations published by many groups of experts. My personnal opinion is not to measure 25OHD in the general population but to focus on some patients such as those with (or at high risk of) osteoporosis, those with CKD, those with malabsorption, and in any exploration of calcium/phosphate metabolism when serum PTH is measured.

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Endocrine Controversies in Sport

S29.1

Female hyperandrogenism and elite sport

Angelica Lindén Hirschberg
Sweden.

Androgens are considered beneficial for athletic performance by potent anabolic effects on muscle mass and bone tissue. Testosterone also increases circulating hemoglobin, which will enhance oxygen uptake. Furthermore, androgens may exert behavioral and psychological effects of importance for athletic performance including increased mental drive and competitiveness. Studies in men have shown clear relationships with both exogenous and endogenous circulating testosterone to muscle mass, strength and hemoglobin. Corresponding evidence in women is much more limited. However, recent studies have demonstrated associations between circulating testosterone in the normal female range and muscle mass and strength, respectively. Moreover, it has been demonstrated that women with polycystic ovary syndrome (PCOS) are overrepresented in elite athletes. PCOS, which is a mild form of hyperandrogenism, is associated with an anabolic body composition including more muscle mass than in non-PCOS women. There are data to support that PCOS is advantageous for physical performance. This condition could therefore play a role in the recruitment of women to competitive sports. The prevalence of differences of sex development (DSD) is also increased among female athletes. XYDSD may cause a greatly increased production of testosterone in the male range, i.e. 10–20 times higher than in the normal female range. If the individual has normal androgen sensitivity, her muscle mass will develop as in males, along with increasing signs of virilization. Since sports are divided into female and male classification, it could be considered unfair to allow female athletes with endogenous testosterone in the male range to compete against women with normal female androgen levels. This lead the International Association of Athletics Federation and the International Olympic Committee to establish regulations for management of hyperandrogenism in female athletes. However, the regulations are controversial, and have been challenged. Ultimately, it is a question of ensuring fair and meaningful competition in women's sport.

DOI: 10.1530/endoabs.63.S29.1

S29.2

Performance enhancing drugs in young males

Pim de Ronde
The Netherlands.

Abstract Unavailable.

S29.3

Omics to fight doping

Guan Wang
UK.

Erythropoietin, testosterone and growth hormone are drugs of choice for those athletes wishing to gain a competitive advantage as they are most difficult to detect using the current anti-doping methods. The illicit use of such substances violates the spirit of clean sport and fair competition. Since its formation in 1999, the World Anti-Doping Agency (WADA) has been responsible for drug testing. Direct detection of substances complemented by the indirect Athlete Biological Passport (ABP) approach has been developed and implemented by WADA with some success. The similarity between exogenous substances and endogenous products, the limited detection window and the often sophisticated doping strategies challenge the existing anti-doping methods. A paradigm shift is needed that focuses on the identification of biomarkers that are triggered by a doping substance. Recent progress of high-throughput technologies aimed at characterising genetic variation, gene regulation, protein and metabolite, collectively known as an 'omics' profile, is enabling advances of unprecedented speed and efficiency that should encourage a new era not only in medicine but also in the field of anti-doping. New mathematical approaches that are capable of recognising and extracting patterns from the large and complex 'omics' data are in high demand. Notably, deep learning algorithms have great potential to transform a wide range of features (input) to actionable knowledge (output) in data-intensive disciplines albeit challenges remain in interpreting these models and generating testable hypotheses in biology and medicine. In summary, concerted international research efforts across disciplines are required to systematically analyse the multilayered 'omics' data obtained from the high-throughput state-of-art technologies for identifying robust biomolecules indicative of doping, which may be incorporated into the ABP or serve as a stand alone test.

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Personalised Medicine in Diabetes and Obesity (*Endorsed by the European Journal of Endocrinology*)

S30.1

Mechanisms for Cardiovascular Complications of Diabetes – Implications for Personalized Therapy

E Dale Abel
USA.

Cardiovascular disease is the major complication of diabetes that drives mortality and morbidity. Individuals with type 2 Diabetes have a 2-fold increased risk of major cardiovascular events (death, myocardial ischemia and stroke). There is also a 2–4-fold increased risk of heart failure, via mechanisms that are partially independent of underlying coronary disease and myocardial ischemia. Diabetes increases cardiovascular disease via multiple mechanisms including accelerated atherosclerosis, dyslipidemia, increased hypertension, increased thrombosis and increased inflammation. In addition, hyperglycemia and hyperinsulinemia may directly accelerate vascular injury. Additional mechanisms that increase the risk of heart failure in diabetes include altered myocardial energy metabolism, mitochondrial dysfunction, gluco-lipotoxicity and oxidative stress. Some landmark cardiovascular outcomes trials failed to demonstrate a relationship between tight glycemic control and reduction in major adverse cardiovascular complications. More recent trials have indicated that some GLP1R agonists and SGLT2 inhibitors might reduce major adverse cardiovascular outcomes. As such, an evaluation of an individual patients risk for macrovascular disease are now being factored into clinical decision making algorithms regarding the choice of glucose lowering therapies. Given the association between diabetes and atherosclerosis updated guidelines for lipid management emphasize specific guidelines and approaches to lipid management in individuals with diabetes and hypercholesterolemia. Finally, SGLT2 inhibitors and metformin have emerged as agents that might reduce the risk of heart failure in individuals with type 2 diabetes, via mechanisms that are incompletely understood. The presentation will discuss mechanisms that are responsible for the increased risk of cardiovascular disease in type 2 diabetes, particularly those that might be independent of glycemia and discuss the opportunity that this knowledge provides in personalizing therapeutic strategies that may reduce the risk of CVD.

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S30.2

New avenues for novel drugs to treat obesity

John Wilding

Obesity is a chronic disease with significant adverse implications for health. Guidelines recommend first line treatment with lifestyle interventions that include restriction of energy intake, increased physical activity and behavioural modification, but these only reduce body weight by 3–5% initial over 12 months, and weight regain is common. Bariatric surgery is effective, but most suitable for people with more severe obesity or with significant complications such as diabetes. Pharmacotherapy is an adjunct to lifestyle intervention and may help bridge the efficacy gap between lifestyle and surgery. The anti-obesity drugs currently available in Europe are the peripherally-acting intestinal lipase inhibitor, orlistat, a combination of the mu opioid antagonist naltrexone with bupropion, and the GLP-1 receptor analogue liraglutide. In the USA phentermine as monotherapy, or in combination with topiramate, and the 5HT2c receptor agonist lorcaserin are also approved. These drugs provide approximately 3–6% greater weight loss than lifestyle intervention alone over 12 months or more treatment duration. Adverse effects depend on the mode of action, and regulators have focussed on cardiac and neuropsychiatric safety given previous problems with older (now withdrawn) medicines for weight loss such as sibutramine and rimonabant. Lorcaserin was recently shown to be safe from a cardiovascular perspective, and data with the lower dose of liraglutide in people with diabetes suggests cardioprotection in those at high risk. The recently reported results of a phase 2 trial with the GLP1 agonist semaglutide are promising and suggest even greater weight loss is possible with potent long-acting GLP-1 analogues with central effects. Future developments will likely target multiple gut hormone pathways such as GLP1 together with glucagon, amylin or PYY in an attempt to optimise efficacy and approach the weight loss seen with surgical approaches. Drugs for specific monogenic forms of obesity such as metreleptin for leptin deficiency and the melanocortin 4 receptor agonist setmelanotide for patients with POMC mutations will also be discussed.

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S30.3

Curing diabetes with alternatives: bariatric surgery

Jochen Seufert
Germany.

Abstract Unavailable.

Special Symposium: ESE, the International Society of Endocrinology and the Endocrine Society Joint Session - Endocrinology of Aging

SS1.1

Obesity gives you cancer: the bigger picture!

Jeff Holly
UK.

The global obesity epidemic needs no introduction to endocrinologists, but there has also been a parallel growing epidemic in the common epithelial cancers (breast, colorectum and prostate) that has largely coincided in timing and geography. Obesity has some clear effects that may increase the propensity for the development of specific tumors. There are however broader effects that could impact more generally on the most common epithelial cancers. Epithelial cells form barriers in the body that have to be constantly replenished, requiring rapid cell turnover throughout life with a consequence that naturally occurring mutations accumulate with aging. The explosion of genome sequencing data has confirmed this accumulation and revealed the build up of huge numbers of mutations in normal epithelial tissues with advancing years. These numerous mutations are more than sufficient to initiate carcinogenesis, and as a consequence elderly individuals develop many occult neoplastic lesions in epithelial tissues, as consistently confirmed by autopsy studies. Most of these lesions will however not progress to become life-threatening cancers. Such progression appears to depend on context: the tissue ecosystem within our body. This implies that the initiating mutations are not rate limiting and the transformed 'seeds' can be plentiful but they only 'germinate' into clinical cancers if the 'soil' is right. The incidence of these cancers is much lower in the East, but is increasing with Westernisation, and increases more acutely in migrants to the West. Epidemiology has also indicated that metabolic biomarkers are prospectively associated with the incidence and poor prognosis of exactly the same cancers. A Western lifestyle is strongly associated with perturbed metabolism and obesity: these may then provide a fertile soil within the body that could enable the progression of epithelial cancers. Obesity and the associated metabolic disturbance are characterised by insulin resistance and increased levels of glucose and other metabolites, dyslipidemia and altered levels of adipokines, cytokines and growth factors.The latent neoplastic seeds, which naturally accumulate with age, may then be more likely to germinate and grow in this more fertile soil. Evidence from many different fields is increasingly indicating that for the common epithelial cancers our lifestyles and especially our metabolic health, rather than our genes, may be more important for their progression to life-threatening disease. This raises new opportunities for different strategies for prevention and treatment of these cancers.

DOI: 10.1530/endoabs.63.SS1.1

SS1.2

Sleep deficiency: A pathway to obesity

Erin Hanlon
USA.

Worldwide, rates of obesity have been steadily increasing, along with disorders commonly associated with obesity, such as cardiovascular disease and type II diabetes. Simultaneously, average sleep times have progressively decreased. Evidence from both laboratory and epidemiologic studies has consistently associated insufficient sleep or short sleep with increased risk of obesity. In the

laboratory, it is now possible to control sleep behavior and study the link between sleep duration and alterations in circulating hormones involved in feeding behavior, hunger, and appetite. Carefully controlled laboratory studies of systematic sleep restriction in healthy adults have reported alterations in peripherally secreted hormones that modulate feeding. In these studies, participants also displayed increased subjective appetite and hunger ratings, greatest for high carbohydrate and high fat foods. Most importantly, recent studies have shown that short sleep duration is associated with increased actual consumption of snacks and high energy foods. These reported increases in hunger and food intake in a state of sleep debt exceed the energy demands of extended wakefulness therefore suggesting the involvement of hedonically driven eating, i.e. eating for pleasure rather than to fulfill a caloric need. We have recently examined the endocannabinoid system, known to facilitate hedonic eating, following normal and restricted sleep. Our studies show that under normal sleep conditions, blood levels of the most abundant endocannabinoid increase from mid-sleep to early afternoon. After sleep restriction, this increase in endocannabinoid concentration is amplified, coinciding with greater desire for palatable food. The identification of the endocannabinoid system as a mediator of increased hunger following sleep curtailment may help develop novel preventive strategies in the treatment of obesity.

DOI: 10.1530/endoabs.63.SS1.2

SS1.3

Obesity is an economic burden and we know why

Craig Nossel
South Africa.

Abstract Unavailable.

New Scientific Approaches

NSA1

Steroidomics

Stefan A Wudy
Germany.

The 'central dogma of biology' - a term coined by Francis Crick in 1957 - describes the flow of sequential information from genome via transcriptome, proteome and metabolome to the phenotype. Associated with each stage is the respective systems biology '-omics tool', e.g. metabolomics. The metabolome represents the complete set of metabolites (low-molecular weight molecules) in a biological sample and metabolomics describes the systematic study of these small molecules present in this biological sample (Daviss and Bennett 2005). A typical workflow of metabolomics studies implies: i) collection of a biological sample (e.g. a biofluid), ii) sample preparation, iii) multicomponent analysis by analytical platform techniques consisting of a powerful separation technique (gas chromatography (GC) or liquid chromatography (LC)) combined with mass spectrometric (MS) or nuclear magnetic resonance (NMR) based detection, iv) data acquisition, v) data analysis by sophisticated bioinformatics tools (e.g. principal component analysis), and vi) interpretation to finally recognize patterns, characterize disease signatures or biomarkers. If all components in a complex mixture are determined in a non-discriminatory (unbiased) way, such an approach is called 'untargeted'. In case only selected components are recorded, this approach is a 'targeted' one. Early attempts in characterizing normal and pathological human steroid metabolomes (steroid metabolomics, steroidomics) started from the 7th decade of the last century onwards. GC and GC-MS were the dominating techniques pioneered by Sjövall (2004) and Shackleton (2006). From the eighties of last century onwards, LC-MS techniques joined and soon ascended impressively (Wudy and Choi 2016). Focusing on the currently prevailing analytical techniques GC-MS and LC-MS (Wudy *et al.* 2018; Shackleton *et al.* 2018), this talk will demonstrate the roles of these techniques in various examples from steroid research and clinical endocrinology with respect to delineation of steroid metabolomes, characterization of disease signatures and new biomarkers.

DOI: 10.1530/endoabs.63.NSA1

NSA2

Single cell spatial reconstruction of endocrine organs

Keren Bahar Halpern
Israel.

Mammalian tissues are composed of heterogeneous populations of cells, interacting in highly structured microenvironments to achieve physiologic goals. Understanding the design principles of endocrine tissues organization requires approaches to analyze spatially-resolved sub-populations of cells within the tissue. The mammalian liver consists of hexagonal-shaped lobules, radially polarized by blood flow and morphogens. Key liver are differentially expressed along the lobule axis, a phenomenon termed zonation. These diverse functions are carried out by hepatocytes that closely interact with supporting cells termed non-parenchymal cells (NPCs). Spatially resolved single-cell RNA sequencing (scRNAseq) is a powerful approach to infer connections between tissue coordinates and molecular identities. We have recently combined two powerful technologies - Single cell RNAsDefault (scRNAseq) and single molecule Fluorescence In-Situ Hybridization (smFISH) to reconstruct the spatial gene expression gradients of both hepatocyte and liver endothelial genes. Using this approach, we obtain the zonation profiles of all liver genes with high spatial resolution. Our work revealed an unexpected breadth of liver spatial heterogeneity, with $\sim$50% of liver genes expressed in spatially non-uniform patterns. The spatial division of labor we uncovered is in line with previous theory suggesting that liver zonation confers optimality for liver function. Pancreatic beta cells are heterogeneous at multiple levels. However, interrogating transcriptional heterogeneity in the intact tissue has been challenging. We used an optimized smFISH protocol to identify a sub-population of 'extreme' beta-cells with elevated mRNA levels of insulin. Extreme beta cells contain higher ribosomal and proinsulin content, but lower levels of insulin protein in a fasted state, suggesting that they may be tuned for basal insulin secretion. In addition, the proportion of extreme cells increases in *db/db* diabetic mice, potentially facilitating the required increase in basal insulin. Our results thus highlight a sub-population of beta-cells that may carry distinct functional roles along physiological and pathological time scales. Understanding the relation between structure of tissues and their single-cell gene expression patterns in healthy states can help up reveal how these interactions are perturbed in disease.

DOI: 10.1530/endoabs.63.NSA2

NSA3

Intelligent image based *in situ* single cell isolation

Gabor Tamas
Hungary.

Abstract Unavailable.

NSA4

How can AI create value for the endocrinologist? Challenges and opportunities for AI-enabled solutions

Anca Bucur
The Netherlands.

The risk of unsustainability faced by many healthcare systems drives the focus on leveraging technology for effective solutions to key problems. Technologies such as AI, enabling to better leverage the power of data in healthcare, hold the potential to play a transformative role and contribute to improvements in both efficiency and quality. AI-enabled solutions may lead to lower costs, better patient outcomes, increased safety, streamlined information flows, and free healthcare professionals of tedious and frustrating data handling tasks. These solutions must support patient-empowerment as well, turning patients into informed partners in the medical decision making processes and fostering a shift towards preventive care. An important enabler for AI is increasing data quality. Tailored data transformation and information extraction need to be developed to augment data quality at clinical sites and help leverage all relevant information. Techniques for at-integration data extraction and in-flight classification with AI models need to be combined to unlock valuable information. Emerging Open Data initiatives could add significant value by accelerating research and development in AI, reducing innovation cost, and introducing community-wide standards and best practices. The adoption of AI in healthcare relies on the ability to provide proper, privacy-preserving use of data, and to ensure that the outputs are adequately validated, transparent, and explainable. Moreover, the new solutions must seamlessly fit in the clinical workflows, which is a non-trivial challenge, and users need to be appropriately trained to use them and to correctly interpret the outputs. The diversity of business models under which different AI assets are monetized to make the whole ecosystem sustainable, complicates things even further. A healthcare-specific AI platform that helps efficiently address the above challenges is essential to scaling the development and deployment of AI assets. The talk will introduce our ongoing work and discuss new ideas for research and collaboration.

DOI: 10.1530/endoabs.63.NSA4

NSA5

Genome-wide effects of vitamin D on chromatin

Carsten Carlberg
Finland.

Vitamin D_3 can be produced endogenously in UV-B exposed skin, but during winter months it should be supplemented via fortified foods or pills. The main physiological functions of vitamin D are the control of cellular metabolism and immunity via regulating calcium homeostasis and modulating the response of cells of the innate and adaptive immune system, respectively. The vitamin D metabolite 1α,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) directly affects the epigenome and transcriptome of vitamin D receptor (VDR) target tissues and cell types. THP-1 human monocytes represent a model system that has studied most comprehensively for epigenome- and transcriptome-wide effects of $1,25(OH)_2D_3$. These data are the basis of the chromatin model of vitamin D signaling describing how VDR's spatio-temporal binding profile provides key insight into the pleiotropic action of vitamin D. Some 300 primary vitamin D target genes are regulated by VDR in concert with the pioneer transcription factors PU.1 and CEBPA and the chromatin organizer CTCF. Moreover, $1,25(OH)_2D_3$ directly affects histone markers of active promoter and enhancer regions as well as chromatin accessibility. Epigenome- and transcriptome-wide data obtained in context of the short-term vitamin D intervention study VitDbol (NCT02063334), where before and 24 h after a vitamin D_3 bolus chromatin and RNA were prepared from peripheral blood mononuclear cells. Comparable principles of vitamin D signaling were confirmed in this *in vivo* model concerning target gene responses as well as changes in chromatin accessibility. Interestingly, the VitDbol study subjects showed a personalized response to vitamin D and

could be distinguished into high, mid and low responders. In conclusion, short-term vitamin D supplementation studies represent a new type of safe *in vivo* investigations demonstrating that vitamin D and its metabolites have direct effects on the human epigenome and modulate the response of the transcriptome in a personalized fashion.

DOI: 10.1530/endoabs.63.NSA5

NSA6

Diving into the brain: deep brain imaging techniques in conscious animals

Pauline Campos
France.

Survival of most species relies on the fact that small populations of endocrine neurons located in the hypothalamus determine critical functions such as reproduction, growth, and metabolism. These neurons are so finely regulated that their functions have been conserved across evolution; nonetheless, the mechanisms underlying these regulatory features remain hazy. Indeed, research efforts have been hindered by the complexity and inaccessibility of the hypothalamic-pituitary system, and the study of neuroendocrine function has been dominated by techniques that consist of studying *in vitro* or *ex vivo* preparations that lack many of the important regulatory mechanisms functioning *in vivo* at the level of the brain, pituitary and periphery. Nowadays, it is possible to exploit the advantages of neuronal transfection and advanced imaging techniques to study hypothalamic neuron activity *in situ*, in real time, and in conscious animals. Genetically-encoded calcium indicators have now become widely used for calcium imaging in living organisms. Their always-improving characteristics make them not only an excellent proxy for electrical activity, but also a versatile tool that allows diverse imaging techniques. Deep-brain imaging of calcium activity can be performed through gradient-index lenses that are chronically implanted and permit imaging of multiple neurons at single-cell resolution. Depending on the research question and the imaging quality required, visualisation of the neurons can be carried out in head-fixed configuration using bench-top microscopes, or in freely-moving configuration using miniature head-mounted microscopes. Alternatively, population-level neuronal calcium activity can be recorded in freely-moving animals using fibre photometry; here, an optical fibre delivers excitation light and collects the overall fluorescence of neurons expressing a calcium indicator. Importantly, using any of these techniques, it becomes possible to correlate the impact of neuronal activity on other functions, for example, blood sampling can be performed whilst recording neuronal activity in order to provide a link between the activity of specific hypothalamic neuron and the resulting peripheral hormonal release. Overall, the use of deep-brain imaging techniques in conscious rodents has the potential to broaden our understanding of how the brain controls endocrine function. It also gives us the opportunity to study why endocrine functions become disrupted in pathophysiological conditions, and how these changes may lead to the development of pathological consequences.

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Debates

Food Addiction in Humans: To Be or Not to Be?

D1.1

PRO: Food addiction in humans: to be or not to be?

Fernando Fernandez-Aranda
Spain.

The **food addiction** (FA) construct has become a topic of great interest in the scientific community; however, its diagnostic, clinical and potential therapeutic implications remain unresolved. Although there is not enough evidence to confirm its diagnostic utility, given that some of the findings obtained in preclinical research associating the addictive capacity of certain palatable foods have not yet been replicated in humans, there are signs of neurobiological vulnerability and greater susceptibility to using food as a means of coping with problems and negative affect. While the first human studies focused on obesity and the general population, later research concentrated on eating disorders (ED), bariatric surgery patients and other psychiatric disorders. FA seems to reflect a transdiagnostic condition that is shown to be more prevalent in subjects with obesity (ranging from 18 to 24%) and even higher in patients with ED, particularly binge eating disorder and bulimia nervosa (ranging from 70% to 95%, respectively), but also in behavioral addictions. Considering the literature, published so far, FA is frequently associated with higher ED severity and more general psychopathology, but also with more dysfunctional personality traits and neuropsychological impairments, associated with decision making and attentional bias to food neural circuitry. The few prospective studies have shown higher food addiction to be negatively associated with treatment outcome, as well in bulimia nervosa, as pre and post-operatively in bariatric surgery. The addictive model has the potential to open new avenues of conceptualization and management in obesity and eating disorders, providing potentially new targets that might be complementary to the complex models of treatment needed in those disorders.

DOI: 10.1530/endoabs.63.D1.1

D1.2

CON: Food addiction in humans: to be or not to be?

Paul Christiansen
UK.

Abstract Unavailable.

Surgical Treatment of Phaeochromocytoma - Query Pre-treatment?

D2.1

PRO: Surgical treatment of phaeochromocytoma - query pre-treatment?

Henri Timmers
The Netherlands.

Pheochromocytomas/paragangliomas (PPGLs) are catecholamine secreting tumors that, if missed or not properly treated, can be devastating due to potential lethal cardiovascular complications. The 2014 Endocrine Society clinical practice guideline on PPGL includes recommendations regarding optimalperi-operative care [1]. The main goal of preoperative management is to prevent a patient from developing anesthesia- or surgery-induced catecholamine storm. This warrants the involvement of an expert team of endocrinologists, surgeons and anesthesiologists. It is recommended that all patients with a hormonally functional PPGL should undergo preoperative adrenergic blockade, primarily with alpha-adrenergic receptor blockers such as phenoxybenzamine, doxazosin, prazosin or terazosin. During 10–14 days prior to surgery, doses are gradually increased until blood pressure is steadily controlled. Beta-adrenergic blocking agents such as propranolol, atenolol and metoprolol are needed when significant tachycardia or a catecholamine-induced arrhythmia occurs. A beta-blocker should not be used in the absence of an alpha-blocker because this will exacerbate epinephrine-induced vasoconstriction by blocking its vasodilator component. Calcium channel blockers or, in rare cases, the tyrosine hydroxylase inhibitor metyrosine, can be added when maximum doses of alpha- blockers are insufficient to achieve hemodynamic control. Salt and fluid loading are given to expand blood volume to prevent pre-operative orthostatic hypotension and severe post-operative hypotension. Anesthesiological management should be in experienced hands. Despite pre-operative blockade, intra-operative blood pressure may still vary, necessitating the use of short acting drugs such as phentolamine, nicardipine and sodium nitroprusside. Post-operatively the patient is monitored in the ICU for at least 24 hours to manage potential complications such as hypotension and hypoglycaemia.

Reference

[1] Lenders, *et al.*, *J Clin Endocrinol Metab*, 2014. 99(6): pp. 1915–42.

DOI: 10.1530/endoabs.63.D2.1

D2.2

CON: Surgical treatment of phaeochromocytoma - query pre-treatment?

Martin Walz
Germany.

Abstract Unavailable.

T4 is Not Enough

D3.1

'Yes, T4 is not enough'

Birte Nygaard
Denmark.

Most L-T4 treated hypothyroid patients return to normal health without complaints. However, persistent symptoms such as tiredness, depression, decreased cognitive function, weight increase and musculoskeletal symptoms are described in 25% of L-T4 treated hypothyroid patients compared to 15–20% in controls. It has been assumed that all the necessary T3 could be derived from peripheral de-iodination of orally administered L-T4. Nevertheless, data has pointed towards a possible need for supplementary T3 in selected patient groups to fully restore the balance between TSH, TRH, thyroid hormones, de-iodinase and metabolism. Data show a 15–20% lower serum FT3/FT4 ratio given a stabile serum TSH after thyroidectomy than before and in thyroidectomized rats it is only possible to restore normal concentrations of FT3 in all tissues by giving a combination of L-T4 as well as L-T3. A meta-analysis in 2006 of data from more than 1200 unselected patients could not confirm an effect of L-T4/L-T3 combination therapy. However, the included studies were heterogeneous, including unselected patients. A minor study in a highly selected patient-group with Hashimoto' disease and overt hypothyroidism as well as persistent symptoms demonstrated significant effects in seven out of eleven quality of life scores and preference for L-T3/L-T4 combination therapy in 49% compared to L-T4 monotherapy in 15% ($P=0.002$). A suggested explanation for a possible need for a T3 substitution as well as T4 has been related to a change in the feedback in the hypothalamic-pituitary-thyroid axis induced by high dose og T4 and a possible relative inactivation of deiodinase 2 and hereby lower values of T3. Another possible suggested explanation is polymorphisms in the deiodinase 2 gene (D2-92 Ala) or to the cellular membrane transporter (MCT10) and by this a potential decrease in the transportation of thyroid hormone from plasma to the intracellular space and a decreased deiodination of T4 to T3. However, extended research is needed to explore the exact effect of these and other polymorphisms.

DOI: 10.1530/endoabs.63.D3.1

D3.2

'No, T4 is enough'

James Hennessey
USA.

To date, all major guidelines designate LT4 as the standard. Are symptoms a reliable indicator of the presence of hypothyroidism? Fatigue in primary care, predicts a lifetime diagnosis of depression or anxiety more frequently than other outcomes. Tiredness has been examined in 26 meta-analyses. Only 4.3% of tired subjects have identifiable somatic disease (includes anemia, diabetes and

hypothyroidism). In studies with control groups, the prevalence of somatic diseases was identical, an association that was clearly not causal. Based on symptoms, thyroid function testing occurs frequently but correlation with thyroid function is not significant. Symptoms or mild 'elevations' in TSH result in labeling individuals as hypothyroid and the initiation of LT4. Reports show similar symptoms in euthyroid, subclinically hypothyroid (SCHypo) and overtly hypothyroid (OHypo) patients, overlap between the groups is clear. Others reinforce the non-specificity of symptoms especially among older women. Do circulating T3 levels correlate with symptoms of hypothyroidism or predict response to LT4/LT3? Several studies demonstrate no correlation between serum T3 (on LT4) and QOL and mood. Massolt et al. demonstrated no correlation of QOL with serum T3 levels but recognized positive factors such as the time since the diagnosis of the thyroid cancer and a negative correlation with the number of all drugs ingested by the subjects. Two studies showed that T3 levels measured while on LT4 or after treatment with LT4/LT3 did not predict a positive response to LT4/LT3. Two patient surveys, shed light on patient satisfaction. The most satisfied patients are followed by primary care physicians, ingest thyroid hormone extract (DTE), have lower TSH values and adjust their doses based on symptoms. The second study reported equivalent overall satisfaction on LT4 or LT4/LT3 while DTE was superior. Dissatisfaction with weight, fatigue, mood, and memory were similar in those on LT4 and those on LT4/LT3 while DTE users complained less. Symptoms are imprecise. Utilizing T3 levels to make clinical decisions and/or predict the outcome of LT4/LT3 is not substantiated. Pending further research in new areas like DIO2 SNPs and LT4/LT3 sustained release, I will continue to utilize levothyroxine monotherapy.

DOI: 10.1530/endoabs.63.D3.2

Pituitary Pathology: Do We Care?

D4.1

Yes, we care about pituitary pathology!

Olivera Casar-Borota
Sweden.

Complex embryonal development of pituitary gland and sellar region explains a huge diversity of sellar neoplastic lesions. The spectrum ranges from the most frequent pituitary neuroendocrine tumours via craniopharyngiomas and tumours arising from the posterior pituitary, meninges or other mesenchymal tissues to high grade malignant primary or secondary malignancies. Furthermore, benign cysts and an increasing number of inflammatory conditions should be considered in differential diagnosis. As the clinical symptoms and imaging manifestations of different sellar lesions may be overlapping, histopathological examination of the specimen obtained during the surgery is the way to secure a diagnosis. Clinically relevant classification of pituitary neuroendocrine tumours and identification of potentially aggressive tumour types cannot be achieved without histological and immunohistochemical evaluation. Histopathological and immunohistochemical methods are important tools in the assessment of prognostic and predictive biomarkers. Moreover, tissue availability is essential for the identification of molecular therapeutic targets in several types of tumours occurring in the sellar region. A thorough histological characterisation of tissue specimens used in experimental and clinical studies is a prerequisite for high-quality research on pituitary tumours. Well-established histological and tissue-based molecular techniques enable high throughput analyses of the vast number of tumour specimens. In this debate, I will present my arguments in favour of pituitary pathology as an essential part of the clinical management of patients with sellar lesions and a tool to bring pituitary research to its height.

DOI: 10.1530/endoabs.63.D4.1

D4.2

No, we don't care about pituitary pathology

Sven Schlaffer
Germany.

Abstract Unavailable.

MicroRNAs as hormones?

D5.1

PRO: MicroRNAs and extracellular vesicles as hormones?

Edit Buzás
Hungary.

Abstract Unavailable.

D5.2

CON: MicroRNAs and extracellular vesicles as hormones?

Alberto Davalos
Spain.

The capacity of microRNAs (miRNAs) to simultaneously repress multiple targets provide a mechanism to treat disease by modulating entire biological networks. miRNAs are present in the systemic circulation and other biological fluids associated with extracellular microvesicles, exosomes, Ago2 complex or HDL. Even exogenous miRNAs have been described in our circulation. The active secretion of miRNAs by the cells has been suggested to mediate intercellular communication. The inter-organ and intra-organ cross-talk, traditionally mediated by hormones, was recently evidenced to be also regulated by extracellular vesicles. However, the biological significance, the factors that modulate their extracellular secretion and the mechanisms by which they reach the target tissue still remains elusive. Exosomes are stable nanovesicles that transport bioactive molecules (i.e. miRNAs) to target cells. One of the advantages of exosomes is that they can easily cross the blood-brain barrier without use of an additive vehicle. Recent evidence suggest that breast milk exosomes contain miRNAs that can be transferred from mother to infants, producing a potential inter-individual communication *via* miRNAs. Moreover, increasing evidence suggest that exogenous miRNAs can be transferred from diet (i.e. plants-derived miRNAs) and taken up by mammalian cells where they exert a biological effect. Their transport in extracellular vesicles might avoid their degradation by extracellular/intracellular RNases, being active signaling molecules involved in the intercellular communication. However, their real *in vivo* biological effects are under debate. In addition, how much extracellular miRNAs reach the target cell to exert a hormone-like effects is poorly understood. We here discuss some relevant biological process to understand the potential of extracellular miRNAs as hormones. The many barriers when reaching the circulatory system, the biological barriers before entering any target-cells and bypass the many intracellular barrier to reach the appropriate subcellular localization in order to exert any effects is also point out.

DOI: 10.1530/endoabs.63.D5.2

Should We Treat Young Osteoporotic Patients?

D6.1

Yes, we should treat young osteoporotic patients

Serge Ferrari
Switzerland.

Abstract Unavailable.

D6.2

'No, we shouldn't treat young osteoporotic patients'

Barbara Obermayer-Pietsch
Austria.

Low bone mass and a high fracture risk in young individuals has only recently become a focus of interest in bone research and health care as compared to elderly patients. In fact, according to WHO criteria, 'osteoporotic' T-scores in bone mineral density (BMD) below −2.5 can be found in less than 1% of women

before menopause, and 'osteopenia' as defined by T-scores between −2.5 and −1 in only about 10–15% of a healthy population. However, secondary causes of osteoporosis, such as inflammatory bowel disease, rheumatoid arthritis or coeliac disease have a prevalence of low BMD and/or fragility fractures between 15 and 50%. This is also true for patients with anorexia nervosa or patients on insulin therapy due to type 1 diabetes mellitus. Many other endocrine diseases, neuromuscular or metabolic disturbances and even medications with impact on the musculoskeletal system including anticancer therapy and systemic glucocorticoids have been identified to increase fracture risk. In addition, the perception of bone status or fracture risk among young patients regarding the severity of the disease or the adherence to osteoporosis prevention strategies has been reported to be very low. From a medical perspective, low BMD and/or the occurrence of low trauma or multiple fractures should alert doctors in various fields of medicine to start further investigations of their patients' bone status. A diagnostic workup should therefore include clinical exams, imaging including DXA and laboratory analyses including bone biomarkers and a large panel of investigations for secondary underlying disorders and/or medications potentially associated with osteoporosis. Therapeutic implications cover lifestyle-associated factors, physical activity for the preservation of muscle and bone mass and adapted nutritional intake. Indications and contraindications of osteotropic therapeutics will be discussed as well as general guidance for young osteoporosis patients.

DOI: 10.1530/endoabs.63.D6.2

Meet the Expert Session

MTE1

The road from flash glucose monitoring to hybrid closed loop systems: keys to success.

Christophe De Block
Belgium.

Living with type 1 diabetes (T1D) is challenging and requires intensive glucose monitoring and titration of insulin in order to obtain near-normal glucose levels to reduce the risk of complications. However, changes in dietary intake and level of activity can cause large glucose excursions. Continuous glucose monitoring systems, either intermittently scanned either real-time, can provide a comprehensive picture of glucose profiles, allowing patients to make therapeutic adjustments to improve metabolic control. The use of CGM systems has proven to positively impact the management of type 1 diabetes with the potential to lower HbA1c, enhance time spent in range, reduce frequency and time spent in hypo- and hyperglycemia, lower glycemic variability, and improve quality of life. Intermittently scanned CGM or flash glucose monitoring (FGM) is beneficial for patients using multiple daily injections (MDI). For patients being treated by continuous subcutaneous insulin infusion (CSII), RT-CGM devices are better suited. Several stand-alone RT-CGM devices exist, but the next step is the combination of both, called sensor-augmented pump (SAP) therapy. Low glucose suspend (LGS = Paradigm Veo pump) and predictive low glucose suspend (PLGS = 640G pump) have shown improvements in HbA1c, hypoglycaemia and quality of life, and are particularly advantageous for people with hypoglycaemia unawareness. However, for brittle type 1 diabetic patients with erratic life style, a hybrid closed-loop system (670G pump) seems the best option so far. In this review we will highlight benefits and limitations of use of FGM/CGM for open-loop control and recent progress in closed-loop control systems. We will also discuss different patient profiles for the different systems, educational aspect which are key to successful use of the systems and touch upon costs.

DOI: 10.1530/endoabs.63.MTE1

MTE2

Long-term endocrine-metabolic effects of bariatric surgery: do the benefits really outweigh the risks?

Roberto Vettor
Italy.

Abstract Unavailable.

MTE3

The management of primary aldosteronism

Andrzej Januszewicz
Poland.

Abstract Unavailable.

MTE4

Management of a life-long disease in CAH

Nicole Reisch
Germany.

Abstract Unavailable.

MTE5

Risk classification of thyroid nodules by ultrasound and indications for FNA

Laurence Leenhardt
France.

Objectives
Thyroid ultrasound (US) is a key examination for the management of thyroid nodules. Thyroid US is easily accessible, noninvasive, cost-effective and is a mandatory step in the workup of thyroid nodules. Thyroid US assessment of the risk of malignancy is crucial in patients with nodules, in order to select those who should have a fine needle aspiration (FNA) biopsy performed. Specific US features suggestive of malignancy have been recognized and described in literature, namely hypoechogenicity, irregular or blurred margins, microcalcifications, taller than wider shape and vascular signals. These features have been included in different US classifications developed over the years by many scientific societies: the American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), Associazione Medici Endocrinologi (AME), Korean Society of Thyroid Radiology, American College of Radiology and European Thyroid Association who built the European Thyroid Imaging and Reporting Data System, called EU-TIRADS. Therefore, these societies set up guidelines about indications for FNA.
Methods
We aimed to estimate and compare the performance and the limits of the different US classifications in discriminating nodules for malignancy. We compared the indications for FNA among the different US scoring systems. The non indication for FNA and the relevance of repeated FNA were also discussed.
Results
Despite some differences between the US scoring systems, we observed that all the US classifications provide an effective malignancy risk stratification for thyroid nodules, demonstrated the ability of these schemes in selecting nodules for FNA. It is time to figure out a unique international TIRADS system that will gather the strengths of the different US scoring systems and refine the indications of FNA in thyroid nodules.

MTE6

Primary hyperparathyroidism: surgical vs. medical therapy

Tomaz Kocjan
Slovenia.

Primary hyperparathyroidism (PHPT) is a common endocrine disorder that is characterized by hypercalcaemia and elevated or inappropriately normal levels of parathyroid hormone (PTH), which is excessively secreted from one or more parathyroid glands. Classical disease is nowadays only seldom seen due to widespread biochemical screening. Most patients are asymptomatic and have more subtle, but clinically important skeletal and renal involvement. A normocalcaemic variant of the disease with high PTH levels and persistently normal serum calcium values is sometimes diagnosed during the evaluation of osteoporosis. Parathyroidectomy is the only curative option and the procedure of choice for all patients with symptomatic PHPT. Guidelines for surgery in asymptomatic disease include age <50 years, increased serum calcium >0.25 mmol/l (1 mg/dl) above upper limit of normal, reduced bone mineral density (BMD) by DXA to a T-score of <-2.5 S.D. at any site and/or a vertebral fracture by imaging, creatinine clearance <60 ml/min, kidney stone or nephrocalcinosis by imaging, hypercalciuria >400 mg/day accompanied by biochemical stone risk profile placing patient at risk of kidney stones. Patients who do not meet surgical criteria or those who decline surgery should be monitored for signs of disease progression. If surgery is not an option, pharmacological approaches are available and effective. Medical management starts with correction of dietary calcium and vitamin D insufficiency. Cinacalcet is a calcimimetic agent that effectively reduces calcium levels, but does not appear to have any effect on BMD. On the other hand, alendronate improves BMD without any changes in the serum calcium. Less data is available for other bisphosphonates and denosumab. Recently, thiazides have re-emerged as a potentially effective and safe option for controlling hypercalciuria in selected patients with PHPT, but careful monitoring for hypercalcemia is required.

DOI: 10.1530/endoabs.63.MTE6

MTE7

Non functional pituitary tumours - not always easy

Davide Carvalho
Portugal.

Tumours of the pituitary gland and sellar region represent approximately 15% of all brain tumours. The most common tumours are by far pituitary adenomas, confined to the sella. However, several types of tumours may involve the sellar region, reflecting its complex anatomy. The differential diagnosis of nonpituitary sellar masses is broad and includes inflammatory and infectious diseases, cell rest tumours, germ cell tumours, lipomas, gliomas, meningiomas, metastatic tumours, and vascular lesions. Nonadenomatous sellar lesions do not present with any hypersecretory syndrome but rather with neurologic or hypopituitary symptoms as a result of the mass-effect mechanism. Neurologic symptoms include headache, visual disturbance, cranial neuropathy, hydrocephalus, and mental changes. Hypopituitarism most often is characterized by growth hormone deficiency and gonadal dysfunction, followed by secondary hypothyroidism and adrenal insufficiency. Hyperprolactinemia secondary to stalk compression is a common cause of hypogonadism. Diabetes insipidus is highly suggestive of nonadenomatous sellar lesions, especially in sarcoidosis and in metastatic sellar involvement. For most of these tumours, surgery is first choice intervention. Resolution of headaches and amelioration of visual field defects occur shortly after surgery in the majority of patients. The recovery of visual fields is progressive, with an early fast phase of improvement during the first week after surgery, an early slow phase (4–6 months postoperatively) by the end of which most of the eventual recovery takes place and a late phase (up to 3–5 years) in which mild further improvement may still occur. Regarding pituitary function, in most but not all series, normalization of one or more hypothalamo-pituitary-axis function has been reported after surgery, whereas worsening of pituitary function is less common. The degree of improvement is variable. Patients in whom tumour has been completely excised usually are follow-up in an expectant way. In contrast, the best management of patients in whom residual tumour is detected on postoperative MRI is controversial, and may include surgery, radiotherapy, and medical therapy namely the use of dopamine agonists.

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MTE8

Comorbidities in Turner syndrome

Claus H. Gravholt
Denmark.

Treatment with growth hormone (GH) during childhood and adolescence allows a considerable gain in adult height. SHOX deficiency explains some of the phenotypic characteristics in TS, principally short stature. Puberty has to be induced in most cases, and female sex hormone replacement therapy should continue during adult years. These issues are normally dealt with by the paediatrician, but once a TS female enters adulthood it is less clear who should be the primary care giver. The proper dose of hormone replacement therapy (HRT) with female sex steroids has not been established, and, likewise, benefits and/or drawbacks from HRT have not been thoroughly evaluated. In most countries it seems that the transition period from paediatric to adult care is especially vulnerable and the proper framework for transition has not been established. Likewise, no framework is in place for continuous follow-up during adult years in many countries. During the transition period many young females opt out of longitudinal follow-up, probably because they feel well and cannot clearly see the need for continued medical surveillance, which has to be thoroughly and well explained to patients. However, osteoporosis, diabetes, both type 1 and 2, hypothyroidism, obesity and a host of other endocrinological diseases and conditions are seen more frequently in Turner syndrome in the long term. Prevention, intervention and proper treatment is only just being recognized. Hypertension is frequent and can be a forerunner of cardiovascular disease. The description of adult life with Turner syndrome has been broadened and medical, social and psychological aspects are being added at a compelling pace. With the new international guideline for TS a proposed setup for management is presented. In summary, Turner syndrome is a condition associated with a number of diseases and conditions which need the attention of a multi-disciplinary team both during childhood and adulthood.

DOI: 10.1530/endoabs.63.MTE8

MTE9

Co-morbidities in Klinefelter syndrome

Anne Skakkebæk
Denmark.

Klinefelter syndrome (47,XXY; KS) is still a diagnostic challenge. Many patients are misdiagnosed, or remain undiagnosed, and thereby prevention and treatment of associated comorbidities is often delayed. The presence of the additional X chromosome is associated with a number of health problems involving multiple organs and consequently are both morbidity and mortality significantly increased. The increased morbidity seen in KS is due to an increased risk of developing physical diseases such as diabetes, metabolic syndrome, obesity, cardiovascular disease, infections, osteoporosis, as well as psychiatric diseases. However, the degree of co-morbidity seen between KS patients display great heterogeneity. Recent studies in genetics indicate that global DNA methylation and RNA expression changes may play a central role for the phenotype. Recommendations for improving clinical practice, including neonatal KS screening programs, and a multidisciplinary approach to KS treatment will be discussed.

DOI: 10.1530/endoabs.63.MTE9

MTE10

NCAH and female reproduction

Melek Eda Ertorer
Turkey.

Nonclassical Congenital Adrenal Hyperplasia (NCAH) usually due to 21 Hydroxylase deficiency (21OHD) is an autosomal recessive disease, occurring in upto 1/200 of Caucasians and more often in certain ethnic groups. Common CYP21A2 mutations from most severe to mildest are; null, I2 splice, I172N, P30L, and V281L. Mutations leaving 20–70% of enzyme activity is responsible for NCAH, mostly caused by V281L mutation. About 25–50% of patients are homozygous or compound heterozygous for two mild (nonclassical) alleles. Remaining have one severe (classical) and one mild mutation. Carrier frequency for a severe CAH mutation is about 1/60, whereas mild mutations are detected ranging from 1/5 to 1/16 of the population. Thus, preconception counseling is very important for avoiding birth of classical CAH babies to NCAH mothers. Probability of a NCAH mother having an infant affected by classic CAH is about 1/480. Following confirmation with dynamic hormone testing, analysis for 21-hydroxylase gene can determine the underlying mutation and disease risk for the fetus. Male partner of a NCAH female carrying a severe mutation should also be genetically examined. There is an overlap between the stimulated serum 17OHP levels of heterozygotes for 21OHD and unaffected subjects. Although heterozygotes do not need medical treatment, they should have genetic counselling. In adults, first symptoms of NCAH are usually acne, hirsutism, oligo-menorrhea. Symptoms of a NCAH individual with one classic allele is more severe and 17OHP level is more elevated than the one with homozygous mild mutations. Infertility is the presenting symptom in only 13%. Glucocorticoid (GC) therapy is the treatment of choice for hyperandrogenism and infertility. It usually takes about three months for the reversal of complaints. This treatment also seems to shorten the time to conceive and reduce miscarriage rates. Ovulation induction with clomiphene citrate or aromatase inhibitors can be performed for selected NCAH females.

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MTE11

'Shifting treatment paradigms in osteoporosis'

Núria Guañanens
Spain.

In recent years a number of paradigms have changed the way we go about therapy and its monitoring. So, what has changed? Bisphosphonates were until recently the cornerstone of osteoporosis treatment, but in the last few years new drugs and treatment concepts have appeared. Thus, anabolics such as teriparatide are established as the gold standard in patients with high risk of vertebral fractures. In addition, monoclonal antibodies against bone turnover regulators such as denosumab have found their place in the osteoporosis scope. Furthermore, the new drug almost on the market: romosozumab, is another monoclonal antibody, inhibitor of sclerostin, which is proving to be a potent anabolic drug in major trials. New drugs with prolonged anabolic effects are needed. But, from my point of view the main paradigm change is how to figure out all the different kinds of

sequential treatment. We know now that after an anabolic agent a potent antiresorptive treatment must be started and in a concise way; a next immediate medication should be planned after denosumab and romosozumab discontinuation. The last paradigm shift is how bone turnover markers are gaining momentum in monitoring, in addition to bone mineral density and bone fracture outcomes. To conclude, with these new concepts we should be open-minded about both new therapies and monitoring strategies.

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MTE12

Fracture risk prediction in benign and tumoral bone: new insights

Cyrille Confavreux
France.

Among the different functions of bone, the biomechanical one is the most evident. Biomechanical function of bone allows locomotion and protection of essential organs like brain and in a way can be considered as a survival function. Optimal bone strength maintenance through bone remodeling is an active energy consuming process. When a fracture occurs, two sides of the phenomenon should be evaluated: the trauma and the bone resistance including bone mass and bone quality. Bone resistance impairment leads to fragility fractures which is source of pain, local complications, disability, surgery and excess mortality. Performing a diagnostic assessment to understand origin of bone resistance impairment is the first key step for the physician. Etiologies are numerous including osteoporosis, osteomalacia, bone metastases, chronic kidney diseases, genetic disorders, endocrine diseases such as hyperparathyroidism. The second key step is fracture risk evaluation to advise patients on bone targeted treatments and lifestyle. The available tools are not the same in a benign bone fragility context and in bone metastases. In benign bone fragility, physicians will use bone densitometry (DXA), clinical risk factors, FRAX® score tool, TBS, or bone remodeling markers. Some device like HR-pQCT, MRI and qCT may also be useful. For bone metastases, some scores like the Mirels, the SINS, or the Tokuashi's scores, have been developed. These scores have limitations and we will point out the difficulty to assess fracture risk and the need for new tools.

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MTE13

Flushing, blushing and sweating

Pierre Bouloux
UK.

Abstract Unavailable.

MTE14

How multidisciplinay care and tailor-made transition save lives of young adults with Prader-Willi syndrome

Laura de Graaff
The Netherlands.

Introduction
Due to improved pediatric care, life expectancy of children with complex genetic syndromes (CGS) is increasing. Many children with CGS now do reach adult age and have to make the transition to adult endocrine healthcare. However, many adult endocrinologists are not yet prepared for the increasing number of adults with CGS. Although patients receive multidisciplinary (MD) care at the pediatric department, MD care is not yet available for most adults with CGS. Also, for most of the CGS, little is known about the manifestations at adult age as patients used to die before reaching adult age. As the number of CGS adults is rapidly increasing, it is important to know which medical problems we can expect and how we should treat them.
Methods
We have launched a MD outpatient clinic (OPC) for adults with rare CGS with (suspected) internal/endocrine problems. We perform thorough medical screening in all patients in order to detect and treat undetected health problems. We routinely collect clinical data to get an overview of the health problems at adult age, which are yet unknown for most CGS.
Results
In the first three years since start of the MD OPC, we have helped over 520 new CGS patients, of which 124 have Prader-Willi syndrome (PWS). We found a striking number of undetected and untreated health problems, like hypogonadism, osteoporosis, diabetes mellitus, hypothyroidism, obesity and cardiovascular disease.
Conclusion
Adults with CGS often have endocrine disorders as part of their syndrome, and therefore adult endocrinologists should know at least the basics of each syndrome. PWS is one of the CGS in which comorbidity often goes undetected due to atypical presentation of health problems. Undetected endocrine and cardiovascular problems can lead to significant morbidity and mortality. Knowledge of PWS can prevent painful and expensive complications.

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MTE15

To what degree does hypopituitarism exist after TBI?

Marianne Klose
Denmark.

Abstract Unavailable.

MTE16

Is it all in your head or just in the lab?

Julio Abucham[1] & Martin Bidlingmaier[2]
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Abstract Unavailable.

EYIJC1

The metabolic effects of SGLT2 inhibitors – Does the increase in ketone bodies protect the heart?

Esben Søndergaard

Type 2 diabetes causes excess cardiovascular mortality and microvascular disease. Therefore, the results of the EMPA-REG OUTCOME trial were received with great excitement, since this was the first trial with cardiovascular end points to show a benefit for persons suffering from type 2 diabetes. The striking benefit of a 38% reduction in cardiovascular mortality during SGLT2 inhibitor treatment was surprising and exceeded what was expected based on the relatively modest reductions in glycemic levels, blood pressure and body weight observed in the trial. Therefore, alternative explanations for the cardioprotective effects are sought. It has been suggested that the increase in circulating ketone bodies, observed during SGLT2 inhibitor treatment, could mediate these effects by acting as a superfuel for the heart. This remains controversial since experimental evidence regarding the metabolic effects of SGLT2 inhibitor treatment is limited, however, we have recently demonstrated a striking effect with a 50% reduction in glucose uptake during ketone infusion. In our ongoing study, we continue to investigate the hypothesis, that the increase in circulating ketone bodies will reduce oxygen consumption and improve the efficiency of the heart by increasing ketone body oxidation at the expense of FFA and glucose oxidation. We are doing this in a randomized, placebo-controlled crossover study in persons with type 2 diabetes. Using a novel combination of PET tracer techniques, we measure oxygen consumption, energy efficiency, and FFA and glucose oxidation in the heart. Uniquely, this allows previously inaccessible in-vivo measurement of cardiac substrate metabolism. The results of the study will provide new important mechanistic insight into the role of ketone bodies in the cardioprotective effects of SGLT2 inhibitors. A beneficial effect of an increase in ketone bodies could lead to development of targeted treatment to promote ketogenesis in people suffering from type 2 diabetes or ischemic heart disease.

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Meet the Basic Scientist Session

MTBS1

New tracers for PET in humans: Hopes, aims and current evidence

Lars Christian Gormsen
Denmark.

Positron emission tomography (PET) using the glucose analog tracer fluoro-deoxy-glucose (FDG) is today a widely available and highly useful functional imaging modality. Thus, FDG-PET has proved its clinical worth in particularly malignancy detection and treatment monitoring and is now often a first-line choice in the diagnostics of a range of diseases. However, PET is also an excellent tool for non-invasive measurement of metabolic processes, pathophysiology and pharmacokinetics, since virtually any molecule, drug or metabolite can be labeled with a PET-isotope. Simultaneous measurement of tracer input coupled with detection of tracer buildup in various organs or tissues of interests allows for accurate tracer kinetics and therefore also of tracer transfer between tissue compartments. In this talk, I will cover the basic set-up of metabolic PET as it is practiced in a tertiary university unit. Different approaches to basic research questions as well as some basic kinetic models will be presented with examples drawn from our own experience coupled with recent interesting studies from other centres. Finally, the use of PET to image tissue ketone body utilization (by 11C-hydroxybutyrate), peripheral organ damage in early Parkinsons disease (by 11C-Donepezil), drug pharmacokinetics (by 11C-metformin) and cholinergic signaling in inflammation (by 18F-FEOBV) will be presented. Combined, these examples will highlight the use of PET as a tool to image not only whether tissue is metabolically active (traditional FDG PET) but also as a biomarker suited for precision medicine.

DOI: 10.1530/endoabs.63.MTBS1

MTBS2

Genetically tailored pig models in translational endocrine and metabolic research

Eckhard Wolf
Germany.

The pig is an interesting model species for translational endocrine and metabolic research. Many organ systems relevant for endocrine research, including pancreas and gastrointestinal tract, are more similar to the corresponding human organs than those of other species. The human-like size and weight of pigs allows direct transfer of medical products, surgical techniques and *in vivo* imaging techniques to applications in human patients. Moreover, metabolic tests, such as glucose tolerance tests, can be performed with frequent blood sampling of volumes sufficient for a broad spectrum of clinical-chemical, metabolomic and other analyses. Due to the establishment of efficient and precise techniques for genetic modification of pigs, it is possible to generate tailored pig models, which resemble human disease mechanisms on a molecular and functional level. To mimic the markedly reduced insulinotropic action of glucose-dependent insulinotropic polypeptide (GIP) in type 2 diabetic patients, we generated transgenic pigs expressing a dominant-negative GIP receptor ($GIPR^{dn}$) in the pancreatic islets. $GIPR^{dn}$ transgenic pigs exhibit an impaired incretin effect due to a blunted insulinotropic action of GIP, a progressive deterioration of glucose control due to delayed and – at later stages – quantitatively reduced insulin secretion, and an impairment of physiological age-related expansion of beta-cell volume. $GIPR^{dn}$ transgenic pigs provide a unique opportunity to screen for biomarker candidates during the pre-diabetic period and to test therapeutic strategies targeting the glucagon-like peptide 1 (GLP1) receptor. In addition, we generated transgenic pigs expressing INS^{C94Y} as a model for mutant *INS* gene-induced diabetes of youth (MIDY). MIDY pigs show early-onset clinical diabetes mellitus, markedly reduced body weight gain and beta-cell volume associated with a marked reduction of insulin secretory granules and severe dilation of the endoplasmic reticulum in the beta cells. MIDY pigs can be used for insulin treatment studies or for testing the efficacy of gene or cell therapies as well as islet transplantation. Secondary lesions of diabetes mellitus are another interesting area of research. We thus established the Munich MIDY pig biobank as a unique resource for studying systemic consequences of chronic insulin deficiency and hyperglycaemia. A multi-omics analysis (transcriptome, proteome, metabolome, lipidome) of liver samples revealed increased activity in gluconeogenesis, ketogenesis, amino acid metabolism and oxidation of fatty acids in the MIDY samples, whereas pathways related to extracellular matrix and inflammation/pathogen defence response were less active than in wild-type samples. The multi-omics data set provides a valuable resource for comparisons with other experimental or clinical data sets.

DOI: 10.1530/endoabs.63.MTBS2

MTBS3

The gravitostat – possible relation to hormones

John-Olov Jansson
Sweden.

There are several regulatory systems the body that keep body functions, like body temperature and blood glucose, constant. In this study we have added and removed weight loads from experimental animals and measured the effects on biological body weight. The results of these experiments indicate that there is a novel regulatory mechanism to keep the body weight constant, mostly by adjusting the body fat mass. The mechanism was dependent on intact bone cells. We hypothesize that there is a sensor for body weight in the long bones of the lower extremities acting as 'body scales'. This is part of regulatory system, a gravitostat, that keeps body weight and body fat mass constant. Later findings demonstrate that the gravitostat regulates fat mass in obese mice while leptin regulates fat mass only in lean mice with low endogenous serum leptin levels. We propose that activation of the gravitostat primarily protects against obesity while low levels of leptin protects against undernutrition.

DOI: 10.1530/endoabs.63.MTBS3

Nurse Session

NS1.1

Overview of immunotherapy: Indications and adverse effects

Christelle de la Fouchardière
France.

Abstract Unavailable.

NS1.2

Immunotherapy-induced Endocrinopathies: Assessment, management and monitoring

Daniel Morganstein
UK.

Checkpoint Inhibitors have emerges as a major breakthrough in cancer therapy. Side effects are largely immune mediated, termed immune related adverse events. Whilst the majority of these respond to immunosuppressive treatment, most frequently glucocorticoids, endocrinopathies are amongst the more frequent adverse events, and usually lead to permanent hormone deficiency, requiring life long hormone replacement. There are differences in the pattern of endocrinopathy between different checkpoint inhibitors. The CTLA-4 inhibitor ipilimumab results in hypophysitis in up to 20% of individuals, usually resulting in multiple anterior pituitary deficiencies, whilst thyroid changes are often mild and sub-clinical. In contrast the PD-1 and PD-L1 inhibitors cause both a destructive thyroiditis with a transient thyrotoxic phase, often progressing to hypothyroidism, or *de novo* hypothyroidism. They are also associated less frequently with isolated ACTH deficiency and insulin requiring diabetes closely resembling type 1 diabetes. The non-specific symptoms of many endocrine disorders, coupled with the frequency of symptoms in patients with advanced cancer and other immune related adverse events means a high index of suspicion for the development of endocrine adverse events is required, aided by an understanding of the pattern of expected adverse events for each agent. Although initial management closely resembles that of more common endocrine dysfunction, the longer term outcomes and likelihood of recovery of hormone function are currently unknown. In addition, around a third of patients receiving checkpoint inhibitors require high dose steroids for management of non-endocrine toxicity, with a significant incidence of steroid induced hyperglycaemia and adrenal suppression, both of which may require the input of the endocrine team.

DOI: 10.1530/endoabs.63.NS1.2

NS1.3

The role of the endocrine nurse in managing patients with immunotherapy-induced endocrinopathies

Sherwin Criseno
UK.

Abstract Unavailable.

MTNE1

Nursing approach to the holistic care of patients with intellectual disability

Ruth Northway
UK.

People with intellectual disabilities are known to face many inequalities in healthcare that lead to poor health as well as premature and preventable death. They often experience multiple comorbidities, often at a younger age than the wider population, and often these include endocrine disorders. However, many of the barriers they face to accessing timely and appropriate health care are preventable and/or their impact can be reduced. This presentation aims to highlight both the nature of these barriers and the strategies that nurses can use to overcome them. First the presentation will consider the wide range of ability and disability encompassed in the term 'intellectual disability'. It will draw upon relevant literature to identify the prevalence of common endocrine disorders in people with intellectual disabilities. The barriers that may exist to identification of such disorders will also be explored. Literature, personal experience and personal research will be used to discuss the physical, cognitive, communication, economic, ethical, organisational and intrapersonal barriers that may impact upon access to healthcare for people with intellectual disabilities who have endocrine disorders. Strategies that can be used by nurses to facilitate holistic person centred care will be considered and the concept of reasonable adjustments to care will be introduced. In particular the implications for self-management (or supported self-management) of long term conditions will be explored. It will be concluded that nurses working in partnership with others can do much to promote holistic person centred care for people with intellectual disabilities and hence reduce the health inequalities they so often experience. However, this has implications for the development of nurse education and practice and such developments need to be underpinned by a robust evidence base. Potential future developments will thus be proposed.

DOI: 10.1530/endoabs.63.MTNE1

NPD1

Update from the ESE nurses working group, future projects and presentation of poster awards

Sofia Llahana

Abstract Unavailable.

NPD2

Testosterone replacement: 'The best practice'

A Hawkins, E Casey & K Nikookam
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Testosterone deficiency syndrome (TDS) may well contribute to a number of co morbidities and multitude of symptoms which may affect one's daily activities adversely. TDS prevalence in UK is 1:500 and certain groups of patient's are at higher risk of TDS, in particular elderly and patients with diabetes mellitus where 42% are known to have TDS. A retrospective audit was carried out to bench mark our practice in line with a publication of a recommended National/European guidelines of 'A practical guide for the management of men with suspected testosterone deficiency'. We obtained and analysed the medical records of 35 patients who attended our endocrine services over a 6 month period. 31 of them had already been started on testosterone from the year before. Seven patients were excluded due to lack of data availability. The age in our cohort ranged from 31 to 72 years with a mean age being 53 years. Initial testosterone and PSA results ranged between 0.4 nmol/l to 9.4 nmol/l (normal 8.4–28.7 nmol/l) with mean of 5.9 nmol/l and 0.1 ug/l to 2.1 ug/l (normal 0–3.0 ug/l) with a mean of 0.7 ug/l respectively. We found, the time lapse between initial blood results and testosterone initiation where from 1 to 18 months, with a mean of 7 months. The guidelines suggests; prior to testosterone initiation PSA and a rectal examination (PR) should be carried out. Within our patient group only 5/28 (18%) had a PR, 21/28 (75%) had PSA,16/28 (57%) had USS of prostate and 16/28 (57%) of our patients have had neither a PR nor an USS. 18/28 (64%)of the patients who had been started on testosterone were on Nebido 1 g injection, 15 of whom had this administered by their GP, the other 3 by the hospital Endocrine Specialist Nurse (ESN). The 3 ESN treated patients had an ultra sound scan (USS) before commencing treatment. Recommended on-going monitoring of 3 to 6 monthly intervals in the first year was achieved on 23/25 (92%) of our patients.

Conclusion

We recommend a dedicated andrology service and a shared care pathway with community colleagues to ensure all patients have received the best possible care by means of investigations, treatment and follow up care in line with National/European guidelines.

DOI: 10.1530/endoabs.63.NPD2

NPD2.1

Hypoparathyroidism: Aetiology, diagnosis and challenges in management

Ansgar Heck

Hypoparathyroidism is an endocrine disease resulting in hypocalcemia due to inappropriately low circulating parathyroid hormone levels. It is defined as an orphan disease by the European Commission, and commonly managed by endocrinologists and endocrine units. All healthcare personnel involved in the management of patients with chronic hypoparathyroidism should have knowledge about symptoms, treatment and potential complications.

Causes

In adults, hypoparathyroidism most commonly is an acquired condition due to neck surgery or autoimmunity. Idiopathic or autoimmune hypoparathyroidism can occur isolated or in a setting of other associated autoimmune endocrinopathies. In children, adolescents and young adults, underlying genetic conditions have to be considered.

Symptoms

Acute symptoms of hypoparathyroidism are caused by decreasing and low circulating levels of calcium. Patients with rapidly changing calcium levels have more severe symptoms than patients with gradually decreasing levels. In the latter, symptoms can be surprisingly few and weak despite low calcium levels. Common and early neuromuscular symptoms of hypocalcaemia are numbness, tingling and muscle spasm in hands, feet and face. Many patients report muscle stiffness and cramps, slow thinking, lack of concentration and initiative, often described as 'brain fog'. Severe hypocalcaemia can result in life threatening symptoms as tetany, seizures, larynx spasms and ventricular arrhythmias. In patients with chronic hypoparathyroidism, it is important to have basic knowledge about symptoms and treatment of hypercalcemia as overtreatment frequently occurs. Symptoms of hypercalcemia include: nausea, anorexia, constipation, polyuria, dehydration, bradycardia, muscle weakness, confusion and coma.

Treatment and management

As primary treatment, activated vitamin D analogues (calcitriol and alfacalcidiol) plus calcium supplements in divided doses are recommended. Treatment should aim serum calcium levels in the low normal range and serum phosphate within the normal range. A high intake of Calcium supplements (>1000 mg/day) should be avoided. Sufficient dietary intake or supplement of magnesium and conventional vitamin D (cholecalciferol or ergocalciferol), and a phosphate low diet may result in more stable serum calcium levels and lower risk for long term complications. Recently, a synthetic PTH-analogue has become commercially available. This replacement therapy may improve treatment. But so far, this treatment is costly and there is only limited documentation of improved outcomes. The lecture will focus on a patient orientated, team based approach in the management of chronic endocrine conditions as hypoparathyroidism. Team based endocrine care should include assessment of symptoms, eventually aided by disease specific questionnaires, patient education, nutritional advice and follow up of compliance of pharmacologic treatment.

DOI: 10.1530/endoabs.63.NPD2.1

NPD3

How to use the Textbook in Advanced Endocrine Nursing and Competency Framework to develop your clinical practice (Adrenal Insufficiency)

Abstract Unavailable.

NPD4

MY DIABBY - Improving skills and competence in diabetes education

Abstract Unavailable.

NPD5

How to use the textbook in advanced endocrine nursing and competency framework to develop your clinical practice (Acromegaly)

Abstract Unavailable.

Uems Session

UEMS1.1

The role of UEMS in Europe and the distinct and independent but allied pathway with ESE

Maeve Durkan
Republic of Ireland.

Abstract Unavailable.

UEMS1.2

Update on European exam in endocrinology

Graham Roberts
Republic of Ireland.

Abstract Unavailable.

UEMS1.3

The microenvironment of pituitary neuroendocrine tumors: focus on folliculostellate cells

Mirela Diana Ilie
France.

The tumor microenvironment can comprise more than 50% of the tumor mass and includes resident and infiltrative non-tumor cells, as well as extracellular matrix proteins, signaling molecules, and blood and lymph vessels (Balkwill et al., 2012). In recent years, the tumor microenvironment has begun to be considered both a prognostic tool and a therapeutic target (Hui and Chen, 2015). While the existence of the tumor microenvironment is well accepted and described in numerous cancers, little is known about the tumor microenvironement of pituitary neuroendocrine tumors. Even less is known about the folliculostellate cells in the context of the microenvironment of pituitary neuroendocrine tumors. Folliculostellate cells are resident cells of the normal anterior pituitary, comprising 5–10% of the normal anterior pituitary. Beside the role folliculostellate cells have in the normal anterior pituitary, their identification in pituitary neuroendocrine tumors suggests they may also have a major implication in these tumors. Therefore, better characterization of pituitary neuroendocrine tumor-associated folliculostellate cells and understanding of their contribution and their functional interactions with tumor cells and tumor-associated stroma may provide important indications regarding the mechanisms that drive tumorigenesis-associated processes such as immune escape, proliferation, local invasion, dedifferentiation, and ultimately tumor aggressiveness. The research project in which I was involved during the fellowship aimed at better characterizing folliculostellate cells within pituitary neuroendocrine tumors, and it involved a combined exploration of their histological characteristics and of their cellular properties.

DOI: 10.1530/endoabs.63.UEMS1.3

Oral Communications

Calcium and Bone

OC1.1

Genetic testing for hereditary hyperparathyroidism in a large UK cohort

Sashi Mariathasan, Katrina Andrews, Edward Thompson, Ruth Armstrong, Soo-Mi Park & Ruth Casey
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Primary hyperparathyroidism (PHPTH) is a common endocrine disorder and it is estimated that 10% of cases are hereditary, related to syndromes including; multiple endocrine neoplasia (MEN) type 1, MEN type 4, MEN2A and hereditary hyperparathyroidism jaw tumour syndrome. Further hereditary cases can occur in the absence of syndromic features such as familial hypercalcemia hypocalcuria. Identifying cases of hereditary PHPTH enables a personalised medicine approach. Current guidelines recommend that genetic testing is considered for patients i) presenting with PHPTH <40 years of age, ii) with multi-glandular/ recurrent disease, iii) with a personal or family history suggestive of an endocrine neoplasia syndrome or iv) a family history of PHPTH.

Aims and methods

A retrospective review of patients referred for genetic testing for suspected hereditary HPTH over a 4 year period at Cambridge University Hospital NHS Foundation Trust was performed. Genetic analysis was performed by next generation sequencing of a gene panel including; *MEN1*, *RET*, *CDC73*, *CDKN1A*, *CDKN2B*, *CDKN2C*, *CaSR*, *AP2S1*, *GNA11*. Aims of this study were to better define testing criteria for suspected hereditary PHPTH in a UK cohort.

Results

75 patients were included in this study (54 female) with a mean age of 40 (SD 16.4). A pathogenic germline variant was identified in 17.3% ($n=13$) and a variant of uncertain significance was identified in 5 patients (6.7%). A pathogenic variant was identified in *CDC73* in a single patient, *MEN1* in 3, *CaSR* in 8 patients and *AP2S1* in a single paediatric case. Five of the eight patients with a *CaSR* mutation had a calcium creatinine ratio (CaCrR) <0.01 and there was a significant difference in the mean CaCrR in those patients with an identified *CaSR* mutation versus those without ($P=0.0078$). Age at diagnosis, histology showing hyperplasia and gender were not predictive of a pathogenic germline variant ($P=0.28$) ($P=0.57$) and ($P=0.31$) but a positive family history was ($P=6.4e-05$). 20 patients were $>$ 50 years of age and the diagnostic rate of a pathogenic variant was 10% in those patients $>$ 50 years compared to 19% in those $<$ 50 years. Two patients $>$ 50 years were diagnosed with a pathogenic variant in *MEN1* and *CaSR* but both patients had at least one risk factor for genetic testing. Family history was a strong predictor of hereditary PHPTH in this cohort. Pathogenic variants can be identified in older patients particularly those with additional risk factors. Such patients should therefore should be considered for genetic testing.

DOI: 10.1530/endoabs.63.OC1.1

OC1.2

Urinary magnesium as predictor of nephrolithiasis in patients with asymptomatic primary hyperparathyroidism

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The 4th International Workshop for the management of asymptomatic PHPT included the presence of hypercalciuria (dUCa$>$ 400 mg/day) and increased stone risk by biochemical stone risk profile as criteria for surgery. Our aim was to evaluate the complete stone risk profile in 176 consecutive patients with asymptomatic PHPT. We recorded clinical and biochemical data, including 24 hours urinary measurements of the following parameters: volume and pH, creatinine, calcium, magnesium, sodium, potassium, ammonium, uric acid, oxalate, citrate, phosphate, inorganic sulphate and chloride and kidney ultrasound. In our cohort dUCa$>$400 mg/day showed a low sensitivity and positive predictive value (PPV) for nephrolithiasis with high specificity (46.2, 32.7, 73.0% respectively), while hypercalciuria by 4 mg/kg/bw (d-UCa$>$ 4 mg/kg) had a high sensibility, with low PPV and specificity (79.5, 27.7, 40.1%). Daily hypomagnesuria (d-HypoMg), but not any other urinary parameter, was an independent predictor of nephrolithiasis in the univariate (OR 2.97 CI 1.27–7.09 $P=0.014$) and multivariate analyses adjusting for age, sex, BMI, and eGFR (OR 3.13 CI 1.17–8.42 $P=0.02$). In the regression analyses with urinary calcium d-HypoMg was relatively lower in patients with nephrolithiasis compared with those without. The mean ratio between (dUCa) and (dUMg) was higher in patents with nephrolithiasis compared with those without (4.6 ± 2.0 vs 3.3 ± 4.1; $P<0.001$). In the univariate and multivariate analyses the dUCa/dUMg ratio was a significant predictor of nephrolithiasis [OR 4.9 (2.3–10.5); $P<0.001$; OR 5.3 (2.4–11.6), $P<0.001$, respectively]. The AUC using the dUCa/dUMg ratio as variables was 0.69 (CI 0.60–0.79; $P<0.0001$). The best cut-off value, set at the highest Youden index, was equal to 4.0, with a sensitivity of 59.0% and a specificity of 77.4%. In patients with hypercalciuria ($>$400 mg/24-hour) dUMg was positively correlated with dUCa in those without nephrolithiasis ($r=0.50$, $\beta=0.2$, $P=0.002$) but not in those with nephrolithiasis ($r=0.05$, $\beta=0.014$; $P=0.8$). In patients without hypercalciuria we found that hypomagnesuria remained a predictor of nephrolithiasis using either 400 mg/die ($P=0.002$, OR 5.12 (1.84–14.24) or 4 mg/kg bw ($P=0.014$, OR 6.24 (1.45–26.8). Moreover, the OR for nephrolithiasis improved using the combination of d-HypoMg with d-UCa$>$4 mg/kg (OR 8.12, CI 1.92–34.18, $P=0.004$), but not with dUCa$>$ 400 mg/day. The current urinary calcium threshold of $>$400 mg/24-hour has a low sensitivity in detecting nephrolithiasis; our data suggest that sensitivity, specificity and positive predictive value could be improved including dUMg, dUCa/dUMg ratio and the combination of d-HypoMg with d-UCa$>$4 mg/kg in the stone risk evaluation.

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OC1.3

Menin and EZH2 activities modulate the expression of the long non-coding RNA *HAR1B* in parathyroid tumors

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Epigenetic deregulation is emerging as a component of the parathyroid tumorigenesis. We identified a long non-coding RNA (LNCRNA) signature clearly distinguishing parathyroid adenomas (PAds) and carcinomas from normal glands. Among the deregulated LncRNAS, *HAR1B* was upregulated in PAds harboring the common chromosome 11q loss of heterozygosity (Chr11q-LOH; $n=10$) compared with PAds harboring normal chromosome 11 haplotype (Chr11q-WT; $n=12$; $P<0.0001$), suggesting its involvement in Chr11q LOH-related parathyroid tumorigenesis. Considering the oncosuppressor *MEN1* mapping on Chr11q, transient silencing of the *MEN1* gene expression in PAds-derived cells ($n=5$) increased *HAR1B* expression levels. We tested the hypothesis that other genes mapping on Chr11q may be involved in *HAR1B* modulation: *EED* and *DPF2* genes, whose proteins are components of the polycomb repressive complex 2 (PRC2) and BAF complex, respectively, map on Chr11q. Interestingly, the *MEN1* product menin is known to cooperate with EZH2, the PRC2-methyltransferase, to repress a number of genes, and the *HAR1B* promoter is predicted to be regulated by EZH2. We investigated the role of EZH2 activity in this context: treatment with Tazemetostat, a selective inhibitor of EZH2 activity, increased the *HAR1B* expression levels in HEK293T cells. Notably, H3K27me3 protein levels, modulated by the EZH2 activity, were lower in Chr11q-LOH compared with Chr11q-WT PAds, and, analyzing the expression levels of the EZH2 target genes AXIN2, *CCND1* and *CDKN1A/p21* in the series of genotyped PAds, all transcripts significantly differed between Chr11q-LOH and Chr11q-WT PAds, suggesting the occurrence of reduced EZH2 activity in Chr11q-LOH PAds. Investigating the *HAR1B* functional role, we detected in HEK293T cells silenced for HAR1B, upregulation of *LEF1* and *WNT1* mRNA levels and a decrease in *CDKN2B*/p15 protein levels, while silencing of the *HAR1B* gene in PAds-derived cells ($n=3$) did not induce significant changes in the expression of the parathyroid specific genes *CASR, VDR* and GCM2, though a trend in *PTH* transcripts increase could be observed. Further experiments to investigate the function of *HAR1B* are ongoing. In conclusions, *HAR1B* emerges as a new candidate gene in Chr11q-LOH-related parathyroid tumorigenesis, likely as consequence of reduced menin and EZH2 repressive activity. Our data suggest a new function of menin as modulator of the LncRNAs expression.

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OC1.4

Risk of sepsis, respiratory infections, and kidney or other genitourinary (GU) infections in patients with chronic hypoparathyroidism (HypoPT): a retrospective cohort study

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Background

Prior small studies have suggested increased risk of infections in patients with hypoparathyroidism (HypoPT). This study using a large managed care cohort evaluated whether chronic HypoPT is associated with increased risk of sepsis, respiratory infections, and kidney or other genitourinary (GU) infections.

Methods

A retrospective cohort study using a US commercial claims database (Q1 2007–Q2 2017) was conducted to examine the association between chronic HypoPT and the risk of each infection category (sepsis, respiratory, and kidney or other GU; all identified using diagnoses codes). The study cohort included chronic HypoPT patients (identified using diagnosis codes; excluding those receiving parathyroid hormone) and randomly selected non-HypoPT patients during 5 years of follow-up. For HypoPT patients, the first date of follow-up (i.e., index date) was the earliest HypoPT diagnosis date $\geq$6 months after the initial HypoPT diagnosis (to establish chronic HypoPT); for non-HypoPT patients, it was the date of a randomly selected medical claim. Patient characteristics at baseline (the 6 months prior to index date) and risk of each infection category were compared between cohorts. The risk of each infection category was assessed among patients free of the infection category during the baseline period using Kaplan-Meier analysis and Cox proportional hazards models adjusting for baseline demographic characteristics (age, sex, race, region, and index year).

Results

The study included 8097 chronic HypoPT patients and 40,485 non-HypoPT patients. At baseline, HypoPT patients were older than non-HypoPT patients (58.6 years vs. 47.3 years), a higher proportion were female (76.2% vs. 54.4%), and higher proportions had sepsis (1.4% vs. 0.8%), respiratory infections (20.6% vs. 16.6%), and kidney or other GU infections (10.8% vs. 5.9%) (all $P<0.001$). Kaplan-Meier analyses showed HypoPT patients had an increased risk of developing sepsis, respiratory infections, and kidney or other GU infections, as compared with non-HypoPT patients (all $P<0.001$). The adjusted hazard ratios (95% confidence intervals) associated with HypoPT versus non-HypoPT were 1.64 (1.42, 1.90) for sepsis, 1.20 (1.14, 1.25) for respiratory infections, and 1.41 (1.32, 1.50) for kidney or other GU infections (all $P<0.001$).

Conclusions

Chronic HypoPT was associated with increased risk of new occurrence of sepsis, respiratory infections, and kidney or other GU infections. Further research is warranted to understand the potential mechanisms for the relationship of chronic HypoPT and the observed risks of these infections.

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OC1.5

Renal function in 711 patients with hypoparathyroidism during more than 4 years of therapy

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Patients (pts) with hypoparathyroidism (HypoPT) are at risk to develop renal failure possibly caused by hypercalciuria and nephrocalcinosis. We retrospectively evaluated the data of 711 Patients with HypoPT in 3 endocrine centres in Germany.

Methods

Records of 711 pts with HypoPT were reviewed. Patients were predominantly female ($n=592$, male: $n=119$; age 50.9 ± 14.1 years, range 12 – 99 years). The following parameters were documented during treatment and follow-up (MW 52 ± 40.9 months, time range 2–334 months): medication, calcium in serum and urine, phosphate, calcium-phosphate-product (CPP), glomerular filtration rate (GFR) calculated by CKD-EPI formula.

Results

Of these 711 pts. 29 had idiopathic HypoPT, 10 HypoPT after parathyroidectomy, 669 after thyroid operation. At first visit 4.0% of pts <40 years, 11.1% in the age group 40–59, 28.4% in the age group 60–69, and 49.0% in pts >69 years had a GFR $<$ 60 ml/min. At the last visit no worsening of renal function was observed (GFR $<$ 60 ml/min in 5.9% <40 years, 9.8% in the age group 40–59, 17.1% in the age group 60–69, 36.0% >69 years). An elevated CPP $>$ 55 mg^2/dl^2 was found in 25 pts (3.5%). In these pts the proportion of GFR $<$ 60 ml/min was 33.5% compared to 21.1% of those with normal CPP. In comparison of the therapeutic strategies pts treated exclusively with dihydrotachysterol renal function was the lowest ($n=46$; mean GFR 70.2 ± 26.2 ml/min). In pts treated with calcitriol and calcium ($n=226$) mean GFR was better than in all other treatment groups (84.9 ± 20.9).

Conclusion

We saw no worsening of renal function in a large cohort of patients with HypoPT during 4 years of therapy. High CPP was associated with lower GFR. Different treatment strategies of HypoPT seem to affect kidney function.

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Diabetes 1

OC2.1

Every fifth patient with type 1 diabetes suffers from an additional endocrinological autoimmune disease – a finnish nationwide study

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Autoimmune diseases tend to coexist in the same subjects and are more often present in women than in men. Finland has the highest incidence of type 1 diabetes (TID). However, the coexistence of autoimmune diseases and excess risk compared to individuals without T1D in unknown. This study compares the proportion of autoimmune hypothyreosis and hyperthyreosis, Addison's disease and celiac disease in adults in Finland with and without T1D. The study included 4,758 patients with T1D from the Finnish Diabetic Nephropathy (FinnDiane) Study. For each patient with T1D, three nondiabetic control individuals, who were matched for sex, age, and place of residence in the year of diagnosis of diabetes in the FinnDiane patient, were selected from the Finnish Public Register Centre, altogether 12,710 controls. The autoimmune diseases were identified by linking the data with Finnish nationwide health registries such as the Finnish Care Register for Health Care (data available for the years 1970–2015), the Finnish National Drug Reimbursement Register (available for years 1965–2015) and the Drug Prescription Register (available for years 1993–2015). The median age of the FinnDiane patients at the end of follow-up in 2015 or at death was 51.4 (IQR 42.6–60.1) years. The most prevalent additional autoimmune disease was hypothyreosis, that was three times more common in patients with T1D compared to controls; 18.1% vs 6.0%. Hyperthyreosis was present in 2.4% of patients compared to 0.8% in controls resulting in a 2.9-times higher risk. Addison's disease was 24 times more common in patients with T1D; 0.38% vs 0.016%. The risk of celiac disease was 4.4 times higher in the patients; 4.4% vs 0.99%. Women had higher risk of all autoimmune diseases than men, i.e. 2.5 times higher risk of hypothyreosis, 2.8 times of hyperthyreosis, 2.2 times of Addison's disease and 1.5 times of celiac disease. 21.6% of patients with T1D had at least one additional autoimmune disease and 2.9% had two additional autoimmune diseases. Of the controls 7.3% had one, and 0.6% had two autoimmune diseases. The median age at diagnosis of hypothyreosis was lower in the patients with T1D, 41.0 (IQR 30.0–51.0) years, than in the controls, 48.0 (38.0–56.0) years ($P<0.0001$). This is the largest study quantifying the risk of coexisting autoimmune disease in adult individuals with T1D in Finland, the country with the highest incidence of T1D. Notably, these results highlight the importance of screening for other autoimmune diagnoses, if the patient presents with new symptoms.

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OC2.2

Elevated glucose uptake in skeletal muscle with increased sarcolemma translocation of GLUT4 and glycogen synthesis contributes to bariatric surgery mediated diabetes remission

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Background
Bariatric surgery can profoundly ameliorate hyperglycemia and improve insulin sensitivity thus contribute to diabetes remission. However the detailed mechanisms underlying this effect is yet to be revealed. The aim of this research is to investigate the metabolic alterations in skeletal muscle after bariatric surgery and explore the possible mechanisms to further explain the diabetes remission effect of bariatric surgery.
Methods
Duodenal-jejunal bypass (DJB) and sleeve gastrectomy (SG) were performed in diabetic rats induced by high fat diet and low dose of streptozotocin. Glucose uptake was evaluated in vivo by positron emission tomography (PET) with fluorine-18 labelled fluorodeoxyglucose. Insulin signaling pathway, glucose transporters GLUT1 and GLUT4, and translocation related molecules such as AS160, TBC1D1, Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) were evaluated in skeletal muscle. PAS stain and western blot of glycogen synthase (GS), phospho-GS, glucose synthase kinase β (GSK3β) and phospho-GSK3β were performed to evaluate the glycogen synthesis activity. We also preformed gas chromatography-mass spectrometry-based metabolomics to identify the altered metabolic pathways in skeletal muscle.
Results
PET scan showed remarkably increased glucose uptake in skeletal muscle in both DJB and SG groups. Though no difference was found in expression of total GLUT1 and GLUT4, the sarcolemma level of GLUT4 significantly increased in both DJB and SG group, combined with up-regulated phosphorylation of AMPK and AS160. PAS positive rate in DJB and SG group is significantly higher than that of SHAM group. Protein level of GS is also increased with a down-regulated phosphorylation of GS, followed with decreased level of glycogen synthase kinaseβ. Pathway analysis of metabolomics revealed alterations in several amino acid metabolism pathways, which are strongly related to enhanced GLUT4 translocation and improved glycogen synthesis.
Conclusion
DJB and SG facilitate glucose uptake in skeletal muscle with improved sarcolemma translocation of GLUT4 and enhanced activity of glycogen synthesis. This effect is probably due to altered amino acid metabolism.

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OC2.3

Identification of oxygen-18 isotope of breath carbon dioxide as a non-invasive marker to distinguish type 1 and type 2 diabetes

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Background
There is a pressing need to develop a new and an effective strategy for early detection of T1D and to precisely distinguish T1D from type 2 diabetes (T2D). The aim of the present study was to find out the potential link between the erythrocytes carbonic anhydrase (CA) activity and ^{18}O-isotopic exchange of breath CO_2 in T1D and T2D.
Methods
Fasting and post-dose breath and blood samples were collected simultaneously after ingestion of 75-gm normal glucose dissolved in 150-ml water. Blood samples were analysed to measure the CA activity. The breath samples were utilised to measure the carbon dioxide isotopes ($^{12}C^{16}O^{16}O$, $^{13}C^{16}O^{16}O$ and $^{12}C^{16}O^{18}O$) by a laser based high-precision carbon dioxide isotope analyzer.
Results
The CA activities are markedly altered during metabolism of T1D and T2D and this facilitates to oxygen-18 (^{18}O) isotopic fractionations of breath CO_2. In our observations, T1D exhibited considerable depletion of ^{18}O-isotopes of CO_2, whereas T2D manifested isotopic enrichments of ^{18}O in breath CO_2, thus unveiling a missing link of breath ^{18}O-isotopic fractionations in T1D and T2D. The optimal diagnostic cut-off points were determined to be $\delta^{18}_{DOB}O‰ = 2.1‰$ and $\Delta CA = 3.15$ U/min/mL for screening T1D and T2D individuals.
Conclusions
Our findings suggest the changes in erythrocytes CA activities may be the initial step of altered metabolism of T1D and T2D, and breath ^{18}O-isotope regulated by the CA activity is a potential diagnostic biomarker that can selectively and precisely distinguish T1D from T2D and thus may open a potential unifying strategy for treating these disease.

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OC2.4

Empagliflozin attenuates the progression of atherosclerosis in APO-E knockout mice

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Background
Sodium glucose co-transporter 2 inhibitors reduce the incidence of cardiovascular events in patients with type 2 diabetes mellitus based on the results of recent cardiovascular outcome studies. Herein, we investigated the effects of long-term treatment with empagliflozin on biochemical and immunohistochemical markers related to atherosclerosis development in apolipoprotein E knockout [Apo-$E^{(-/-)}$] mice.
Methods
At the age of 5 weeks, mice were switched from normal to high-fat diet. After 5 weeks, Apo-$E^{(-/-)}$ mice were divided into control-group ($n=10$) treated with 0.5% hydroxypropyl methylcellulose and Empa-group ($n=10$) treated with Empagliflozin (10 mg/kg/day) *per os*. After 10 weeks of intervention, animals were culled, and heart and aorta were removed. Sections stained with hematoxylin–eosin (H&E) were used for histomorphometry. Immunohistochemistry was performed to evaluate protein expression of MCP-1, CD68, α-SMA, MMP-2, MMP-9, TIMP-1, ICAM-1 and VCAM-1. mRNA expression of matrix metalloproteinases and their inhibitors, ICAM-1, VCAM-1, IL-6, MCP-1 was measured by q-PCR. Blood pressure, heart rate and biochemical indices were measured at the onset and by the end of the intervention in both groups.
Results
Empa-group mice had lower glucose levels and HDL-cholesterol ($P<0.01$), while totalcholesterol, LDL and triglycerides did not change significantly compared to control group. Diastolic blood pressure and heart rate were significantly lower ($P\leq0.01$ and $P<0.05$ respectively) in Empa-group compared to control-group. Histomorphometry of the aorta root revealed that 6 in 10 Empa-group mice versus 8 in 10 control mice developed atheromatosis. The lumen area was wider (approximately 50%) in Empa-group compared with control-group reaching statistical significance ($P=0.06$). Empagliflozin administration significantly reduced VCAM-1 and MCP-1 mRNA levels ($P<0.05$ and $P\leq0.01$ respectively) while marginally induced TIMP-1 and TIMP-2 mRNA expression ($P\leq0.08$ and $P=0.1$ respectively). There were no significant alterations in IL-6, ICAM-1, MMP-2 and MMP-9 mRNA levels compared to controls; however, TIMP-1/MMP-2 mRNA ratio was significantly higher in Empa-group ($P<0.05$) compared to control-group. Immunohistochemistry staining of aortic root sections revealed that treatment with Empagliflozin led to border line increase in TIMP-1 ($P=0.1$) and marginal reduction in VCAM-1 and MMP-9 ($P=0.1$) without affecting the expression of ICAM-1, MMP-2, TIMP-2, MCP-1, CD68 and α-SMA in atherosclerotic lesions.

Conclusions
Empagliflozin attenuates the progression of atherosclerosis, reducing (1) hyperglycemia, and (2) inflammatory process by lowering the expression of inflammatory molecule VCAM-1. Moreover, it increased TIMP-1/MMP-2 mRNA ratio expression possibly leading to increased plaque stability.

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OC2.5

5β-reductase (AKR1D1) deletion drives hepatic inflammation, fibrosis and tumour development *in vitro* and *in vivo*

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The enzyme 5β-reductase (AKR1D1) catalyses an essential step in bile acid synthesis, but in addition, controls intra-cellular steroid hormone availability by generating 5β-reduced dihydrosteroid metabolites. As disturbances in steroid hormone and bile acid metabolism have potent effects on metabolic health and lipid homeostasis, we hypothesize that AKR1D1 may play a role hepatic lipid accumulation and contribute to the development of metabolic disease. We generated a global AKR1D1 knockout (KO) mouse, which were fed either normal chow (NC) or the American lifestyle induced obesity syndrome diet (ALIOS; 45% fat, 55% fructose: 45% glucose in H_2O), which replicates the clinical features of non-alcoholic fatty liver disease (NAFLD), for 52 weeks. Metabolic phenotyping was undertaken at 37 and 52 weeks. Weight gain was similar in WT and KO normal chow and ALIOS treated animals. However, in WT mice, the ALIOS diet induced liver inflammation and fibrosis in comparison with NC. AKR1D1 KO mice fed the ALIOS diet had increased hepatic steatosis in comparison with WT mice (WT: 16.7±3.3, KO: 21.7±3.6 mg/g, $P<0.005$). In addition, there was evidence of increased hepatic inflammation on H&E stained sections in male AKR1D1 KO mice on a NC, but not ALIOS diet (1.6 vs. 1.1, $P<0.01$). However, at 37 weeks of age, liver biochemistry was significantly elevated in AKR1D1 KO mice fed the ALIOS diet in comparison with WT mice (ALT; WT: 140.7±51.9, KO: 404.7±171.4U/l, $P<0.05$. AST; WT: 136.7±39.0, KO: 360.7±121.7U/l, $P<0.05$). Endorsing observations in our rodent model, AKR1D1 knockdown experiments in human hepatoma cells (Huh7 and HepG2) increased mRNA expression and secretion of the pro-inflammatory cytokines IL1β, IL-6 and IL-8 as well as inducible nitric oxide synthase (iNOS). Hepatic inflammation is a key driver of fibrosis. AKR1D1 KO mice fed the ALIOS diet for 52 weeks had increased hepatic fibrosis as quantified by sirius red staining (WT: 5.4±2.6%, KO: 10.0±4.9%, $P<0.01$). Furthermore, it is well-established that advanced fibrotic metabolic liver disease increases the risk for the development of hepatocellular carcinoma (HCC) and AKR1D1 mice were more prone to tumour development in comparison with WT mice (WT: 11.5%, KO: 42.1%, $P<0.05$). Deletion of AKR1D1 in combination with a dietary stress evokes increased hepatic triacylglycerol content and fibrosis, which could exacerbate the progression of NAFLD to NASH and potentially fuel the development HCC. These data suggest that AKR1D1 may have a pivotal role in the regulation of the NAFLD progression.

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Cushing's and Acromegaly

OC3.1

Osilodrostat provides clinical benefit over 48 weeks in patients with Cushing disease: Results from the LINC 3 study

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Introduction
Osilodrosat is a potent oral 11β-hydroxylase inhibitor. During the 24-week, single-arm, open-label period of the Phase III LINC 3 study (NCT02180217), osilodrostat treatment demonstrated rapid, sustained reduction in mean urinary free cortisol (mUFC) in most Cushing disease (CD) patients. In the subsequent 8-week, double-blind, randomized-withdrawal phase, a significantly higher proportion of patients receiving osilodrostat maintained normal mUFC at week (W)34 without a dose increase versus placebo (86.1% vs 29.4%; OR: 13.7, $P<0.001$ [primary efficacy endpoint]; Pivonello R *et al.* ICE 2018;abstract 1025). The effects of osilodrostat on CD signs/symptoms/biochemistry parameters are reported here for the first time.
Methods
137 adults with CD and mUFC > 1.5xULN (ULN = 138 nmol/24h; baseline median mUFC = 3.5 × ULN) initiated open-label osilodrostat 2mg bid with dose adjustments every 2 weeks (maximum 30 mg bid) until W12 based on mUFC and safety. At W26, 71 eligible patients (mUFC ≤ ULN at W24 without up-titration after W12) were randomized to continue osilodrostat ($n=36$) or matching placebo ($n=35$) in an 8-week double-blind phase (ineligible patients continued open-label osilodrostat; $n=47$), followed by open-label osilodrostat until W48. Cardiovascular-related metabolic parameters and CushingQoL and Beck Depression Inventory (BDI) scores were evaluated at baseline, every 2, 4 or 12 weeks (depending on study phase), and at end of treatment (W48).
Results
By W48, in all patients ($N=137$), mean absolute change ± SD from baseline in signs/symptoms/biochemistry parameters were: weight, −3.8±5.7 kg; BMI, –1.4±2.2 kg/m^2; waist circumference, –4.6±7.8 cm; fasting plasma glucose, –0.5±1.3 mmol/L; HbA_{1c}, –0.4±0.7%; total cholesterol, –0.5±0.9 mmol/L; LDL cholesterol, –0.2±0.8 mmol/L; HDL cholesterol, –0.3±0.3 mmol/L; triglycerides, –0.1±0.9 mmol/L; systolic blood pressure (BP), –9.8±15.5 mmHg; diastolic BP, –6.3±11.1 mmHg. Mean ± SD CushingQoL score (including physical problems and psychological issues subscores) improved by 52.4±107.4% and BDI score by –31.8±65.0%. Osilodrostat was generally well tolerated; most common AEs were nausea (42%), headache (34%), fatigue (29%). Hypocortisolism-related AEs were experienced by 51% of patients, occurring mainly during dose titration (W0–12) as a single episode. Anticipated AEs of interest (based on osilodrostat mechanism of action) were manageable; those leading to discontinuation were adrenal insufficiency ($n=4$ [2.9%]), hypokalaemia, increased diastolic or systolic BP, and electrocardiogram QT prolonged ($n=1$ [0.7%] each).
Conclusion
Reductions in mUFC during 48 weeks of osilodrostat treatment were accompanied by weight, waist circumference, glucose, and systolic/diastolic BP improvements, as well as improved CushingQoL and BDI scores. Osilodrostat was effective and generally well tolerated, showing promise for the treatment of patients with CD.

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OC3.2

Outcomes after primary treatment for Nelson's syndrome: a study from 13 UK centres

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Nelson's syndrome (NS) is a potentially severe complication following bilateral adrenalectomy for Cushing's disease (CD). Series assessing outcomes of treatments for NS are limited by small sample size, often short follow-up and variability of success criteria. We performed a UK multi-centre study aiming to review outcomes of primary treatment for NS. Clinical, laboratory, imaging data were collected. Kaplan-Meier method, log-rank test, Cox regression analysis were used for statistical analyses. 68 patients from 13 centres were included [58 females, median age at CD diagnosis 30 years (11-69)]. Management of CD included surgery + adrenalectomy ($n=32$, 8 had two and 1 had three operations), surgery + radiotherapy + adrenalectomy ($n=15$, 2 received >1 course of irradiation), radiotherapy + adrenalectomy ($n=1$), adrenalectomy ($n=20$). NS diagnosis relied on i) imaging (adenoma growth or identification of tumour if previous scan negative) combined or not with increasing ACTH levels and/or pigmentation ($n=53$), ii) only increasing ACTH levels and/or pigmentation ($n=14$) (no information for one patient). Diagnosis of NS was between 1969–2018 (in 59/68, after 1990) at median interval 3 years after adrenalectomy (3 months-32 years). Primary management of NS included surgery ($n=10$), radiotherapy ($n=22$), surgery + radiotherapy ($n=18$, one had also carmustine implant), observation ($n=16$), pasireotide ($n=2$). Imaging follow-up data were available for 64 patients; there was no significant difference in probability of tumour progression between the primary management groups (10-years cumulative probability of progression-free survival: total group 76%, surgery 75%, radiotherapy 83%, surgery + radiotherapy 73%, observation 68%). Based on cases with relevant available data, sex, age at CD diagnosis, adenoma size at diagnosis (micro/macro), presence of adenoma on imaging before adrenalectomy, extent of adrenalectomy (complete/or not), interval between adrenalectomy and NS diagnosis (<3 or ≥ 3 years) and diagnostic criteria for NS (positive imaging/or not) were not predictors of tumour progression. However, type of management of CD was predictor ($P<0.05$); thus, in comparison with surgery + adrenalectomy, hazard ratios for surgery + radiotherapy + adrenalectomy were 5.5 (95%CI 1.8–17.1) and for adrenalectomy 0.3 (95%CI 0.7–1.1). This finding persisted even after adjusting for type of primary treatment of NS. Median follow-up between NS diagnosis and last review was 16 years (0–48); 13 patients had died and in three the cause was related with NS. At 10-years follow-up, 24% of the Nelson's tumours will show progress after various management approaches. Complexity of CD treatment, possibly reflecting corticotroph adenoma aggressiveness, is a significant predictor of Nelson's tumour progress.

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OC3.3

Monosynaptic inputs to corticotropin-releasing hormone neuron in hypothalamic paraventricular nucleus of mice at the whole brain scale

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Corticotropin-releasing hormone (CRH), a 41-aminoacid peptide that is mainly produced in the hypothalamic paraventricular nucleus (PVN), plays a crucial role in stress response and is considered to be the central driving force in the activity of hypothalamic–pituitary–adrenal (HPA) axis. Previous studies of neuronal input to the PVN were limited by experimental techniques and could not be restricted by a single neuron type. In the present study, by using a novel deficient rabies virus combined with the CRF-Cre transgenic mouse, which not only limits the start neurons within CRF neuron in PVN, but also restrict the input neurons to monosynaptic scale, we investigated the input projections of CRH neurons in the PVN. We observed the monosynaptic input projections received by CRH neurons in the whole brain and discovered projection neurons in forebrain, midbrain, hindbrain and other brain regions except in olfactory bulb. Basal forebrain, preoptic area, hypothalamus, brainstem reticular nucleus all had a large number of fluorescence-labeled projection neurons. Remarkably, the direct projections from cortex have not been reported before. These neurons distributed in layer 5 and 6 of orbital cortex, motor cortex and piriform cortex, and other sub-regions. Benefit from the good neuronal morphology revealed by virus tracing, we could observe that most of the labeled neurons obviously had the morphological characteristics of pyramidal neurons, such as the apical dendrites and branches, basal dendrites and the axon structures extending downward in cortical surface. Dendritic spines could also be clearly visible. We further obtained the input projection imaging data of CRH neurons with single cell resolution in the whole brain range using fluorescence micro-optical sectioning tomography system (fMOST). After data processing, we obtained the 3D distribution pattern of input projection neurons in the entire brain which demonstrated the detail morphologies of projection neurons inside mPFC, BST, amygdala and PVN, etc. as well as their local connections. We also dissected the entire morphologies of labeled pyramidal neurons within mPFC and traced their axons to the region near the injection site. The above neuronal tracing and reconstruction experiments have demonstrated the CRH-neuron-specific monosynaptic inputs to PVN at the whole brain scale for the first time.

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OC3.4

Restoration of basal glucose turnover after disease control in acromegaly depends on treatment modality: a prospective, investigator-initiated trial

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Background
Growth Hormone (GH) reversibly suppresses insulin-stimulated glucose uptake in skeletal muscle, but less is known about GH effects on glucose metabolism in the basal state. Somatostatin suppresses GH as well as insulin, and may also exert direct effects in skeletal muscle. This may have therapeutic implications in the treatment of acromegalic patients with a somatostatin analogue (SA).
Aim
To study basal and insulin-stimulated glucose metabolism in patients with acromegaly before and after disease control by either surgery-alone (surgery) or SA treatment.
Patients and methods
21 patients (10 surgery and 11 SA) were studied before and after treatment during a 3 h basal period followed by a 3 h hyperinsulinemic, euglycemic glucose clamp (HEC) combined with glucose tracer infusion, indirect calorimetry, muscle biopsies, and MR spectroscopy to quantify ectopic lipid in liver (IHL) and muscle (IMCL).
Results
IGF-I levels (μg/l) normalised after treatment [696 ± 57 vs. 211 ± 21] with no treatment-specific difference ($P=0.72$). GH-dependent gene expression in muscle (IGF-I and SOCS2) also declined after treatment ($P< 0.05$). The glucose infusion rate (GIR) during the HEC (mg/kg/min) increased after treatment ($P=0.001$) regardless of modality ($P=0.51$) [GIR: 3.3 ± 0.4 (before) vs. 4.7 ± 0.5 (after)]. Basal glucose levels declined after surgery but not after SA, whereas SA significantly suppressed insulin levels compared to surgery ($P<0.000$). Treatment decreased the basal state endogenous glucose production (EGP) [1.96 ± 0.1 vs. 1.47 ± 0.1 ($P=0.007$)], but less so after SA ($P=0.02$). By contrast, basal state glucose disposal (Rd) was lower after SA compared to surgery ($P<0.000$). Moreover, Rd after SA was dominated by non-oxidative glucose disposal, whereas the opposite was true after surgery ($P < 0.01$). Ectopic fat did not predict insulin sensitivity in either group.
Conclusions
1) Stimulated insulin sensitivity (HEC) improves after disease control in acromegaly independent of treatment modality, 2) Basal glucose metabolism also restores after disease control but less so, after SA, 3) The absence of association between insulin sensitivity and body composition including ectopic fat is unique for acromegaly.

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OC3.5

T2-signal intensity, SST receptor expression and first-generation somatostatin analogues efficacy predict hormone and tumor responses to pasireotide in acromegaly

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Background
Previous studies indicate that PAS-LAR can achieve control of insulin-like growth factor I (IGF-I) levels and may reduce tumor size, however a subset of acromegaly patients responds poorly. T2-signal intensity, somatostatin receptor (SST) subtype 2 and 5 expression, and the response to first-generation somatostatin receptor ligands (SRLs) are recognized predictors of therapy response. Valid prediction of the response to PAS-LAR can alter treatment stratification.
Aim
To analyze T2-signal intensity and SST receptor expression in relation to the hormone and tumor response during PAS-LAR treatment, and to determine to what extent this equals SRLs responsiveness.
Methods
We included 45 patients initially receiving SRLs, followed by a combination therapy including pegvisomant, and finally treated with PAS-LAR. The hormone response to PAS-LAR was evaluated using IGF-I (x ULN) levels at 24 weeks. T2-weighted MRI signal intensity of the adenoma was visually assessed and quantified by region of interest measurement. A tumor volume change of $\geq$25% from baseline was considered significant. SST receptor expression in adenomas was evaluated in 13 out of 45 patients using a validated immunoreactivity score (IRS). The clinical characteristics and the hormone and tumor response to PAS-LAR were assessed using multivariable regressions.
Results
Patients with the lowest percentage IGF-I (x ULN) reduction during SRLs also showed weak IGF-1 (x ULN) control during PAS-LAR and, however, more significant tumor shrinkage ($r=0.41$, $P=0.006$; $P=0.036$). Lower IGF-I (x ULN) levels during PAS-LAR were associated with higher T2-signal intensity and less significant tumor shrinkage (ß$=-0.29$, $P=0.045$; ß$=0.34$, $P=0.035$). With regards to tumor response, adenoma volume at baseline was associated with higher random GH levels at diagnosis and greater absolute tumor shrinkage during PAS-LAR (ß$=69$, $P=0.0018$; ß$=1.05$, $P=0.020$). Significant tumor shrinkage was associated with female patients, higher IGF-I (x ULN) levels during PAS-LAR and borderline significant with non-hypointense adenomas at baseline (OR$=6.35$, 95% CI$=1.42$–36.4; OR$=13.2$, 95% CI$=2.14$–129.1; OR$=5.97$, 95% CI$=0.91$–65.5 respectively). Lower IGF-I (x ULN) levels after PAS-LAR correlated with higher ($r=-0.68$, $P=0.011$; $r=-0.52$, $P=0.083$), while significant tumor shrinkage correlated with lower SST_2 levels and SST_2/SST_5 ratio ($P=0.040$; $P=0.024$).
Conclusions
Patients not responding to somatostatin analogs with particularly large adenomas, low SST_2 receptor expression and higher T2-signal intensity are more prone to show tumor shrinkage during PAS-LAR than patients with high SST_2 receptor expression and T2-hypointense adenomas. Surprisingly, tumor shrinkage is not accompanied by lower IGF-I (x ULN) levels, which are associated with a high SST_2 receptor expression and a higher T2-signal intensity.

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Thyroid 1

OC4.1

Subclinical hypothyroidism troughout pregnancy in TPOAb positive pregnant women

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Background and objective
According to recent studies, endocrine societies have modified the treatment criteria of subclinical gestational hypothyroidism, increasing TSH upper-limit value commonly set at 2.5 μU/ml to a new threshold set at 4 μU/ml. This change in criteria has responded to numerous studies which seem to indicate that the obstetrical complications do not generally increase despite this variation of the threshold TSH value. A further discussion lays now on whether euthyroid (TSH$<$ 4 μU/ml) pregnant women with autoimmune thyroid disease may still benefit from treatment within this 2.5–4 μU/ml TSH range, as some authors found a higher risk of developing subclinical gestational hypothyroidism in this population. This study aims to evaluate the progression towards subclinical hypothyroidism (TSH$\geq$4 μU/ml) throughout gestation of healthy first-trimester pregnant women with and without positive TPOAb status.
Methods
A prospective observational study was performed, in which TPOAb, TSH and FT4 levels were measured between 8th and 12th weeks of pregnancy from Nov 2017 to Dec 2018 at the screening visit. Later, TSH and FT4 levels were also measured in the third trimester. New hypothyroidism diagnosis in third trimester was recorded, and women were divided in two groups according their TSH value in the first trimester. First group those with TSH$<$2.5 μU/ml and the second group included those with TSH between 2.5 and 4 μU/ml.
Results
From the 1042 pregnant women who participated in the study, 6.24% (65) were positive for TPOAb. 23 of them were treated with levothyroxine: 13 due to a first-trimester TSH $>$ 4 μU/ml and 10 owing to an abnormal thyroid palpation in women within 2.5–3.9 μU/ml TSH range. Regarding the group that did not receive treatment (42), 35 showed a TSH$<$2.5 μU/ml and 7 of them were 2.5–3.9 μU/ml. None (0%) of the pregnant women from this not-treated group developed a subclinical hypothyroidism (TSH$\geq$4 μU/ml) in the third trimester. In the group of negative thyroid autoimmunity (977), the progression towards subclinical hypothyroidism was of 1.53% (15).
Conclusions
- In our population there is no development to hypothyroidism in those women who were not initially treated in the first trimester despite positive TPOAb. The criteria to indicate thyroid hormone was TSH$\geq$4 μU/ml or TSH 2.5–3.9 μU/ml with abnormal thyroid exploration.
- In fact, the incidence of subclinical hypothyroidism in the third trimester was higher in those with negative TPOAb, although it is low (1.53%).
- These results require further studies.

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OC4.2

Thyroid dysfunction and mortality in cardiovascular hospitalized patients – a 12 year follow-up observational study

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Background
Thyroid dysfunction is associated with increased cardiovascular morbidity and mortality. Early detection may influence the clinical management of the patients. There is insufficient data about the prevalence and clinical significance of thyroid dysfunction in cardiovascular hospitalized patients.
Aims
To study the prevalence of thyroid dysfunction in cardiovascular hospitalized patients, to characterize patients with high prevalence of thyroid dysfunction and to determine the mortality rate of this population.
Methods
A retrospective analysis of a medical records database of all adult patients admitted not-electively to the Cardiology Department at Shaare-Zedek Medical Center, Israel, between 2005–2017. Blood test for Thyroid Stimulating Hormone (TSH) level was performed as a routine test in all patients, and T4 and T3 levels were checked according to TSH result. Statistical analysis was performed on demographic and clinical characteristics, as well as mortality data, of the entire cohort.
Results
During the described period there were 19281 non-elective hospitalizations of 14388 patients. TSH was available for 14384 patients during their first hospitalization. The mean age was 67$\pm$15. Thyroid dysfunction was present in 10% of the patients (2% TSH$>$10 mIU/L; 5% TSH 5–10 mIU/L; 2% TSH 0.1–0.35 mIU/L; 1% TSH $<$0.1 mIU/L). The prevalence of thyroid dysfunction was significantly higher in elderly patients (age$>$70 y; prevalence 12.1%, Odds ratio[OR]$=1.4$) and in patients with atrial flutter/fibrillation (14%, OR$=1.4$), pulmonary hypertension (14%, OR$=1.4$), chronic renal failure (14%, OR$=1.5$), heart failure (15%, OR$=1.5$), hypothyroidism treated with Levothyroxin (28%, OR$=3.3$) and patients treated with Amiodarone (24%, OR$=3$). Adjusted multivariable analysis showed increased mortality during the study period, for TSH$<$0.35 mIU/L, TSH 5-10 mIU/L and TSH$>$10 mIU/L (hazard ratio 1.44, 1.27 and 1.4, respectively).

Conclusion
The prevalence of thyroid dysfunction in cardiac hospitalized patients is 10% and is even higher in specific patient-groups. Thyroid dysfunction is associated with an increased mortality rate. Screening for thyroid function may be considered in cardiology departments, especially for selected high risk groups.

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OC4.3

Prognostic impact of microscopic extrathyroidal extension (mETE) on recurrence-free survival in patients with papillary thyroid carcinoma (PTC)

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Background/objective
mETE has shown no effect on survival, and the 8th edition of the AJCC classification no longer considers mETE in the pT3 definition. Therefore, tumors with mETE below 40 mm are now staged pT1/pT2. However, controversy remains regarding mETE impact on disease recurrence. This study assessed the risk of recurrence of PTC patients previously classified as pT3 because of mETE, compared to PTC patients staged pT1-pT2.
Methods
Monocentric retrospective analysis of prospective database of patients treated by total thyroidectomy and radioactive iodine (RAI) from 1998 to June 2013. All patients had available data on pathology report, uni or multifocal PTC <40 mm, with or without mETE, with or without lymph node involvement (LNI) and at least 5 years of follow-up. mETE was defined as extra-capsular invasion without skeletal muscle involvement. The primary outcome, recurrence free survival (RFS), was defined as the time between initial surgery and recurrence treatment. Follow-up of recurrence-free patients was censored after 5 years. In univariate analyses, the 5-years RFS (with standard error) curves were estimated using the Kaplan Meier estimator and compared using the Log-rank test. Multivariate modelling was performed fitting the proportional hazard Cox model. The candidate prognostic factors were: mETE (presence/absence), LNI (N0-Nx, N1a, N1b), aggressive pathological type (Yes/No), margin resection involvement (R1/R0), pathological tumor size in mm ($<=10$,]10; 20],]20, 40]) and advanced age (>55 years).
Results
The overall 5-years RFS was 80.2% (2.3%). In univariate analyses, the 5-years RFS was 62.4% (5.0%) for tumors with mETE and 88.1% (2.2%) for tumors without ($P<0.001$). The 5-years RFS were 88.8% (2.1%), 76.6% (6.2%) and 25.0% (7.7%) in N0-Nx, N1a and N1b tumors respectively ($P<0.001$). The 5-years RFS was 37.7% (17.1%) in aggressive pathological types and 81.4% (2.3%) in others ($P<0.001$). It was 60.0% (12.6%) in R1 tumors, and 81.3% (2.3%) in R0 tumors ($P=0.048$). Neither advanced age ($P=0.125$) nor tumor size ($P=0.890$) were significantly associated with prognosis. In multivariate analysis, mETE ($P=0.002$) and LNI ($P<0.001$) were independent prognostic factors, whereas neither aggressive pathological type ($P=0.440$) nor resection completeness (0.776) were significantly associated with prognosis. In this model, mETE was associated with a hazard ratio of 2.55 (95% CI 1.48–4.40), and N1a and N1b tumors with hazard ratios of 1.67 (95% CI 0.81–3.46) and 8.94 (95% CI 4.92–16.26) respectively, without interaction between mETE and LNI ($P=0.205$).
Conclusion
These results suggest that mETE is a pejorative factor in recurrence risk, regardless of LNI.

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OC4.4

Cardiac and vascular characteristics of thyroid hormone resistance syndrome in France

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Introduction
The syndrome of reduced sensitivity to thyroid hormone (SRSTH) due to mutations of thyroid hormone receptor β *(TRB)* consists of an inappropriate secretion of TSH with elevated levels of thyroid hormones. Cardiovascular manifestations are often the ones that affect patients. Our aim was to evaluate the cardiac and vascular characteristics of patients with SRSTH due to *TRB* mutations.
Materials and methods
We analysed clinical, electrocardiogram and cardiac ultrasound data of 287 patients, collected in our Reference Centre of Rare Thyroid Diseases. Data was recorded on diagnosis or during the follow-up of patients. When several sets of the same data existed, the last ones were taken into account. For each variable, 65 to 181 patients could be analysed.
Results
Patients are mainly female (59.6%) with an average age of 28.6 years old at the time of diagnosis. Clinical symptoms were represented by elevated blood pressure (30%), tachycardia (45.7%) and palpitations (45.8%). Electrocardiogram abnormalities were present among 43.3% of patients: 20.2% supraventricular arrythmia (flutter or fibrillation), 15.4% sinusal tachycardia, 3.9% conduction abnormalities and other abnormalities (3.8%). Few patients had ischemic history (4.4%) or cardiac failure. Cardiac ultrasound abnormalities were found in 9.1% of patients including 48% of valvular heart disease and 20% of hyperkinesia. Left ventricular ejection fraction was altered in 3.5% of patients. Many patients used cardiac or blood pressure medications: 18.8% used beta blockers for cardiac indications, 7.30% used an antihypertensive medication, and 4.9% had an anti-coagulant therapy. The study of the genotype-phenotype association is ongoing.
Conclusion
Our study is one of the largest on cardiac and vascular characteristics of patients with *TRB* mutations. We confirm that patients are mainly affected by tachycardia, palpitations and supraventricular arrythmia that require specific treatment. A regular screening of these cardiovascular manifestations is needed.

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OC4.5

A comprehensive assessment of the interplay between the thyroid function and the immune system: results from the Human Functional Genomics Project

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Background
Accumulating evidence indicates the presence of bidirectional cross-talks between the endocrine and the immune system. However, no data are available on the influence of either the thyroid hormones or TSH within the normal range on the immune cell function in healthy humans.
Aim
To comprehensively investigate the effects of the hypothalamic-pituitary-thyroid axis on the variation of immune responses in a cohort of healthy volunteers.
Methods
The immune phenotype was characterized at the level of immune cell subpopulations counts, circulatory mediators of inflammation, platelet function, and production of six cytokines after stimulation with 19 microbial and non-microbial stimuli. The study was performed in a cohort of 534 well described healthy individuals (the 500 Human Functional Genomics cohort (500FG)). Results were obtained using systems biology-based approaches and were subsequently validated in an independent cohort of 324 healthy volunteers with comparable demographic characteristics.
Results
T4 and TSH did not affect cytokine production, circulatory mediators of inflammation (except for the TSH association with leptin) and innate immune cell population numbers. In contrast, we found significant and distinct effects of TSH and T4 on lymphocyte populations in the 500FG cohort. TSH was positively associated with 36 of the 73 independent cell types, particularly the total

circulating lymphocyte counts and T-cell populations. Interestingly, T4 correlated positively with 18 of the 73 independent cell types, mainly circulating B-cell populations. These results were validated in the independent cohort of 324 healthy volunteers. Furthermore, we performed a GWAS on a SNP array covering around 8.8 million SNPs. We identified a high degree of overlap, with 35 SNPs being associated with both the TSH (22 SNPs) or T4 (13 SNPs) concentrations and the cell counts. Some SNPs had strong eQTLs influencing the expression of important genes such as a genetic variant within the *PTGER3* gene and a SNP between *ZC3H7A* and *TXNDC11*, the latter being involved in folding of DUOX proteins involved in H_20_2 generating system within the thyroid.

Conclusion

T4 and TSH have a minimal impact on innate immune responses in healthy volunteers. However, there is a strong interaction between TSH and T4 and adaptive immune responses, particularly with the lymphocyte numbers. These findings represent the first step in understanding the biology of these newly identified interactions, and pave the way towards assessing their impact in clinical situations. Furthermore, the novel genetic loci have to be tested in future experiments, to decipher their precise role in thyroid-immune biology.

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Adrenal 1

OC5.1

Positive impact of genetic test on the management and outcome of patients with paraganglioma and/or pheochromocytoma

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Context

Paragangliomas and pheochromocytomas (PPGL) are rare neuroendocrine tumors, characterized by a strong genetic component. Indeed, up to 40% of patients carry a germline mutation in a PPGL susceptibility gene. In accordance with the international recommendations, genotyping of PPGL susceptibility genes is therefore proposed to all patients with PPGL, but it has actually never been shown whether the identification of a germline mutation in one PPGL susceptibility gene changes the outcome of mutation-carriers.

Objective

Our objective was to evaluate how a positive genetic test impacts the management and outcome of propositus patients with PPGL carrying a germline mutation in one of the four major PPGL susceptibility genes (*SDHB, SDHD, SDHC* and *VHL*).

Design

We performed a multicentric retrospective study on 221 propositus carrying a *SDHB, SDHD, SDHC* or *VHL* germline mutation and followed in 24 French clinical centers of the Group of Endocrine Tumors and/or the COMETE network. Patients were divided into two groups: *Genetic* patients, who were informed of their genetic status within the year following the first PPGL diagnosis, and *Historic* patients who only benefited from the genetic test several years after initial PPGL diagnosis.

Results

Compared to *Historic* patients, *Genetic* patients had a better follow-up, with a higher number of examinations and a reduced number of patients lost to follow-up (9.6% *versus* 72%). During follow-up, smaller (18.7 mm *versus* 27.6, $P=0.0128$) new PPGL and metastases as well as lower metastatic spread were observed in *Genetic* patients. Importantly, these differences were reversed in the *Historic* cohort after genetic testing. *Genetic* patients who developed metachronous metastases had a better 5-year survival than *Historic* ones ($P=0.0127$).

Conclusion

Altogether our study clearly shows the positive impact of the identification of an *SDHx* or *VHL* mutation in the management, clinical outcome and survival of patients with PPGL. It reveals, for the first time, the clinical benefits of the practice of oncogenetics for patients with a rare cancer and strongly strengthens the recommendations of the Endocrine Society to consider PPGL genetic testing in all patients affected by PPGL.

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OC5.2

Pheochromocytoma aggressiveness induced by tumor microenvironment depends on the SDH subunit involved

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Pheochromocytoma/paraganglioma (Pheo/PGL) are rare neuroendocrine tumors generally benign. About 30–40% of Pheo/PGL are due to germ-line mutations in one of the susceptibility genes, including those encoding the succinate dehydrogenase subunits A-D (*SDHA-D*). Up to 80% of patients affected by *SDHB* mutated Pheo/PGL develop metastatic disease with no successful cure at present. In this study, we evaluated the different effect of tumor microenvironment on tumor cell migration/invasion by co-culturing tumor cell spheroids with primary cancer-activated fibroblasts (CAFs). To this end, we used three dimension (3D) cultures of a mouse pheochromocytoma cell line (MTT) silenced or not (wild type = Wt) for the catalytic SDHB or the anchoring SDHD subunit. We measured matrigel invasion of spheroid cells by the computation of the migratory areas. Intriguingly, we observed that *SDHD* silenced spheroids had an intermediate migration pattern compared to the highest migration capability of *SDHB* and the lowest one of the Wt spheroids. Interestingly, by confocal

microscopy, we found that all the conditioned spheroids (Wt, *SDHB* and *SDHD* silenced ones) developed long filamentous formations, but only *SDHB* silenced cells invaded the surrounding space moving collectively probably using those filamentous as binaries. Wt and *SDHD* silenced spheroids tended to move individually. Ongoing experiments are aimed to understand if these long outgrowths are neuronal structures (dendrites or axon) or not. To characterize the molecules involved in promoting tumor cell migration, conditioned medium of CAFs was divided into two fractions depending on molecular weights of its components by using cut-off filters. The upper fraction contains molecules with a molecular weight higher than 3000 Da, while the lower fraction is constituted by small molecules (MW $<$ 3000 Da). When the spheroids were conditioned with only the upper or only the lower fraction of conditioned medium we did not observe a significant increase in migration compared with unconditioned spheroids, as suggesting a synergistic role of both fractions in inducing cell migration. This synergy is particularly evident in *SDHB* silenced spheroids. These results suggest that the interplay between tumor microenvironment and *SDHB* silenced spheroids is distinctive compare to the ones of Wt or *SDHD* silenced spheroids. The characterization of the specific factors causing migration may open new approaches for medical therapy.

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OC5.3

SF3B1 as novel target for the treatment of multiple endocrine-related cancers

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The intrinsic heterogeneity of endocrine-related cancers (ERCs) hampers the identification and development of global and effective therapeutic treatments for these pathologies. However, the dysregulation of the splicing process has been postulated as a new common hallmark shared by most cancer types, since it is associated with the appearance of splicing variants with oncogenic potential (e.g. *CD44v6*, *BCL-Xs*, *AR-v7*, *SST5TMD4*, *In1-ghrelin*). Yet, the putative alteration, pathophysiological role and potential therapeutic utility of the elements involved in the control of the splicing process [i.e. spliceosome components (SCs) and splicing factors (SFs)] remain still unknown. For this reason, we have analysed the expression levels of a representative set of SCs ($n=18$) and SFs ($n=27$) in different cohorts of ERCs [i.e. growth hormone secreting pituitary tumors ($n=96$); non-functioning pituitary tumors ($n=23$); pancreatic neuroendocrine tumors ($n=20$); prostate cancer ($n=126$); and in four *in silico* cohorts of liver cancer (HCC; $n=445$, $n=115$, $n=75$, $n=45$)]. Our results showed that the SF3b subunit 1 (*SF3B1*) gene, which encodes a protein necessary for spliceosome assembly, was consistently overexpressed in all the ERCs evaluated in this study. Interestingly, *SF3B1* expression was positively correlated and associated with clinical and molecular aggressiveness features (e.g. histopathological grade, presence of metastasis, expression of oncogenic splicing variants, etc.) in these ERCs. *In vitro* analyses revealed that the specific blockade of SF3B1 activity, using the pladienolide-B compound, exhibited potent and relevant antitumor effects (reducing cell proliferation, migration, tumorospheres and colonies formation, hormone release and inducing apoptosis) in the vast majority of representative models of ERC cells tested herein (primary ERCs cell cultures and cell lines such as BON-1, QGP-1, LNCaP, 22Rv1, PC-3, HepG2, Hep3b or SNU-387). Remarkably, the antitumor effects of pladienolide-B treatment were further validated *in vivo* in that we found a significant reduction of tumor volume after 9-days of local treatment of pladienolide-B in a xenograft model of ERC. Moreover, we found that pladienolide-B treatment modulated an ample repertoire of molecular events, such as inhibition of major oncogenic signalling pathways (e.g. PI3K/AKT and JNK), modulation of the expression of key tumour markers (e.g. *MKI67*/*CDK6*/*CDKN2A*) and oncogenic splicing variants (e.g. *AR-v7*/*In1-ghrelin*), and regulation of the expression pattern of key components of mRNA homeostasis-associated machineries (spliceosome and SURF/EJC). In conclusion, these results indicate that SF3B1 is consistently overexpressed in different ERCs and associated to malignant features and that its pharmacological blockade with pladienolide-B could represent a novel, global and effective therapeutic approach for ERCs.

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OC5.4

The splicing factor NOVA1 is overexpressed in pancreatic neuroendocrine tumors and related to increased aggressiveness and malignancy

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There is increasing evidence that alterations in alternative splicing can be linked to key tumor features in cancer. Dysregulations in the splicing machinery constitute the underlying cause in many of these alterations and, consequently, splicing and its control are emerging as a novel and transversal cancer hallmark, due to its association with different dysfunctions of tumor cells. In line with this, we discovered the existence of aberrantly spliced variants of somatostatin receptor 5 (SST_5TMD4) and ghrelin (In1-ghrelin), which are overexpressed and linked to malignancy features in pancreatic neuroendocrine tumors (PNETs). In this study, we aimed at characterizing the pattern of expression of pivotal components of the splicing machinery, its potential dysregulation and its relation with aggressiveness of PNETs, with the ultimate goal of identifying novel, useful biomarkers for diagnostic and treatment of these tumors. To this end, we designed an array that allowed to determine the expression levels of 45 splicing machinery components using a microfluidic-based technology in 20 pancreatic NETs samples and their control-adjacent non-tumoral tissues. This revealed that the expression of several splicing factors and spliceosome components was altered in tumor tissue compared to non-tumoral adjacent tissue, suggesting a profound dysregulation of the splicing machinery in PNETs. Then, we selected one of the most altered components, NOVA1, to explore its properties in two PNETs model cell lines, BON-1 and QGP-1, by measuring signaling pathways and aggressiveness features, including proliferation and growth of xenografted tumors in mice. This showed that levels of NOVA1, a splicing factor highly overexpressed in tumors, correlated with relevant clinical features, including higher Ki-67 index and necrosis. In vitro assays in BON-1 and QGP-1 cell lines demonstrated that NOVA1 overexpression increased cell proliferation; conversely, NOVA1 silencing markedly decreased cell proliferation. Interestingly, overexpression or silencing of NOVA1 led to opposite changes in the activation/inhibition of key signaling pathways and in the expression of key molecular markers. Of note, alteration of NOVA1 in these cells affected their responsiveness to everolimus in terms of proliferation. Finally, NOVA1 overexpression increased the growth of BON-1 xenografted tumors in nude mice. These results demonstrate that splicing is altered in PNETs, and provide compelling evidence for a role of the splicing factor NOVA1 in PNETs oncogenesis and aggressiveness, thus paving the way to explore its possible value as a biomarker and therapeutic target in PNETs.

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OC5.5

Impact of adrenal insufficiency on patient-centred health care outcomes in adult medical inpatients

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Background
Patients with adrenal insufficiency suffer from increased morbidity and mortality. Quantitative evidence on the health-care burden of either primary (PAI) or secondary adrenal insufficiency (SAI) among hospitalized medical patients is scarce.
Methods
In this observational cohort study, we analysed nationwide acute care hospitalizations from patients with PAI or SAI, respectively, between 2011 and 2015 using prospective administrative data. Patients with either PAI or SAI were compared with propensity score-matched (1:1) controls, based on age, gender, citizenship, hospital volume, year of admission, Charlson Comorbidity Index, and relevant medical diagnoses. The primary outcome was in-hospital mortality. Secondary outcomes were intensive care unit (ICU) admission, intubation rate, length of hospital stay, and 30-day-readmission.
Results
We included 594 patients with PAI and 4880 patients with SAI. Compared with matched controls, in-hospital mortality was comparable among patients with PAI (odds ratio (OR) 1.12 (95% CI 0.65 to 1.95)) and SAI (OR 1.14 (95% CI 0.88 to 1.24)), respectively. Patients with adrenal insufficiency were more likely to be admitted to the ICU (PAI: OR 2.56 (95% CI 1.69 to 3.90), and SAI: OR 3.03 (95% CI 2.60 to 3.54)). The risk for intubation was 3-fold higher in SAI patients (OR 3.04 (95% CI 2.40 to 3.84)), whereas there was a trend in PAI patients (OR 1.77 (95% CI 0.93 to 3.37)). The mean length of hospital stay was 1.8 days longer in PAI patients (8.9 vs. 7.1 days; difference 1.83 (95% CI 0.81 to 2.86)) and 4.6 days longer in SAI patients (12.1 vs. 7.5 days; difference 4.62 (95% CI 4.20 to 5.04)). The risk for 30-day hospital readmissions was increased in SAI patients (OR 1.48 (95% CI 1.33 to 1.64)) but not in PAI patients (OR 1.34 (95% CI 0.93 to 1.93)).
Conclusion
Among medical inpatients, adrenal insufficiency was associated with significant health-care burden, leading to higher rates of ICU admission, intubation and prolonged length of hospital stay. Whether these compromised outcomes can be improved by a more comprehensive diagnostic and therapeutic work-up needs to be addressed in clinical Trials.

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Obesity

OC6.1

Impaired glucose homeostasis in leptin-deficient ob/ob mice is corrected by AZP-3404, a 9-amino acid peptide analog derived from insulin-like growth factor-binding protein 2, a key mediator of leptin action

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The key metabolic hormone, leptin, acts in part through the liver to regulate glucose homeostasis, as well as the maturation of both adipocytes and osteoblasts. These actions have been demonstrated to be mediated by insulin-like growth factor binding protein 2 (IGFBP-2), independent of its ability to bind IGF1. The effects of IGFBP-2 on adipocyte and osteoblast maturation can be localized to a short peptide sequence within the unique heparin binding domain (HBD-1) of IGFBP-2. AZP-3404 is a 9-amino acid peptide analog derived from the HBD-1 of IGFBP-2 that reproduces the activity of IGFBP-2 on adipocyte and osteoblast maturation. The present study examines whether AZP-3404 can likewise reproduce the ability of leptin/IGFBP-2 to restore glucose homeostasis in the leptin-deficient ob/ob mouse. Carotid artery glucose levels were continuously monitored in unanesthetized, unrestrained, male B6.Cg-Lepob/J mice fitted with wireless HD-XG telemetric devices (Data Sciences International). The mice were randomly assigned to groups ($n=8$) that received either AZP-3404 or vehicle, b.i.d., for four weeks. By day 27 of treatment, AZP-3404, administered at either 1 or 3 mg/kg, reduced the average daily glucose concentration by 64 ± 29 and 100 ± 16 mg/dl, respectively, from the pretreatment mean level of 507 ± 102 mg/dl. Glucose levels in the vehicle-treated mice slightly increased by 14 ± 29 mg/dl. To assess the efficiency of glucose disposal, an intraperitoneal glucose tolerance test (IPGTT: 1 g glucose/kg) was administered on days 7, 14, 21 and 28 of treatment, following a 24-hour fast. After 28 days of treatment with either 1 or 3 mg/kg AZP-3404, fasting glucose was reduced by 8 and 20%, respectively, as compared with fasted levels on day 7. The IPGTTs demonstrated that AZP-3404 progressively and dose-dependently improved glucose disposal in the severely insulin-resistant ob/ob mice, reducing post-challenge glucose levels by 40% after treating with 3 mg/kg AZP-3404 for 4 weeks. In addition, we have demonstrated that AZP-3404, both alone and in an additive manner with insulin, increases glucose uptake by mouse C2C12 differentiated myotubes through activation of AMP-activated protein kinase (AMPK), suggesting that at least a portion of the observed effect of AZP-3404 in the ob/ob mouse may be by promoting glucose uptake by muscle. These results demonstrate that AZP-3404 is able to reproduce the ability of IGFBP-2 to restore glucose homeostasis in the ob/ob mouse and support the development of AZP-3404 as a novel therapy for syndromes of severe insulin resistance.

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OC6.2

Deep Transcranial Magnetic Stimulation modulates body temperature in obesity

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Obesity is known to be associated with increased heat production. To maintain normothermia, heat retention in areas of the body with greater adiposity is counteracted by an augmented heat release from the extremities, as the fingernail-beds of hands. A possible cause of the altered thermoregulation in obesity is a dysfunction of the neuro-endocrine system. Repetitive deep Transcranial Magnetic Stimulation (dTMS) was proved to be an effective tool in inducing long lasting changes in neural excitability and dopamine release, causing satiety and weight loss. Aims of this study were to investigate the acute and chronic effects of dTMS on body temperature measured by Infrared Thermography in obese subjects. Twenty-nine obese subjects (6 M, 23 F; 48.3 ± 11.8 years; BMI: 37.7 ± 4.3 kg/m^2), seeking treatment for weight control, were randomized into 3 groups receiving 15 sessions (3 per week for 5 weeks) of high frequency (18 Hz), low-frequency (1 Hz) or sham stimulation. Under neutral thermal conditions, fingernail-bed of both hands, abdominal and interscapular skin temperature was measured by Infrared Thermography (AVIO TVS700 camera, 320×240 pixel, spatial resolution 1.4 mrad, temperature resolution 0.08°C). After a single session of 18 Hz dTMS, the average fingernail-bed of both hands temperature significantly decreased (right hand: $-4.4\pm0.3\%$, $P<0.05$ vs baseline; left hand: $-2.7\pm0.2\%$, $P<0.05$ vs baseline). Concurrently, was found a significant increase of norepinephrine ($+18.8\pm7.7\%$, $P<0.05$ vs baseline) and of β-endorphin ($+14.3\pm5.4\%$, $P<0.05$ vs Sham). After a single session of both 18 and 1 Hz dTMS, a trend to increase in abdominal skin temperature was observed (18 Hz group: $+0.9\pm0.9\%$, $P<0.01$ vs Sham group; 1 Hz group: $+1.2\pm1.7\%$, $P<0.05$ vs Sham group). In 2 subjects receiving high frequency stimulation, an increase of interscapular temperature was observed ($+6.0\pm1.0\%$), suggesting an activation of brown adipose tissue. After 15 dTMS sessions, analysis revealed a significant decrease of body weight ($-4.1\pm0.6\%$, $P<0.05$ vs baseline, $P<0.05$ vs Sham) and a decrease of abdominal skin temperature ($-2.3\pm2.9\%$, $P<0.05$) in 18 Hz group. Deep TMS revealed to be effective in modulating body temperature in obese subjects, reversing obesity-induced alterations in heat production and dissipation.

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OC6.3

Role of hypothalamic bile acid-TGR5 signaling in the regulation of energy balance

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Bile acids (BA) are cholesterol-derived molecules that are mostly known for their involvement in lipid digestion and absorption. Recent evidence recognizes them as metabolic integrators able to reduce body weight (BW), increase energy expenditure (EE) and improve glycemic control by activating their specific receptor, the Takeda G protein-coupled receptor 5 (TGR5) in peripheral organs. These outcomes have increased importance in the context of diet-induced obesity and associated metabolic alterations, implying a therapeutic role for TGR5. Here we have hypothesized that TGR5 is also present in the hypothalamus, a major brain structure involved in the regulation of energy balance and whole-body metabolic responses, and that modulation of hypothalamic TGR5 activity is relevant for the control of energy balance, particularly under diet-induced obesity. In order to investigate this hypothesis, we used a multidisciplinary approach, spanning from pharmacological activation of TGR5 to genetic strategies for the hypothalamic deletion of TGR5, associated with evaluation of changes in food intake, body weight, adiposity and other metabolic outputs. Our data demonstrate that TGR5 and BA transporters are expressed in the mediobasal hypothalamus and that diet-induced obese mice have significantly decreased circulating and hypothalamic BA levels. Acute intracerebroventricular (icv) administration of BA or synthetic TGR5 agonist significantly decreased food intake and body weight, particularly in diet-induced obese mice. Similar outcomes were observed after acute administration of TGR5 agonist directly in the mediobasal hypothalamus. Four-weeks continuous icv administration of TGR5 agonist in diet-induced obese mice significantly reduced food intake, body weight, fat mass and improved insulin sensitivity. Effects on body weight and adiposity were in large part due to increased energy expenditure, in turn driven by increased sympathetic activity. Accordingly, chemical sympathectomy or thermoneutrality were able to prevent effects of central TGR5 agonism on body weight and adiposity. Conversely, virally-mediated deletion of TGR5 in the mediobasal hypothalamus of $TGR5^{flox/flox}$ mice caused a rapid increase of food intake, body weight, and fat mass, accelerating the development of diet-induced obesity or worsening the phenotype of already obese mice. These changes were associated to blunted sympathetic activity, which favored the appearance of the obese phenotype. Overall, our results prove the existence of a functional BA-TGR5 hypothalamic system. We show for the first time that the activation of TGR5 in the mediobasal hypothalamus mediates a myriad of effects that improve metabolic parameters, which are particularly relevant in the presence of diet-induced obesity.

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OC6.4

Fat mass impact of sirolimus after clinical islet transplantation, a case control study

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Introduction
Sirolimus, a mTOR (mechanistic Target of Rapamycin) inhibitor, is well known for its impact on glucides and lipids metabolism. These effects vary according to factors such as dose and treatment duration, species, cell types and environmental factors. *In vitro* and *in vivo*, sirolimus inhibits adipogenesis by decreasing adipocytes number and size, as well as pre-adipocytes differentiation, leading to subcutaneous and visceral fat mass decrease in murine models of obesity. Little is known on the long-term impact of sirolimus in human. We hypothesized that sirolimus could have a specific role on adipose tissue, possibly influencing islet transplantation prognosis. The aim of this study was to compare body composition and metabolic markers in 2 groups of islet–transplanted patients according to the immunosuppressive regimen including or not sirolimus.

Patients and Methods
We compared body composition and fat markers (weight, DEXA-fat and lean mass, and metabolic parameters) in two groups of non–obese islet-transplanted (ITA) patients treated ($n=18$) or not ($n=13$) with sirolimus, before and one year after islet transplantation for type 1 diabetes (T1D). Continuous variables were expressed as median (interquartile range [IQR]). 'Sirolimus' and 'non-sirolimus' groups were compared with a non-parametric Mann-Whitney test.
Results
Before transplantation, metabolic, renal and body composition parameters were similar in the 2 groups. Compared to baseline, we observed a significant decrease of weight (−6.3 kg (−9.67; −3.85), $P=0.0131$), BMI (−2.2 kg/m^2(−3.17; −1.35), $P=0.009$), leptinaemia (−3.25 ng/ml (−7.6; −0.65), $P=0.0103$) and DEXA fat-mass(−5.5% (−10.7; −1.4), $P=0.0384$), after one year of treatment in the sirolimus-group, while there is no significant modificationt in the 'non-sirolimus' group. One-year after transplantation, weight, BMI, % of fat mass, metabolic and renal parameters did not differ between the 2 groups, except for leptinemia decrease of which was significantly higher in the 'sirolimus' *vs.* the 'non-sirolimus' group ($P=0.008$).
Conclusion
In non-obese T1D patients treated with sirolimus, islet-transplantation was associated with a significant fat loss, concomitant to metabolic improvement. Sirolimus exposure was also associated with a significant reduction of leptin as compared to 'non-sirolimus' islet –transplanted patients,. These findings could be related to the quality of adipose tissue, potentially modulating insulin resistance and innate immunity. On a broader scale, mTOR inhibitors, also used in the treatment of neuroendocrine tumors, could participate to crosstalk between cancer and immunity.

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OC6.5

Lipolysis defect in white adipose tissue and rapid weight regaining

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Weight regain after weight loss is a well described-phenomena in both humans and animal models of obesity and thought to be related to reduced energy expenditure and increased food intake. Reduced lipolysis in white adipose tissue has been described in obesity. We hypothesized that lipolytic defect in adipose tissue in the obese state persists after weight loss increasing efficiency of lipid storing and promotes weight regain. We utilized a mouse model of obesity memory (OM): C57BL/6 mice with diet induced obesity were subjected to 60% caloric restriction to achieve lean body weight, followed by a short period of high fat diet (HFD) re-challenge. Age-matched lean mice without OM which were fed HFD for the first time were used as control. Upon re-challenge with HFD, mice with OM had rapid weight gain compared to the control group. Despite comparable body weight and lean body mass, mice with OM showed higher respiratory exchange ratio than control mice, suggesting higher glucose rather than fatty acid oxidation. In *ex vivo* lipolysis assay white adipose tissue explants with OM had comparable lipolytic response after caloric restriction, however reduced functional lipolytic response to norepinephrine was noted as early as 5 days after re-challenge with HFD accompanied by reduction in HSL serine phosphorylation after norepinephrine stimuli. The relative lipolytic defect was associated with increased expression of inflammatory genes, and a decrease in beta adrenergic receptor genes, most notably *adrb3* compared to the control group. Taken together, white adipose tissue of lean mice with OM shows increased sensitization to HFD compared to white adipose tissue with no OM, rendering it relatively resistant to catecholamine induced-lipolysis. This lipolytic defect associated with OM is tissue-autonomous and could play a role in the rapid weight regain observed after weight loss.

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Endocrine Connections 1

OC7.1

Cortisol suppression or peripheral sensitivity and activation are associated with diabetes, hypertension and fragility fractures in postmenopausal eucortisolemic women

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Background
Cortisol excess is associated with a higher prevalence of hypertension (Hy), type 2 diabetes (T2D) and fragility fractures (FX). A possible association between T2D and fragility FX with the degree of glucocorticoid (GC) suppression and peripheral activation or sensitivity even in non-hypercortisolemic subjects has been previously suggested.
Aim
To assess if the degree of GC suppression or peripheral sensitivity and activation are associated with Hy and the simultaneous presence of fragility FX, T2D and Hy in eucortisolemic postmenopausal females.
Patients and Methods
We studied 216 non-hypercortisolemic postmenopausal females (age 50–80 years, 99 with T2D, 108 with Hy, 68 with fragility FX). In all subjects, we assessed 24-hour urinary free cortisol (UFF), cortisone (UFE), their ratio (R-UFF/UFE), cortisol after 1mg-overnight-dexamethasone (F-1mgDST) and the presence of the *N363S* single-nucleotide polymorphism (*N363S*-SNP) in GC receptor gene that is thought to increase GC sensitivity.
Results
In Hy patients, the T2D prevalence and F-1mgDST and R-UFF/UFE levels were higher (64.6%, 1.25 ± 0.43 μg/dL, 0.24 ± 0.13, respectively) while UFE levels were lower (86.9 ± 20.1 μg/24 h) than in non-Hy subjects (35.7%, 1.02 ± 0.41 μg/dL, 0.20 ± 0.08, 94.5 ± 21.9 μg/24 h, respectively, $P<0.05$ for all comparisons). Hy was independently associated with F-1mgDST and with R-UFF/UFE (OR, 95% CI: 6.02, 2.01-17.98, $P=0.001$; 63.3, 1.2-3326.6, $P=0.04$) regardless for *N363S*-SNP and age. The simultaneous presence of Hy, T2D and fragility FX was associated with F-1mgDST, R-UFF/UFE and *N363S*-SNP (OR, 95%CI: 6.67, 1.8–25.2, $P=0.005$; 129.1, 1.8–9108, $P=0.025$; 8.8, 1.7–45.9, $P=0.010$, respectively). The progressive increase of the number of the GC-related comorbidities (i.e. Hy, T2D and fragility FX) was significantly associated with F-1mgDST levels, R-UFF/UFE and with the prevalence of *N363S*-SNP. A eu-cortisolemic postmenopausal female with ≥2 out of *N363S*-SNP, F-1mgDST >0.9 μg/dL (24.8 nmol/L) and R-UFF/UFE >0.18 has a 4.5-fold increased risk of having ≥2 out of T2D, Hy and fragility FX (OR 4.55, 95% CI 1.97–10.53, $P<0.0001$) regardless of age.
Conclusions
In postmenopausal eucortisolemic females, Hy is associated with GC suppression and peripheral activation; the combination of Hy, T2D and fragility FX is associated with GC suppression, peripheral activation and sensitivity.

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OC7.2

Thyroid hormones are new key regulators of glucocorticoid metabolism

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The 11-beta hydroxysteroid dehydrogenase (11βHSD) isozymes are well-known regulators of glucocorticoid hormone metabolism: 11βHSD2, mostly expressed in the distal nephron, converts cortisol [F] into cortisone [E] in humans or corticosterone into 11-dehydrocorticosterone in rodents (11-dehydro derivatives being inactive compounds), and 11βHSD1, ubiquitously expressed but predominantly in the liver, catalyzes the opposite reaction. Under pathophysiological conditions of hypothyroidism in humans, altered glucocorticoid metabolism has been observed, with decreased [F] to [E] conversion (Boonen, NEJM, 2013; Warner, J Endocrinol, 2010). However, direct functional relationship between these two hormonal pathways has never been demonstrated to date. Using bioinformatics analyses, we identified five putative thyroid hormone response elements in the murine promoter region of the *hsd11b2* gene. Therefore, we aimed at investigating whether thyroid hormones (T3) directly regulate expression and/or activity of the 11βHSD2 enzyme. We used three complementary models: human and mouse translational studies and molecular analyses in HEK293T cells and in fully differentiated KC3AC1 cortical collecting duct cells. Children and adults with hypo- or hyperthyroidism were compared either to age- and sex-matched euthyroid controls, or to themselves after reaching an euthyroid status. The urinary [E]/[F] ratio measured by LC-MS/MS method, was used as an index of renal 11βHSD2 activity. Interestingly, a 60% decrease ($P<0.05$) in the [E]/[F] ratio was observed in hypothyroid patients, suggesting a regulation of glucocorticoid metabolism by thyroid hormones. Next, a mouse model of hyperthyroidism, generated by administrating T3 in drinking water, led to a significant 10% increase in renal 11βHSD2 mRNA and protein levels compared to wild type mice ($n=20$, $P<0.05$). We also demonstrated in HEK293T cells that T3 transactivates both the mouse *hsd11b2* and human *HSD11B2* promoter cloned upstream of the luciferase reporter gene *via* the Thyroid Receptor α1 (TRα1) and that transactivations are abolished in the presence of the NH3 antagonist. Finally, we showed that T3 exposure induces a 50% increase in 11βHSD2 mRNA levels in renal KC3AC1 cells, in a dose-dependent and time-dependent manner ($P<0.01$). Actinomycin D also blunted this effect, underlining a direct transcriptional regulatory mechanism. In addition, 11βHSD2 enzymatic activity, quantified by the [F] to [E] conversion ratio measured by LC-MS/MS in cell supernatants, increased significantly by 20% ($P<0.05$) after 24 h exposure to 100 nM T3. ChIP experiments further demonstrated a T3-dependent specific recruitment of TRα1 onto *hsd11b2* promoter region. Altogether, our findings demonstrate that thyroid hormones directly regulate expression and activity of the renal 11βHSD2 enzyme, thereby controlling glucocorticoid metabolism and action.

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OC7.3

Higher dose of burosumab is needed for treatment of children with sever forms of X-linked hypophosphatemia

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Background/aim
Burosumab is a monoclonal antibody against anti-FGF23, which has been recently approved for the treatment of X-linked hypophosphatemia (XLH).

Beyond clinical trials, little is known about its efficacy/safety in clinical practice which is the aim of the present study.
Patients/methods
Thirty-nine children with XLH were switched from conventional therapy to burosumab (starting dose 0.4 mg/kg), on the basis of following indications: non-responder to conventional therapy (persistence of leg deformities, elevated levels of alkaline phosphatase, need for orthopaedic surgery, presence of neurological, dental, hearing complications, secondary hyperparathyroidism, height < -2SDS); intolerance to conventional therapy (nephrocalcinosis, hypercalciuria) or late diagnosis (> 8 years). Serum phosphate level (sP) was checked before starting burosumab (M0) and monitored every 2 weeks for dose adjustment (target sP > 1.2 mmol/l). Other parameters (weight, height, ALP, $1,25(OH)_2D$, PTH, TmP/eGFR, CaU/CrU, side effects) were checked at M0, thereafter at 3 and 6 months of treatment (M3-M6).
Results
Twenty-five girls/14 boys (mean age 9.6 ± 3.8 years; 84.6% of subjects ($n = 33$) with complications) were treated with conventional therapy for 7.7 ± 3.8 years before starting burosumab. 26 patients completed 6 months of treatment. Upon burosumab, levels of sP, TmP/eGFR, $1,25(OH)_2D$ increased significantly (sP 0.7 ± 1.1 → 1.2 ± 0.2 → 1.1 ± 0.1 mmol/l; TmP/eGFR 0.6 ± 1.1 → 1.1 ± 0.2 → 1.0 ± 0.2; $1,25(OH)_2D$ 26.0 ± 15.3 → 73.4 ± 24.0 → 88.0 ± 34.4 pg/ml at M0-M3-M6, respectively, p for trend = 0.000) and ALP decreased (413 ± 163 → 333 ± 150 UI/l at M0-M6, respectively, $P = 0.3$). However, PTH level and CaU/CrU ratio were not modified during the treatment. At M6, the average dose of burosumab was 1.3 ± 0.5 mg/kg (45 ± 23 mg); 61.5% ($n = 16$) of patients did not achieve target sP level. At M6, 27% ($n = 7$) of subjects received the maximal dose of burosumab (2.0 mg/kg or 90 mg), yet had low sP level. The number of complications was positively associated with the final dose of burosumab (32 ± 13 vs 31 ± 16 vs 57 ± 24 mg for children with 0, ≤2 and >2 complications, respectively, P for trend = 0.004). We did not observe severe adverse events during the treatment, the most frequent side effect being redness at sites of injection.
Conclusion
Treatment with burosumab restores phosphate reabsorption, increases sP and endogenous $1,25(OH)_2D$ synthesis. The dose of burosumab needs to be increased with the severity of the disease.

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OC7.4

Non-invasive detection of GNAS mutations causing McCune-Albright Syndrome with ddPCR on whole blood or circulating DNA

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Context
Postzygotic activating mutations in *GNAS* are responsive for fibrous dysplasia (FD) and McCune-Albright Syndrome (MAS). MAS is a rare disease associating fibrous dysplasia, to skin pigmentation and endocrine disorders. The classic genetic non-invasive methods are insufficiently sensitive to detect *GNAS* mutation, due to a low level of mosaicism in blood. Early diagnostic should allow a follow-up and a therapeutic choice adapted to the MAS context in order to reduce the complications and optimize the quality of life. The development of a sensitive and non-invasive test represents a significant step forward for an early diagnosis improving further monitoring of the patients.
Patients and Methods
We used an ultrasensitive quantitative PCR using digital droplet PCR (ddPCR) technology for the detection of *GNAS* mutations. First we did a validation study of assays targeting the R201C and R201H mutations on 18 patients previously characterized by nested-PCR method. Then we tested the DNA of naive patients presented FD or MAS, after extraction from whole blood and from plasma, i.e. circulating cell-free DNA (ccfDNA).
Results
Seventeen patients presented 1 to 3 FD/MAS lesions were included. Using ddPCR, we detect *GNAS* mutations in whole blood DNA from 7/12 patients; and the combined analyses on both whole blood DNA and ccfDNA led to a FD/MAS molecular diagnosis in 4/5 patients.
Conclusions
We demonstrated the relevance of using ddPCR to screen for *GNAS* mutations in patients with at least one feature of FD/MAS, with considerable benefits in terms of precision, acceptability and cost-effectiveness.

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OC7.5

Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome: French prospective study in a cohort of 25 patients

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Background
APECED syndrome is a rare monogenic disease caused by homozygous mutation of AIRE gene. It classically presents with chronic mucocutaneous candidiasis (CMC), hypoparathyroidism (HP), and adrenal insufficiency (AI) with an early onset in childhood. Non-endocrine manifestations as ectodermic dystrophy, asplenism and pneumonitis are also observed but their incidence remains unknown and their mechanisms not well understood. APECED has been poorly reported in France although it is widely described in several European countries. The aim of this study was to report on rare manifestations of APECED syndrome in a French cohort and to determine the mutational spectrum of the AIRE gene at the national level.
Patients and methods
We performed a multicentric prospective observational study in France in order to collect clinical, biological, immunological and genetic data, after written informed consent in the frame of a PHRC (Hospital Project of Clinical Research #1927). Rare manifestations were systematically investigated in addition to the search of antibodies, analysis of AIRE gene, lymphocyte immunophenotyping and HLA genotyping. This evaluation was carried out 3 times in two years.
Results
We enrolled 25 patients (23 families) between 2009 and 2016. Eleven mutations of the AIRE gene were identified, two of which never previously reported: an intronic variation c.653-70G > A (intron 5) in a patient with hypoparathyroidism as unique manifestation, and c.1066del (p.Arg356GlyfsX22) (exon 9) in a patient from Guadeloupe with composite heterozygous mutations (c.967_979del13; exon 8). The most common AIRE mutation was the Finnish mutation R257X. The median number of manifestations was 7. 76% of patients presented the Whitaker triad. The most common disorders were CMC, AI and HP but pulmonary involvement (62%), ectodermal dystrophy (80%) with ocular involvement (33%), malabsorption (32%) and asplenism (26%) were common. There was an NK lymphopenia with a significant increase in T4 and T8 lymphocytes with age-dependent alteration of B lymphocyte homeostasis (inversion of the naive LB/LB memory ratio) ($P < 0.001$). 100% of tested sera were positive for anti-IFNα-antibodies, 15/18 for anti-IL-22, and 13/18 for anti-IL-17F antibodies.
Conclusion
The French population of APECED patients shows a great genotypic and phenotypic variability. We confirm an alteration of B age-dependent lymphocyte homeostasis. Systematic screening of rare manifestations as asplenism and bronchiolitis could be a useful strategy to make an earlier diagnosis, to prevent infections by vaccination and to treat earlier pulmonary involvement. Antibodies against Th17 cytokines appear as good soluble markers for diagnosis of non-classical presentation of the syndrome.

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Reproduction 1

OC8.1

Dissecting the roles of KNDy-derived kisspeptins in the control of reproduction: Generation and characterization of the Tac2-specific Kiss1 KO (TaK-KO) mouse

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Kiss1 neurons are essential elements in the central pathways controlling the reproductive axis. In rodents, two major hypothalamic populations of Kiss1 neurons exist, in the arcuate nucleus (ARC) and in the rostral periventricular area of the third ventricle (RP3V). The majority of ARC Kiss1 neurons express two others neuropeptides, neurokinin B (NKB; encoded by Tac2) and dynorphin (Dyn); hence, this population has been named KNDy. Yet, NKB-only and Kiss1-only neurons are also found in the ARC, but the relative contribution of the different subsets of Kiss1 populations to the control of reproductive function, and its modulation by metabolic factors, remains unexplored. To define the precise roles of KNDy-born kisspeptin, and hence of KNDy (vs. Kiss1-only) neurons, we report herein the generation and initial characterization of the first mouse line, named TaK-KO, with conditional ablation of Kiss1 in Tac2 expressing-neurons, produced by crossing the JAX Tac2-Cre mouse with our novel Kiss1 loxP mouse. Male and female TaK-KO mice displayed a significant decrease of ARC *Kiss1* mRNA expression at 2-months of age, while Tac2 (NKB) mRNA levels remained unaltered. Despite this drop of ARC *Kiss1* expression, puberty onset (evidenced by vaginal opening and first estrus in females, and preputial separation in males) occurred at normal timing. Further, the absence of Kiss1 in KNDy neurons did not significantly affect basal LH levels, neither did it alter LH responses to Senktide (NKB agonist) or kisspeptin-10. Yet, uterus weights were markedly decreased in 2-mo-old TaK-KO females, suggesting an incipient perturbation of the reproductive axis. This contention is further supported by initial analyses in 6-mo-old TaK-KO female mice, which displayed overt irregularities in estrous cyclicity; characterization of LH pulsatility and ovarian morphology is in progress. In parallel, our initial metabolic analyses suggest that the ablation of Kiss1 in KNDy neurons leads also to significant changes in body composition (increase of fat mass), detectable in 4 mo-old males and females, together with modest changes of glucose and insulin tolerance, mainly noticed in males. In sum, we report herein the first mouse line with conditional ablation of *Kiss1* in KNDy neurons. Our data suggest that KNDy-born kisspeptins are dispensable for puberty onset but required for proper maintenance of reproductive and metabolic homeostasis in adulthood. Ongoing studies, using different metabolic and reproductive challenges, are currently in progress in this novel mouse line to tease apart the specific roles of KNDy-derived kisspeptins in the control of these key bodily functions.

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OC8.2

AMH is a predictive factor for successful sperm retrieval in non-mosaic Klinefelter syndrome patients

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Context
Klinefelter Syndrome (KS) patients, defined by a 47 XXY karyotype, were long considered infertile. Testicular sperm extraction (TESE) now allows some of these patients to access fatherhood. The predictive factors for success, however, remain unknown.
Patients and methods
Non-mosaic KS patients with azoospermia or severe cryptozoospermia on two semen analyses without any other spermatogenesis disorder were included. They were sorted into two age groups: youths, between 15 and 22 years of age, and adults over 23. They had two clinical examinations and blood tests before conventional TESE and one after.
Results
One hundred sixty two KS patients were included between April 2010 and May 2018: 63 youths and 57 adults. Thirty-six gave up before biopsy, 72% of whom were youths. Median age at biopsy was 22 years: 18 years for youths and 31 years for adults. Sperm straws were frozen for 50 patients (41.6%): 26 youths (41.3%) and 24 adults (42.1%). Half of the adults who cryopreserved sperm did at least 1 intra-cytoplasmic sperm injection, leading to 6 pregnancies and 7 live births. Clinical features (BMI, age at diagnosis, testosterone treatment, Tanner stage, and testis volume) were similar between patients with and without successful sperm retrieval. FSH, LH, total and bioavailable testosterone, estradiol and inhibin B levels were not predictive of success. Interestingly, median AMH was significantly higher in patients with successful TESE, at 13 pmol/L [4-31] versus 3 pmol/L [0.9–15.3]; $P = 0.0049$.
Conclusion
Clinical and biological features of a very large cohort of 120 KS patients are described. We show for the first time AMH to be a predictive factor of success for sperm retrieval in non-mosaic KS patients.

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OC8.3

Endocrine Disruptors transgenerationally alters pubertal timing through epigenetic reprogramming of the hypothalamus

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Endocrine disruptors are a rising concern for public health due to their ubiquitous presence affecting reproductive development throughout generations. We aim at studying the transgenerational effect of an EDC mixture on female sexual development and reproduction. Female rats (F0 generation) were orally exposed to a mixture of 14 anti-androgenic and estrogenic EDCs or corn oil for 2 weeks before and throughout gestation and until weaning. The mixture was composed of plasticizers (BPA, DBP, DEHP), fungicides/pesticides (Vinclozolin, Procymidon, Prochloraz, Epoxynazole, Linurone, p-p'-DDT), UV filters (4-MBC, OMC), Butylparaben and the analgesic Acetaminophen. Doses were in the human exposure range (µg/kg). Sexual development and reproductive parameters (vaginal opening, GnRH secretion, estrous cyclicity and folliculogenesis) were studied from F1 to F3 generations. Maternal behavior was measured from F0 to F2 generations. At PND21, mediobasal hypothalamus of the F1 and F3 were removed for gene expression analysis (RNAseq, RT-PCR) as well as for Chromatin Immunoprecipitation of histone modifications at regulatory regions of target genes. The results show multiple multi- and transgenerational effects after ancestral EDC exposure. While F2 and F3 females showed delayed vaginal opening, decreased percentage of regular estrous cycles, decreased GnRH interpulse interval and altered folliculogenesis, no such changes were detected in F1 animals. These alterations were accompanied with transcriptional and histone posttranslational modifications of key hypothalamic genes involved in puberty and reproduction. We observed a downregulation of estrogen signaling (Esr1), genes involved in the GnRH network (Kisspeptin, Grin2d, Tac3R), maternal behavior (Th, Oxt, Avp, Drd1, Drd2) and stress responsiveness (Nr3c1). Upregulated gens involved glucocorticoid activity (Crh) and metabolism (Pomc, Cart). Concomitantly with transcriptional levels, while downregulated genes present higher levels of repressive histone marks (H3K9me3, H3K27me3) and decreased levels of activational histone marks (H3K4me3, H3K9ac), upregulated genes present the opposite pattern. Such histone marks related to changes in the polycomb/thritorax group of protein balance, involved in the control of female puberty. F1 and F2 females displayed decreased licking while spending more time resting alone. F1 RNAseq showed a reduction in Th, *Drd1* and *Drd2* mRNA expression. These alterations on maternal behavior are known to cause transgenerational alterations of the development of the corticotropic and gonadotropic axis. In conclusion, exposure to an environmentally relevant EDC mixture transgenerationally affects sexual development and reproduction throughout epigenetic reprogramming of the hypothalamus. While not yet clear, such effects could be mediated by alterations of maternal behavior caused by exposure to the first generation.

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OC8.4

Conditional ablation of AMP-Activated Protein Kinase (AMPK) in GnRH neurons reveals specific roles in reproductive and metabolic homeostasis

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Reproduction is tightly coupled to body energy and metabolic status. GnRH neurons, the final output pathway for the brain control of reproduction, directly or indirectly receive and integrate multiple signals, including metabolic cues regulating reproductive function. Yet, the molecular underpinnings of such phenomenon remain largely unfolded. AMP-activated protein kinase (AMPK), a fundamental cellular sensor that becomes activated in conditions of energy deficit, has a key role in the control of whole-body metabolism. Fragmentary evidence suggests that AMPK participates also in the control of key elements of the reproductive axis, as Kiss1 neurons, driving an inhibitory valence in situations of energy depletion. However, the physiological contribution of AMPK signaling in GnRH neurons to the metabolic control of reproduction is unknown. We report herein the characterization of the first mouse line, named GAMKO, with conditional ablation of a1-AMPK in GnRH neurons. In keeping with a putative inhibitory action of AMPK in GnRH neurons, GAMKO females displayed earlier puberty onset and exaggerated LH (as surrogate marker of GnRH) responses to kisspeptin-10 at the prepubertal age. In adulthood, GAMKO females retained increased LH responsiveness to kisspeptin and the neurokinin-B agonist, Senktide, and showed partial resilience to the inhibitory effects of conditions of negative energy balance on the gonadotropic axis. Thus, GAMKO females submitted to chronic subnutrition showed a faster recovery of estrus cyclicity after re-feeding. Furthermore, elimination of AMPK from GnRH neurons prevented the physiological drop of LH level after fasting and changed the pattern of LH pulsatility. The modulatory role of AMPK in GnRH neurons seems to require estradiol, since no changes in basal LH levels or pulsatility were detected in ovariectomized GAMKO mice subjected to fasting or subnutrition. Notably, AMPK ablation on GnRH neurons caused also alterations in body composition, with increased fat mass, and modest changes in insulin and glucose tolerance in GAMKO females. In sum, our data document a physiological role of AMPK signaling in GnRH neurons in the metabolic control of the reproductive axis, as conduit of at least part of the inhibitory actions of energy deficit. In addition, our results disclose a putative function of AMPK specifically in GnRH neurons in the control of body composition and glucose homeostasis, whose relevance warrants further investigation.

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OC8.5

The neurokinin 3 receptor antagonist, fezolinetant, is effective in treatment of menopausal vasomotor symptoms: responder analysis results from a randomized, placebo-controlled, double-blind, dose-ranging study

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Background
The brain's thermoregulatory center is stimulated by activation of neurokinin 3 receptor (NK3R) and inhibited by estrogen. In menopause, declining estrogen disturbs this balance, producing vasomotor symptoms (VMS). This study assessed response to the NK3R antagonist fezolinetant in women with menopausal VMS.
Methods
This phase 2b, double-blind trial (NCT03192176) randomized menopausal women (age >40−65 y) with moderate/severe VMS (≥50/wk) to fezolinetant 15, 30, 60, or 90 mg BID or 30, 60, or 120 mg QD or placebo for 12 weeks. Response and percentage reduction in frequency of moderate/severe VMS were prespecified secondary endpoints. Response was defined as ≥50%, 70%, 90%, or 100% reduction in moderate/severe VMS; odds ratios for response were analyzed via logistic regression. Kaplan-Meier was used to estimate time to response, which was summarized descriptively. Least squares (LS) mean percent reduction from baseline in daily VMS frequency was determined with a mixed effect model repeated measures approach.
Results
Of 356 women randomized, 352 received ≥1 dose of study drug (safety population; mean [SD] age: 54.6 [4.7] y; 73% white) and 287 (81%) completed the study (placebo: 84%; fezolinetant: 80%). The percentage of patients with 50% reduction in moderate/severe VMS at last on-treatment assessment was significantly higher with fezolinetant 15, 30, 60, and 90 mg BID (83.7%, 81.4%, 88.1%, and 94.7%, respectively) or 30, 60, and 120 mg QD (82.1%, 88.1%, and 84.1%, respectively) than with placebo (58.5%; all $P < .05$ for odds ratio for response vs placebo). Mean time to 50% reduction in moderate/severe VMS ranged from 2.2–8.4 days with fezolinetant depending on dose, and 15.1 days with placebo (Figure 1). LS mean percentage reduction from baseline to week 12 in daily frequency of moderate/severe VMS were 74.3%, 75.8%, 80.2%, and 86.9% for 15, 30, 60, and 90 mg BID and 75.1%, 77.7%, and 76.9% for 30, 60, and 120 mg QD, respectively (common SE: ∼5; all $P < .01$). Most TEAEs were mild/moderate. No deaths or serious treatment-related TEAEs occurred.
Conclusion
A significantly larger percentage of women treated with most doses of fezolinetant achieved treatment response, compared with placebo, and percentage reductions in daily moderate/severe menopausal VMS were significantly larger with fezolinetant. Kaplan-Meier estimates demonstrate a rapid onset, as early as the first few days.

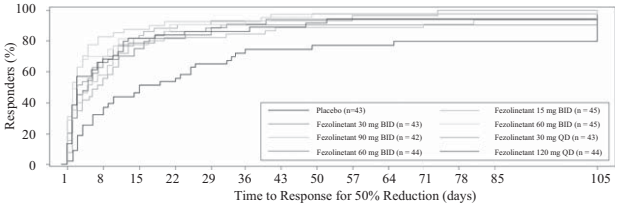

Figure 1 Kaplan-Meier Plot of Time to 50% Reduction in Moderate/Severe VMS.

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Thyroid 2

OC9.1

3D mapping and in silico predictions of the DEHAL1 enzyme as a tool to discriminate pathogenic mutations from non-functional variants in hypothyroidism

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Next Generation Sequencing (NGS) is becoming widely used for genetic diagnosis. While its capacity for detection of human genetic variations (GV) is outstanding, drawbacks is the identification of numerous GV of which functional significance cannot be predicted *in silico* by computer programs (variants of uncertain significance, VUS). Currently, only sensitive (but also expensive and time-demanding) *in vitro* cell assays, can trustfully ascertain pathogenicity of VUSs, generally of selected proteins o signalling pathways, seriously hampering efficiency of genetic diagnostic for the clinic.
Objective
To apply 3D mapping and *in silico* predictions as tools to inform pathogenicity of GVs identified in hypothyroid patients with alleged iodotyrosine deiodinase deficiency, as compared with *in vitro* dehalogenation assays.

Methods
Nine missense DEHAL1 variants identified in goitrous hypothyroid patients were subjected to both *in vitro* functional testing and *in silico* 3D modelling and docking with substrates (MIT, DIT) and cofactor (FMN), using available X-Ray crystallographic information of dimeric DEHAL1. Three (K258N, V265M and R279S) were identified in patients with undisputed diagnosis of iodotyrosine deiodinase deficiency through *in vivo* ^{123}I-MITdeiodination test. The rest (N108S, A202T, R246Q, L260P and E271K) are harboured by patients with clinical suspicion of DEHAL1 defect. The functional assay involved mutagenesis of DEHAL1 variants in expression vectors, transfection in HEK293 cells, addition of MIT, FMN and NADPH to culture medium and determination of % MIT decrease by LC/MS-MS.
Results
The functional assay showed significant decrease of deiodination for K258N (60%) and R279S (58%) versus WT. However, V265M did not, suggesting limitations of our assay to detect less severe mutations. The rest of variants showed normal deiodination with the exception of L260P, which behaved as deleterious (10%). Interestingly, *in silico* studies on K258N, R279S, V265M and L260P revealed that the amino acids changes had damaging effects on the structural stability, electrostatic properties or interaction with cofactor and substrates (FMN and MIT) on the DEHAL1, and provide a structural explanation for the iodotyrosine deiodinase deficiency. Besides, the peripheral location of N108S, A202T, R246Q, and E271K variants in *the* model correlates with the benign nature of such changes in the assay.
Conclusions
Structural modelling and molecular dynamics is a valuable tool to discriminate pathogenic vs VUS changes in human *DEHAL1*, showing consistency with the *in vitro* assay and superior sensitivity to detect some pathogenic changes. An additional advantage of this filtering approach is the prediction of the intrinsic molecular mechanism driving the functional damage of mutations.

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OC9.2

Direct evidence for disulfides in the mechanism of deiodinase 1

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The main product of the thyroid gland, T_4, is a prohormone. 5'-deiodination is needed to convert T_4 into the active, nuclear receptor-binding hormone, T_3. Pharmacological modulation of activating 5'-and inactivating 5-deiodination of iodothyronines would be desirable in a number of medical conditions, including hypothyroidism, hyperthyroidism and various cancers. A structural and mechanistic understanding of deiodinase (DIO) catalysis is a prerequisite of successful pharmacological intervention. Structural data on deiodinases are currently limited on the intracellular catalytic domain of murine Dio3 (1). However, deiodinases are membrane anchored proteins and it is known that the membrane anchor contributes to activity of the enzymes. In order to elucidate the mechanism of deiodinases, we have recombinantly expressed full length human DIO1 as a membrane protein in insect cells. Since these cells do not have the capacity to express selenoproteins, selenocysteine (Sec)126 was replaced by cysteine (Cys). The resulting protein was expressed at high levels and catalytically active in the presence of mM concentrations of DTT as reductant. Similar to murine Dio3, human DIO1 was active in the presence of a physiological reducing system comprising of glutaredoxin (1 μM), glutathione (GSH), GSH reductase, and NADPH. We replaced a series of conserved Cys in DIO1 with Ser or Ala and showed that all these mutations reduced the activity of the enzyme. We could assign different functions to these cysteines. DIO1 is known to function as a dimer. A new finding is that according to mass-spec analyses, Cys95 and possibly Cys105 contribute to stabilization of the dimer via inter-subunit disulfides. In addition, mass-spec analysis for the first time directly demonstrated the formation of a disulfide between Cys124 and Cys(Sec)126 during catalysis as suggested before. Data derived from analysis of mutant DIO1 are compatible with a reducing mechanism similar to that in murine Dio3. Taken together we show for the first time the formation of inter-subunit and intra-subunit disulfides within DIO1. Their function is revealed by the use of a physiological reducing system comprised of Grx, GSH, GR, and NADPH instead of the non-physiological provision of the synthetic DTT reductant.
Reference
1. Schweizer U, Schlicker C, Braun D, Köhrle J, Steegborn C. (2014) Crystal structure of mammalian selenocysteine-dependent iodothyronine deiodinase suggests a peroxiredoxin-like catalytic mechanism. *Proc Natl Acad Sci U S A*. 2014 Jul 22;111(29):10526–31. doi: 10.1073/pnas.1323873111.

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OC9.3

Novel driver mutations in thyroid cancer recurrence

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The incidence of thyroid cancer is rapidly increasing worldwide. Whilst outcome in thyroid cancer is generally good, up to 25% of patients develop recurrence, and have a significantly reduced life expectancy. We hypothesise those thyroid tumours which subsequently recur display a distinct pattern of driver events. Whole exome sequencing data were downloaded from The Cancer Genome Atlas (TCGA). Bioinformatic analysis of data on $N=43$ patients whose tumours recurred was performed, using a Platypus, Annovar and SIFT/PolyPhen2/MutationTaster filtering pipeline. This identified mutations in biologically significant genes, including Inosine-5'-monophosphate dehydrogenase 2 (IMPDH2), 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 4 (PFKFB4) and Dicer 1 ribonuclease type III (DICER1). As in-silico analysis suggested these variants to be potentially pathogenic, we recapitulated mutations from TCGA. Subcellular localisation, proliferation, cellular migration and invasion were investigated in cell lines which represent the most common background driver mutations of papillary thyroid cancer (TPC1: RET/PTC; SW1736: BRAF; Cal62: KRas). In TPC1 cells IMPDH2 mutation significantly increased cell migration at 4, 8 and 24 hrs vs. WT ($P=0.0068$, $P=0.0008$, $P=0.0088$ respectively) and DICER1 mutation induced increased cell migration at 24 hours vs. vector-only ($P=0.0094$). Overexpression of IMPDH2 resulted in altered intracellular localisation into intracellular discrete bodies known as cytoophidia. As recurrence may also affect altered gene expression, we analysed the RNA profile of the recurrent patients ($N=43$) compared to the non-recurrent ($N=457$). In particular, genes involved in matrix adhesion and thyroid cancer pathogenesis were most differentially expressed in recurrence patients, including fibronectin 1 (FN1), thyroglobulin (TG), α3 integrin (ITGA3), SPARC-like protein 1 (SPARCL1), Integral Membrane Protein 2A (ITM2A) and the proto-oncogene mesenchymal-epithelial transition factor (MET) ($P=0.00376$, $P=0.00311$, $P=0.00757$, $P=0.01874$, $P=0.00003$, $P=0.00003$ respectively). Overall, we propose that rare somatic mutations on top of established driver events, as well as specifically altered RNA expression levels, may be key to predicting thyroid cancer prognosis.

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OC9.4

Resistance to thyroid hormone alpha associated with early-onset severe NASH

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Introduction
Resistance to thyroid hormone alpha (RTHα) is characterised by tissue-specific hypothyroidism associated with barely normal thyroid function tests. Clinical features include dysmorphic facies, skeletal dysplasia, growth retardation, constipation, dyspraxia and intellectual deficit. Hormonal assessment often shows decreased/low-normal free thyroxine (fT4) and increased/high-normal free triiodothyronine (fT3) concentrations, resulting in a low fT4/fT3 ratio, with a non-adapted normal thyroid stimulating hormone (TSH) level. We describe the case of a 14-year-old *THRA* mutant girl who was diagnosed at birth with peripheric congenital hypothyroidism and who developed marked hypercholesterolemia and severe non-alcoholic steatohepatitis (NASH). Phenotypical presentation includes marked abdominal obesity, macrocephaly, macroglossia, short and large nose, micrognathia and low-implanted ears, associated with mild intellectual impairment.
Methods
A panel of genes involved in congenital hypothyroidism was explored by next generation sequencing (NGS) on DNA sample. Pathogenic variant was confirmed by Sanger sequencing of exon 10 of the *THRA* gene for the proband and her mother. Functional analysis was performed on HepG2 cell line using plasmid transfection of wild type (wt) TRα1 and TRβ, mutated TRα1 and reporter plasmids containing

thyroid hormone responsive elements coupled to the luciferase gene. Transcriptional effect has been assessed through luciferase activity.
Results
Next generation sequencing identified a heterozygous single nucleotide c.1207G>A (p.E403K) *THRA* mutation on exon 10 resulting in impaired function of α1 receptor isoform. The patient's mother carried the same *THRA* mutation. Transfection studies on HepG2 cells showed a significant lower transactivation effect of the mutant TRα1 compared to wt TRα and a dominant negative transcriptional effect of mutated TRα1 on both wt TRβ and TRα.
Conclusions
This peculiar case associates classical clinical and biological features of RTHα with a previously unreported first-plan metabolic profile: obesity, hyperlipidaemia and severe NASH. Functional *in vitro* studies suggest a dominant negative effect of mutated TRα1 receptor on wild type TRβ, which is the main isoform expressed in the liver, as well as on wild type TRα, which is mainly represented in adipose tissue. Taken together, these data are in favor of a pathogenic role of $TR\alpha1^{E403K}$ in the development of this unique hepato-metabolic profile. This case further strengthens the wide phenotypical variability of RTHα presentation and the pleiotropic effect of TRs.

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OC9.5

Deciphering the origin of the sexually dimorphic thyrotropin secretion in mouse models

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Hypothyroidism refers to a thyroid hormone (TH) deficiency which mainly affects women (10/1 ratio). The higher default incidence in women remains unexplained. Diagnosis of hypothyroidism is based on a single thyroid-stimulating-hormone (TSH) measurement albeit TSH secretion displays pulsatile patterns which are under the positive control of hypothalamic thyrotropin-releasing-hormone (TRH) and negative feedback exerted by THs. Pituitary thyrotrophs form the smallest (2-4%) pituitary endocrine population and the processes which govern their TSH secretion *in vivo* remain largely unknown. The aim of this study is to explore whether pituitary thyrotrophs form, *in vivo*, a functionally-organized and sexually dimorphic cell population capable of generating TSH pulses. Circulating mouse TSH levels were measured using an ultra-sensitive in-house mTSH ELISA, uncovering various pulsatile patterns which would differentially stimulate the thyroid gland. In order to identify the origin of TSH secretion, calcium signals were monitored *in vivo* in mouse models, as a surrogate of the stimulus-TSH secretion coupling and cell-cell communication between thyrotrophs. Using thin needles of gradient-index (GRIN) lenses (7.6 mm long, 0.6 mm diameter) implanted at the pituitary level and a 2g head-mounted miniscope, multicellular calcium activities of the thyrotroph population were monitored in freely-moving TSHβ-cre*x*R26*fl*-*fl*GCaMP6f mice. Such signaling events were monitored during longitudinal studies (weeks to months) in which individual animals act as their own controls. We unveiled that the thyrotroph population functions *in vivo* as a robust generator of recurrent, slowly-evolving calcium waves which propagate between neighboring thyrotrophs and lead to the generation of ultradian TSH fluctuations. To further dissect the mechanisms underlying these sequences of calcium events, we conducted experiments on anesthetized animals, in which hypothalamic (i.e. TRH) inputs were blunted. Several injection patterns of hypothalamic TRH or TSH unveiled how TSH pulses were built-up *in vivo*. In male mice, TSH pulsatility resulted from a finely-tuned combination of prolonged TRH inputs together with an ultrashort intra-pituitary feedback loop exerted by TSH itself. In female mice, distinct patterns of calcium signals were observed in both basal and TRH/TSH-stimulated conditions. Moreover, 3D confocal imaging revealed sexually dimorphic, multicellular thyrotroph motifs (clusters in females vs. columns in males) which were spatially organized in fixed 'cleared' pituitaries. Altogether, our data support that a sexually dimorphic thyrotroph organization underlies a sexually dimorphic stimulus-TSH secretion coupling in animal models.

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Adrenal 2

OC10.1

Steroid metabolomics: a rapid computational approach for accurate differentiation of inborn disorders of steroidogenesis

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Background
Measurement of steroid metabolite excretion in urine by gas chromatography-mass spectrometry (GC-MS) provides a comprehensive profile of an individual's adrenal and gonadal steroid production. It has long been acknowledged as a useful tool for diagnosis of inborn disorders of steroidogenesis leading to congenital adrenal hyperplasia and disorders of sex development. Ratios of steroid metabolites can be employed as surrogates for enzymatic activities of distinct steroidogenic enzymes and can also be applied to single random urine samples, making this a more feasible approach for use with paediatric patients. However, widespread use in the acute setting for diagnosis of these disorders is hampered by the considerable expertise required for interpretation. Here we developed a novel steroid metabolomics approach for the detection and differential diagnosis of inborn steroidogenic disorders, combining mass spectrometry-based steroid profiling with machine learning-based data analysis, suitable for automation and interpretation without specialist expertise.
Methods
We performed multi-steroid profiling by GC-MS, quantifying 34 steroid metabolites, in urine samples from 829 healthy controls and 178 untreated patients with inborn steroidogenic disorders. This cohort included patients with inborn deficiencies in the following enzymes: CYP21A2 ($n=26$), CYP11B1 ($n=12$), CYP17A1 ($n=30$), POR ($n=37$), HSD3B2 ($n=22$), and SRD5A2 ($n=51$). We assessed the diagnostic performance of conventional biochemical assessment employing 15 steroid precursor-to-product ratios, each historically established as indicative of a distinct steroidogenesis disorder. We compared this to the performance of our novel steroid metabolomics approach, which involved analysis of the GC-MS multi-steroid profiles by a custom-designed approach, Angle Learning Vector Quantization (ALVQ), which classifies samples by comparing similarity of their steroid metabolome to representative steroid metabolome prototypes for each enzyme deficiency.
Results
The conventional biochemical steroid ratio approach demonstrated acceptable sensitivity and specificity. However, the automated steroid metabolomics approach (ALVQ) performed significantly superior to this, particularly with regards to specificity. For differentiating patients from healthy controls, sensitivity and specificity of ALVQ were 97% and 98%, respectively. For differentiation of each pathogenic enzymatic defect, ALVQ performed superiorly, with sensitivity and specificity ranging between 95 and 100%.
Conclusion
We present a novel steroid metabolomics approach, able to automatically detect and differentiate six different inborn disorders of steroidogenesis, with improved performance when compared to reference standard metabolite ratios. Steroid metabolomics can expedite and standardise interpretation of complex urinary steroid metabolome data, making this technique more accessible to clinicians, and has excellent potential for implementation in routine clinical practice.

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OC10.2

Glucocorticoid resistance patients exhibit defective cortisol metabolism, responsible for functional hypermineralocorticism

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Glucocorticoid resistance syndrome, a rare genetic disease, is often associated with glucocorticoid receptor (GR) loss-of-function mutations. Six patients carrying heterozygous mutations of *NR3C1* gene encoding GR, either missense R477S, Q501H, L672P or non-sense R469X, R491X, Y660X mutations were studied. Surprisingly, *NR3C1* mutation carriers presented with low kalemia, low plasma renin and aldosterone levels associated or not with arterial hypertension, consistent with functional hypermineralocorticism. Importantly, circulating corticosterone or 11-deoxycorticosterone levels, when measured in these patients, were in the normal range, excluding the involvement of these mineralocorticoid agonist compounds in the pathogenesis of pseudohypermineralocorticism, as initially suggested. In this context, we hypothesize that the clinical and biological features of glucocorticoid resistant patients might be secondary to a partial impairment of GR regulation of *HSD11B2*, leading to an enzymatic defect of the renal 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), considered as a major MR-protecting mechanism, and thus responsible for an illicit cortisol activation of the mineralocorticoid receptor (MR). The 11β-HSD2 catalyzes the conversion of cortisol into cortisone, unable to bind MR. *HSD11B2* promoter presented with putative glucocorticoid response elements. Transient transfections of plasmid expressing the wild-type GR and *HSD11B2* promoter-luciferase construct in HEK293T cells, disclosed a dexamethasone-dependent increase of reporter gene activity that was totally inhibited by cotreatment with the GR antagonist RU486, indicating a GR-mediated transactivation of *HSD11B2* gene. Likewise, a defective GR Q501H mutant fails to stimulate luciferase activity. In the absence of human renal model endogenously expressing 11β-HSD2, we demonstrate a 3-fold increase in DXM-induced *HSD11B2* mRNA levels in human breast cancer MCF7 cells, which was abolished by RU486 or by the transcription inhibitor Actinomycin D, further supporting a GR-dependent transactivation. The 11β-HSD2 activity, evaluated by cortisone/cortisol ratio quantified by LC-MS/MS, was 10-fold higher in the supernatant of DXM-treated cells than controls, strongly suggesting a GR-dependent stimulation of 11β-HSD2 catalytic activity. Collectively, we provide evidence that 11β-HSD2 expression is transcriptionally regulated by GR. In the context of GR haploinsufficiency, these findings bring additional support for a reduced HSD11B2 transcription and 11β-HSD2 activity, driven by GR signaling defect. Thus, patients carrying heterozygous loss-of-function *NR3C1* mutations exhibited an impaired 11β-HSD2 enzymatic activity, leading to a functional pseudohypermineralocorticism. These findings call for a careful monitoring of such patients to prevent or adequately control the hypertension and its associated cardiovascular consequences.

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OC10.3

Genetic predisposition to Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH): next generation sequencing ARMC5, NR3C1 (glucocorticoid receptor) and PDE11A4 (phosphodiesterase 11) in 389 patients

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Introduction
PBMAH is an heterogeneous disease from the clinical, hormonal, and morphological point of view. *ARMC5* inactivating mutations have been reported as a cause of PBMAH. *PDE11A4* variants have been associated with PBMAH and *NR3C1* variants with bilateral adrenal incidentalomas.
Aim
To analyse the frequency of *ARMC5* pathogenic mutations and *PDE11A4* and *NR3C1* variants in PBMAH patients.
Methods
ARMC5, *PDE11A4* and *NR3C1* were sequenced on leucocyte DNA by NGS using Ion Torrent technology in 389 PBMAH index cases. Identified variants were then annotated using Annovar tool. Combined bioinformatic filters (sequence depth more than 5, allelic ratio more than 0,1 and total population frequency according to Exac less than 5%) and visual validation using Integrative Genomics Viewer (IGV) software were used in order to identify and retain the variants.
Results
Pathogenic *ARMC5* mutations are present in 75 patients (20%). *PDE11A4* and *NR3C1*variants were observed respectively in 23.4% and 8.9% of the patients. The overall frequency of PDE11A4 variants was similar in *ARMC5* mutated and wild type (WT) patients (*P*:0.88), while NR3C1 variants were more frequent in the *ARMC5* WT (*P*:0.04). The following *PDE11A* missense variants already known for altering enzymatic activity have been found: p.R804H in 15 patients (13 ARMC5 WT), p.R867G in 14 patients (9 ARMC5 WT), p.M878V (9 ARMC5 WT) and p.D609N (in 1 ARMC5 mutated patient). Interestingly a stop codon mutation initially reported in Micronodular Adrenal Hyperplasia (p.R307X) was identified in 1 ARMC5 mutated and in 3 ARMC5 WT. Five NR3C1 variants have been found: 3 already known as polymorphism: p.R23K, p.F65V, p.N363S. The last one is associated with high glucocorticoid sensitivity and bilateral adrenal incidentalomas (1 in the *ARMC5* mutated, 18 in *ARMC5* WT) whereas the first one is associated with healthier metabolic profile (1 in *ARMC5* MUT, 9 in *ARMC5* WT). Two variants not previously reported have been identified: p.S404P predicted benign in 1 patient; p. N454S predicted pathogenic in 1 patient.
Conclusion
These results show that clear pathogenic mutations of *PDE11A4* and *NR3C1* are probably rare in PBMAH. By contrast variants that might change the activity of the phosphosphodiesterase or the sensitivity to glucocorticoids are present in PBMAH patients regardless of the *ARMC5* status. Genotype/phenotype correlation analysis will help to determine their potential role in the modulation of the disease phenotype, both in term of PBMAH development or complications of cortisol excess.

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OC10.4

Cullin 3 is a partner of armadillo repeat containing 5 (ARMC5), the product of the gene responsible for primary bilateral macronodular adrenal hyperplasia

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Background
Germline mutations of *ARMC5* (Armadillo repeat containing 5 gene) were identified as a frequent cause of primary bilateral macronodular adrenal hyperplasia (PBMAH). *ARMC5* is considered as a tumor suppressor gene regulating apoptosis and steroidogenesis by unknown mechanisms. The ARMC5 protein contains a N-terminal domain made of Armadillo (ARM) repeats and a C-terminal 'Bric-a-Brac, Tramtrack, Broad-complex/Pox virus and Zinc finger (BTB/POZ)' domain. Both domains are important for protein-protein interactions, suggesting that the study of ARMC5 partners might help to understand its cellular function. By co-immunoprecipitation coupled with mass spectrometry, we identified a potential interaction between ARMC5 and Cullin3 (CUL3), also suggested in online databases and in a Yeast-2-Hybrid assay. C*UL3* serves as a scaffold protein and assembles a large number of ubiquitin ligase complexes which mediate ubiquitination and degradation of specific substrates. Therefore, our aim was to confirm this interaction and investigate its mechanisms.
Methods
We performed immunoprecipitation experiments, bioluminescence resonance energy transfer (BRET) proximity assays, protein stability experiments and

ubiquitination assays in order to investigate the interaction of ARMC5 with CUL3.
Results
ARMC5 co-immunoprecipitated with CUL3 and a hyperbolic BRET saturation curve was observed with YFP-CUL3 and ARMC5-Luc indicating a specific proximity between these proteins. We also observed that the *ARMC5* missense mutation in the BTB domain (p.L754P) identified in a patient diagnosed with PBMAH disrupts the interaction with CUL3 and increases ARMC5 protein stability. Moreover, CUL3 overexpression increased ubiquitination of ARMC5 while no effect was observed on ARMC5-p.L754P mutant. Finally, inhibition of the ubiquitin-dependent proteasome system with MG132 induced accumulation of endogenous ARMC5 in secondary cell culture of PBMAH (without ARMC5 alteration), while no effect was observed in a secondary PBMAH cell culture carrying a mutation in the BTB domain (p.H808P) of ARMC5.
Conclusion
In this study we demonstrated the interaction between ARMC5 and CUL3. This interaction leads to the ubiquitination of ARMC5, suggesting that ARMC5 is a substrate for a CUL3-based ubiquitin complex. Moreover, missense mutants in the BTB domain of ARMC5, identified in patients diagnosed with PBMAH, alters the interaction with CUL3 and the ubiquitination by CUL3-based ubiquitin/proteasome system. These data show a new mechanism of regulation of the ARMC5 protein and open new perspectives in the understanding of the pathophysiology of PBMAH.

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OC10.5

Cyclin dependent kinase 4 as promising drug target in adrenocortical carcinoma

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Adrenocortical carcinomas (ACC) are associated with heterogeneous prognosis and limited treatment options for advanced stages. Until now no efficient targeted therapies have been identified. This study aims to identify possible new molecular drug targets for a future personalized therapeutic approach. RNA was isolated from 40 formalin-fixed paraffin-embedded tumor samples from ACC patients (26F&14M, median age 46 yrs) with known genetic background (*Lippert et al. JCEM 2018*). Gene expression of 84 known cancer drug targets was evaluated by RT^2 Profiler PCR Array (Qiagen) and fold change (FC) was calculated with the 2^(-ΔΔCT) formula using 5 normal adrenal glands (NAG) as reference. Most frequently overexpressed genes were *TOP2A* (100% of cases, median FC = 16.5), *IGF2* (95%, FC = 52.9), *CDK1* (80%, FC = 6.7), *CDK4* (62%, FC = 2.9), *PLK4* (60%, FC = 2.8) and *PLK1* (52%, FC = 2.3). CDK4 was chosen as the most promising candidate for functional validation as actionable by approved CDK4/6 inhibitors. ACC samples with copy number gains at *CDK4* locus ($n = 24$) presented significantly higher *CDK4* expression levels ($P = 0.0023$). Nuclear CDK4 protein expression was investigated by immunohistochemistry and significantly correlated with mRNA expression ($R = 0.52$, $P < 0.005$). Efficacy of CDK4/6 inhibitor palbociclib (0.5–16 μM) was tested *in vitro* using two adrenocortical carcinoma cell lines (NCI-H295R and MUC1). We found a concentration- and time-dependent reduction of cell viability, which was more pronounced in NCI-H295R in line with higher CDK4 expression at western blot analysis. Furthermore, we tested palbociclib in combination with dual IGFR/IR inhibitor linsitinib (0.125–4 μM) and showed a synergistic effect on inhibiting cell viability. In conclusion, in this proof-of-principle study we confirm that RNA profiling is useful to discover potential drug targets that could be then investigated by immunohistochemistry in the clinical practice. CDK4/6 inhibitors are promising candidates for treatment of a subset of patients with adrenocortical carcinoma.

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Diabetes 2

OC11.1

Hormonal factors and type 2 diabetes risk in women: a 22 year follow-up study on more than 83 000 women from the E3N cohort study

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Background
Early screening and the treatment of glucose metabolism disorders could lower the risk of further complications. For this purpose it is important to identify the risk factors of type 2 diabetes mellitus (T2DM). The aim of this study was to determine the association between various hormonal factors and the risk of incident type 2 diabetes in the large prospective female E3N cohort study.
Material and methods
The study included 83,799 French women from the Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N) prospective cohort followed between 1992 and 2014. Cox multivariable models adjusted for the main T2DM risk factors were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) between various hormonal factors and T2DM risk.
Results
We observed that the elevated age at menarche (HR = 0.88 [0.81–0.95]), the younger age at first term pregnancy (HR = 0.90 [0.82–0.98]), breastfeeding (HR = 0.90 [0.85–0.95]), the elevated number of total menstrual cycles (HR = 0.75 [0.68–0.82]), the elevated age at menopause (HR = 0.70 [0.63–0.78]) and the elevated duration of sex hormone exposure (HR = 0.66 [0.61–0.73]) was associated with a lower risk of type 2 diabetes. While, the use of contraceptive pills (HR = 1.33 [1.25–1.42]) and the elevated duration of menstrual cycles (HR = 1.23 [1.07–1.41]) was associated with the elevated risk of type 2 diabetes.
Conclusion
It seems that longer exposure to sex hormones but later in life could reduce diabetes. Risk induced by oral contraceptives could lead to personalized advice for young women at risk.

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OC11.2

Molecular mechanisms regulating hepatic sex hormone-binding globulin production: clinical implications in human diseases

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Human sex hormone-binding globulin (SHBG) is produced by the liver and secreted it into the circulation where it binds androgens and estrogens with high affinity. Therefore, SHBG acts as a carrier of these sex steroids and regulates their bioavailability. Low plasma SHBG levels are associated with obesity, fatty liver disease, abdominal adiposity and metabolic syndrome, and predict the development of type 2 diabetes. In addition, an inverse relationship between plasma SHBG levels and risk of cardiovascular disease has been reported. The SHBG gene has changed its tissue expression and therefore its function during the evolution. Rodents express the SHBG gene in the Sertoli cells of the testis. While in humans, the SHBG gene is expressed in the liver and in the germ cells of the testis. This change of function and tissue expression can be explained by the appearance during evolution of new footprinted regions in the human promoter and an alternative promoter. The generation of different transgenic mice expressing the human *SHBG* gene has allowed us to study the SHBG expression and regulation *in vivo*. We have used these mice and HepG2 cells to provide evidences that SHBG expression is regulated by thyroid hormone, proinflammatory cytokines (TNFα and IL1β), adiponectin, monosaccharides, olive oil and resveratrol (red wine). We have described the underlying molecular mechanisms by which all these factors regulate *SHBG* gene expression that involve the regulation of several transcription factors, such as HNF4α, PPARγ and CAR. These findings give an explanation of why diseases such as obesity, type 2 diabetes, hyperthyroidism, fatty liver disease and inflammatory disease (rheumatoid arthritis) have altered plasma SHBG levels. Finally, the generation

of these mouse models has allowed us to demonstrate that SHBG overexpression can protect against obesity and fatty liver development point-out SHBG modulation as a novel therapeutic strategy for the treatment of these prevalent diseases.

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OC11.3

Implications of circulating Meteorin-like (Metrnl) level in human subjects with type 2 diabetes

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Aims
Meteorin-like (Metrnl) was recently identified as a novel adipomyokine induced by exercise and cold exposure. Metrnl improves glucose tolerance, increases systemic energy expenditure, induces white adipose browning, and promotes anti-inflammatory gene programs in obese/diabetic mice. However, the relationship of Metrnl with diabetes and cardiometabolic risk variables in humans has not been explored.
Methods
In 800 subjects (400 patients with type 2 diabetes and 400 non-diabetes), Metrnl concentration was measured with an enzyme-linked immunosorbent assay, and the correlations of Metrnl level with anthropometric parameters, lifestyle factors, body composition values, and laboratory measurements were assessed.
Results
Metrnl concentration was significantly higher in patients with diabetes than in those without diabetes [median (inter-quartile range); diabetes: 1219.9 (1020.6, 1535.6), non-diabetes: 1131.2 (993.1, 1313.6) pg/ml, $P < 0.001$]. After adjustment for age and sex, Metrnl level was significantly associated with fasting plasma glucose, blood pressure, lipid profile, and eGFR, but not with BMI or percent body fat. Multiple stepwise regression analysis exhibited that Metrnl level was independently associated with diabetes status ($P < .001$), eGFR ($P < .001$), and total cholesterol ($P = .026$) ($R^2 = 0.127$). In multiple logistic regression analysis, the odds ratio for the risk of diabetes was 3.53 (95% confidence interval: 2.04–6.10) in the highest tertile of Metrnl compared to the lowest after adjustment for confounding factors.
Conclusions
This study is the first to demonstrate that Metrnl level is elevated in human subjects with type 2 diabetes and is inversely related to various cardiometabolic risk factors, including renal function.

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OC11.4

MiR-30e-5p expression is downregulated in plasma and urine of type 1 diabetic patients with diabetic kidney disease

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Background and aims
Diabetic kidney disease (DKD) is a common microvascular complication that affects 40% of patients with diabetes mellitus (DM). Emerging evidence suggests a role for microRNAs (miRNAs) in the development of DKD. In this context, miR-15a-5p and miR-30e-5p have been shown to regulate the expression of the uncoupling protein 2, a mitochondrial protein that decreases reactive oxygen species (ROS) formation by mitochondria. Since ROS overproduction is a key contributor to the pathogenesis of DKD, dysregulation of these miRNAs may be involved in DKD pathogenesis. Thus, the aims of this study were to compare miR-15a-5p and miR-30e-5p expressions in plasma and urine of type 1 DM (T1DM) patients with DKD (cases) or without this complication (controls) and to perform bioinformatics analyses to investigate their putative targets and biological pathways under their regulation.
Methods
MiR-15a-5p and miR-30e-5p expressions were analyzed in plasma and urine of 17 T1DM controls and 23 DKD cases (12 with moderate DKD and 11 with severe DKD) using real-time PCR. DKD was classified following the Kidney Disease Improving Global Outcomes guidelines, using both urinary albumin excretion (UAE) levels and estimated glomerular filtration rate (eGFR). Bioinformatics analyses were performed using the Cytoscape software.
Results
MiR-30e-5p expression was downregulated in plasma of patients with moderate or severe DKD compared to T1DM controls [severe DKD: 0.53 median (0.25–0.84, 25th–75th percentiles), moderate DKD: 0.25 (0.08–0.82), and T1DM controls: 2.42 (0.51–4.33) n fold changes, $P = 0.003$]. In urine samples, miR-30e-5p expression was only downregulated in severe DKD group compared to the other groups [severe DKD: 0.34 (0.05 – 0.85), moderate DKD: 3.92 (0.23 – 9.66), and T1DM controls: 2.96 (0.99 – 5.97), $P = 0.017$]. No difference was found in miR-15a-5p expression among groups. MiR-15a-5p and miR-30e-5p expressions showed significant negative correlations with UAE ($r = -0.459$, $P = 0.016$ and $r = -0.617$, $P = 0.0001$, respectively) and HbA1c levels ($r = -0.432$, $P = 0.009$ and $r = -0.435$, $P = 0.004$, respectively). No correlation was found between these miRNAs and eGFR or creatinine levels. Bioinformatics analyses indicate that 2197 genes are putative targets of miR-15a-5p and 2208 of miR-30e-5p, being 314 of these genes modulated by both miRNAs. Moreover, these genes participate in pathways related to angiogenesis, apoptosis, cell differentiation, oxidative stress, and hypoxia.
Conclusions
MiR-30e-5p seems to be downregulated in plasma and urine of patients with DKD. Bioinformatics analyses suggested that miR-15a-5p and miR-30e-5p regulate genes involved in key mechanisms related to DKD pathogenesis.

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OC11.5

Bone metabolism and circulating myeloid calcifying cells in diabetic post menopausal women: a case-control study

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Introduction
Diabetes mellitus (DM) is a chronic disease associated with multi-organ complications, including poor bone quality and high risk of frailty fracture. Bone and vascular complications seemed to be connected, as diabetic patients with atherosclerotic lesions show enhanced extrascheletric calcifications which in turn are associated with increased fracture risk. The aim of this study was to assessed bone mineral density (BMD) and trabecular bone score (TBS) in diabetic post-menopausal women and healthy controls, and correlate them with aortic calcifications, markers of bone turn-over, glucose metabolism and myeloid calcifying cells (MCCs).
Materials and methods
23 diabetic post-menopausal women and 25 healthy female subjects matched by age were recruited; all subjects underwent a blood exam for glucose, lipid and bone metabolism profile. MCCs were measured using flow cytometry based on the expression of osteocalcin (OC) and bone alkaline phosphatase (BAP) on monocytes and circulating CD34+ stem cells. Abdominal aortic calcifications were evaluated using Kauppila score.
Results
Bone turn-over markes (β-cross laps, BAP, OC and procollagen I N-terminal) were lower in diabetic group, and were inversely correlated with glycemia and HbA1c. We found differences in lumbar Z-score, total femur BMD, total femur T-score that were lower in the controls (-0.02 ± 1.2 vs 0.735 ± 1.4, $P = 0.048$; 0.820 ± 0.1 vs $0.902 \pm 0 - 1$, $P = 0.010$ and 1.004 ± 0.9 vs 0.330 ± 0.9, $P = 0.011$). A direct correlation was found between BMI and total BMD ($r = 0.519$, $P < 0.001$) and total T score ($r = 0.523$, $P < 0.001$). On the contrary, BMI was negatively correlated with TBS ($r = -0.495$, $P < 0.001$). TBS was significantly lower in diabetic women (1.18 ± 0.2 vs 1.26 ± 0.1, $P = 0.037$). DM-patients presented lower magnesium levels than controls (0.78 ± 0.1 vs 0.84 ± 0.1, $P = 0.012$) and it was linked with total cholesterol ($r = 0.355$, $P = 0.014$) and HDL ($r = 0.378$, $P = 0.009$). MCCs levels did not differ among the two groups of patients and were related with BAP levels. Kauppila score was higher in the diabetic group (4.2 ± 4.8 vs 2 ± 2.7, $P = 0.052$) and it was directly correlated to glycemia ($r = 0.310$, $P = 0.032$) and HbA1c ($r = 0.315$, P 0.029). This score was directed correlated to the percentage of OC+ BAP+/CD34+ cells ($r = 0.304$, $P = 0.036$).
Conclusion
Our preliminary data confirmed that the function of bone tissue is not limited to body support and organ protection; in fact, it plays a pivotal role in regulating both glucose metabolism and cardiovascular complications development in type 2 DM, being at the same time a cofactor and a target of diabetic complications.

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Endocrine Connections 2

OC12.1

Weekly shifts in light-dark cycle disrupt circadian clock gene expression in bone and reduce bone turnover

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The past decade, epidemiological studies have associated disturbances of the biological clock, as occurs in shift work, with low bone mineral density and increased fracture risk. As a large part of the working population participates in shift work (e.g. almost 30% of workers in the U.S.), this demonstrates the need for further research on the risk of skeletal disorders associated with circadian disturbances. In this study, we aimed to investigate to what extent rhythmicity exists in bone, and whether circadian disruption by weekly shifts in light-dark cycle affects bone turnover and structure in mice. To evaluate whether gene expression in bone is rhythmic, tibiae were collected from mice every 6 hours over a 24 hour period ($n=9$/timepoint). In these bones, we found diurnal expression patterns of clock genes (*Rev-erbα*, Bmal1, Per1, Per2, Cry1, *Clock*), as well as genes involved in osteoclastogenesis, osteoclast proliferation and function (*Rankl*, Opg, Ctsk) and osteocyte function (*c-Fos*). To study the importance of this rhythm for bone health, mice were subjected to either normal light-dark cycles or weekly 12 hour shifts in light-dark cycle for 16 weeks ($n=8$/group). Weekly shifts resulted in a disruption of clock gene expression in bone (i.e. reversed rhythm of *Rev-erbα* ($P<0.001$) and *Cry1* ($P<0.01$), and attenuated rhythm of *Bmal1* ($P<0.001$) and *Clock* ($P<0.05$) three days after a shift), and a reduction in plasma levels of procollagen type 1 amino-terminal propeptide (P1NP, -22.4%; $P<0.05$) and tartrate-resistant acidic phosphatase (TRAP; -19.9%; $P<0.01$), suggestive of a reduced bone formation and bone resorption, respectively. Moreover, shifts in light-dark cycle significantly altered trabecular bone structure as determined by micro-CT, and seemed to reduce bone length and weight, consistent with impaired bone growth. Collectively, these results suggest that circadian rhythm is important for bone health, and that circadian disruption negatively affects bone turnover markers and bone structure.

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OC12.2

Epigenetic programming of transgenerational hypertension in preterm birth mice

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Renal and cardio-vascular complications of prematurity are well established, notably those associated with renal tubular immaturity, responsible for major salt loss at birth, as well as early hypertension in adulthood. However, the molecular underlying mechanisms remain poorly understood. Our objective was to investigate the impact of preterm birth on the ontogenesis of renal corticosteroid pathways, to evaluate its implication on perinatal complications and on the emergence of hypertension in adulthood. Swiss CD1 pregnant mice were injected with O111:B4 lipopolysaccharides (LPS) at 18 days of gestation to induce preterm birth at 18.5 days of gestation. Offspring of injected mice, when LPS did not trigger preterm birth, were used as a control to exclude intrinsic LPS effects. Pups were sacrificed at various developmental stages (D0, D7 and M6). Blood pressure and heart rate were measured in males at M6 and their plasma steroid profiles were measured using LC-MSMS. Renal mRNA and protein expression of major players of corticosteroid signaling pathways were measured using RT-qPCR and western-blot analyses. Second (F2) and third (F3) generations, established by mating prematurely born adult females with wild type males, were also analyzed. We performed Methylation DNA Immunoprecipitation-qPCR to study the methylation status of candidate corticosteroid target genes that were differentially expressed between the two populations. As anticipated, preterm newborn mice presented with maladaptation, high neonatal mortality (35%), and a lower birth weight compared to controls (1.29 ± 0.21 *vs* 1.46 ± 0.15g, $P=0.0027$). Former preterm males developed hypertension at M6 (123.1 ± 1.43 *vs* 114.5 ± 0.79 mmHg, $P<0.0001$). We found a robust activation of renal corticosteroid target gene transcription at birth in preterm mice (*αENaC* ($+45\%$), *Sgk1* ($+132\%$), *Gilz* ($+85\%$)), which was not related to modified expression of the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR). Interestingly, a significant increased blood pressure was found in the F2 and F3 males, descendants of the preterm group, concomitantly with increased renal *Gilz* mRNA expression, despite similar MR or GR expression, and plasma aldosterone or corticosterone levels. *Gilz* promoter methylation was reduced in preterm offspring with a negative correlation between methylation and expression ($P=0.008$), highly suggestive of an epigenetic *Gilz* regulation. Our study demonstrates prematurity-related alterations of renal corticosteroid signaling pathways, with a transgenerational inheritance of blood pressure dysregulation and epigenetic Gilz regulation up to the third generation. This study should allow a better understanding of molecular mechanisms involved in essential hypertension, which could partly be due to perinatal epigenetic programming from previous generations.

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OC12.3

Neuronostatin and GPR107 system: a novel therapeutic circuit in prostate cancer

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Somatostatin (SST)-system is a pleiotropic hormonal system composed by several ligands/receptors that is involved in the regulation of multiple pathophysiological functions. Specifically, certain components of the SST-system are dysregulated in several endocrine-related cancer types compared to control tissues, wherein these alterations seem to influence their development/progression. However, the presence and functional role of neuronostatin (NST) and its putative G-protein coupled receptor GPR107, two novel members of the SST-system, have not been fully explored in cancer. Consequently, we aimed to investigate the pathophysiological role of NST and GPR107 in prostate cancer (PC), one of the most diagnosed tumors among men worldwide, whose most aggressive phenotype [Castration-Resistant PC (CRPC)] remains lethal nowadays. Functional parameters (cell proliferation and migration) were analysed in response to NST treatment (10^{-7}M) and GPR107-silencing in different PC derived cell-lines [androgen-dependent (AD) LNCaP and androgen-independent (AI) 22Rv1 and PC-3; which are models of hormone-sensitive and CRPC, respectively)], and in normal prostate (NP) cells (RWPE-1 cell-line and primary cell cultures). Moreover, western-blotting, RT-qPCR and microfluidic-based qPCR-array were implemented to determine the mechanisms of actions associated to NST treatment and GPR107-silencing in PC-cells. NST-treatment significantly inhibited proliferation and migration rate in AI-PC cells, but not in AD-PC or in normal-cells (RWPE-1 or primary cell-cultures). Mechanistically, the antitumor capacity of NST was associated with a reduction in GPR107 expression levels, and a significant down-regulation of the expression of key genes involved in proliferation (*MKI67/CDK6*), migration (*MMP9/PRPF40A*) and PC-aggressiveness (*sst5TMD4/AR-v7/ghrelin/In1-ghrelin/EZH2/MYC*) as well as with the modulation of important oncogenic signalling-pathways (ERK/p-ERK; AKT/p-AKT; JNK/p-JNK). Remarkably, these functional anti-tumor effects exerted by NST on AI-PC cells were blunted after GPR107-silencing, suggesting that the antitumor actions of NST in PC-cells might be mediated via GPR107. Indeed, we found that GPR107 was significantly overexpressed in AI-PC cells compared to RWPE-1 cells, as well as in a cohort of PC samples compared to healthy control adjacent tissues ($n=85$) and in two in silico-independent samples cohorts (Grasso/Varambally). Finally, GPR107-silencing in AI-PC cells induced a significant decrease in proliferation and migration rate and evoked a similar dysregulation in the expression pattern of key

genes previously found in response to NST treatment (i.e. downregulation of *MKI67/MMP9/sst5TMD4/AR-v7/ghrelin/In1-ghrelin*). Altogether, our results demonstrate that NST treatment reduces PC-aggressiveness in CRPC cells via GPR107 and through the alteration of different key molecular signalling pathways, suggesting that NST/GPR107 system might be considered as a novel therapeutic tool for CRPC.

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OC12.4

Long-term follow-up of antitumoral immunotherapy- induced hypophysitis in Lille hospital, France

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Ojective
We characterized the onset and follow-up of hypophysitis in a cohort of 612 patients treated for a cancer by antitumoral immunotherapy between june 2010 and may 2017 in CHU Lille, France. Design and patients: 612 patients treated by anti-CTLA4 and or antiPD-1 for melanoma ($n=426$), lung cancer ($n=166$), hematological cancer ($n=19$) or maxillary epidermoid cancer ($n=1$).
Methods
Follow-up of patients treated by immunotherapy. Symptoms, pituitary function and pituitary imaging at diagnosis of hypophysitis and during the follow-up were recorded.
Results
Of 612 patients treated with Ipilimumab or Nivolumab or Pembrolizumab alone or in association, 29 patients presented an hypophysitis (4.7%). The follow-up was on average 64 weeks (39–142). The maximal follow-up was 9 years. 7 patients have received cerebral radiotherapy before the diagnosis of hypophysitis and 11 had cerebral metastatis when the cancer was diagnosed. The main initial symptom was asthenia, 38% patients were asymptomatic. All patients had at least one hormonal defect: corticotroph 96.5%, thyréotroph 48%, gonadotroph 19%, somatotroph 31% (on 19 patients evaluated); one had transient diabetes insipidus; 31.5% had an abnormal rate of prolactin. 22% had an evocative pituitary imaging. Among the patients, 9 have received high-dose glucocorticoids (for hypophysitis $n=4$, cerebral metastasis progression $n=2$, other adverse event of immunotherapy $n=3$). At the end of follow-up 10 patients continued immunotherapy, 19 had stopped (12 for progression of disease, 3 for remission, 4 because of other adverse event of immunotherapy). Corticotroph deficiency persist in 87% of patients, thyréotroph deficiency in 20%, somatotroph deficiency in 66% of 6 patients evaluated (and 2 new deficiencies), gonadotroph deficiency in 25% (1 new deficiency). There was no difference between the two groups (persistance of deficiency or not) for age, sex, number of injections, cumulated dose, continuation of treatment at the end of follow-up, cerebral radiotherapy, other previous treatments. On the other hand more patients recovered from their deficit if they had no cerebral metastasis ($P=0.043$), if they have received high-dose of glucocorticoids ($P=0.031$). Use of two or more immunotherapy lines seemed to be an adverse factor for the recovery of deficits.
Conclusion
Immunotherapy-induced hypophysitis is a common side-effect with frequent hormonal deficiencies at diagnosis. Hypophysitis happens more frequently in patients treated for melanoma. No cerebral metastasis, high dose glucorticoids appear to be an adverse factor in hormonal recovery. on the other hand use of two or more immunotherapy lines seem to be an adverse factor.

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OC12.5

Sexual desire in transgender persons in relation with gender affirming hormone treatment: Results from ENIGI, a large multicenter prospective cohort study in transgender people

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Background
The effect of testosterone on sexual arousal has been described in testosterone withdrawal and re-adminstration studies in birth-assigned males. In birth-assigned females, the relationship between sex steroids and sexual arousal is complex. Several steps in the transitioning process may affect sexual desire: hormone therapy (HT) and gender affirming surgery. HT in transgender men (TM) generally leads to increased sexual desire, masturbation frequency, sexual fantasies and arousal. Studies in transgender women (TW) are often inconclusive.
Methods
This prospective cohort study was part of the European Network for the Investigation of Gender Incongruence (ENIGI). Upon first clinical contact, psychological questionnaires were completed. Sexual desire (the Sexual Desire Inventory), serum levels of sex steroids, relationship status and surgical interventions were prospectively assessed in 766 participants (401 TW, 364 TM) during a three-year follow-up period, starting at the initiation of HT. Data were analyzed cross-sectionally and prospectively.
Results
Baseline SDI scores were comparable in TW and TM ($P=0.342$). In TW, SDI scores decreased from 39.0 [23.0–54.5] (baseline) to 33.0 [16.3–49.8] (12 months) (-4.77, $P<0.001$), returning to scores comparable to baseline after 18 months ($P=0.114$). After 36 months, SDI scores were higher than baseline scores (51.5 [39.5–61.0], $P=0.003$). In TM, total SDI scores increased from 40.0 [17.0–52.0] (baseline) to 55.0 [40.5–67.0] ($+14.61$, $P<0.001$) (12 months), remaining stable over the following year and returning to scores comparable to baseline scores (58.0 [23.0 – 62.0], $P=0.250$) after 36 months. Factors associated with higher SDI-scores included having a partner ($P<0.001$), having lower levels of self-reported gender dysphoria at baseline (Utrecht Gender Dysphoria Scale, UGDS) (TW only: $P=0.002$) and undergoing hystero-oophorectomy (TW only: $P=0.035$). Serum levels of sex steroids, type of HT and undergoing other types of surgery did not influence cross-sectional SDI scores. Factors associated with a higher prospective increase in SDI scores included undergoing gonadectomy (TW: $P=0.041$, TM: $P=0.001$) and having lower levels UGDS scores at baseline ($P<0.001$). Serum levels of sex steroids, type of HT and undergoing other types of surgery did not influence prospective changes in SDI scores.
Conclusions
Overall, sexual desire scores initially increased in TM and decreased in TW, although three-year results show a small increase in TW and status quo in TM, compared to baseline scores. We observed no association between sexual desire and serum levels of sex steroids. Other factors, such as undergoing gonadectomy, relationship status and gender dysphoria may influence sexual desire in transgender people.

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Anterior and Posterior Pituitary 2

OC13.1

Arginine-stimulated copeptin measurements - a new test for diabetes insipidus

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Background
The differential diagnosis of diabetes insipidus is challenging. The most reliable diagnostic approach is hypertonic saline-stimulated copeptin measurements. However, as this test is based on the induction of hypernatremia, it is associated with adverse effects and needs close sodium monitoring. We hypothesized that arginine-stimulated copeptin measurements provide an alternative, simple and safe diagnostic test for diabetes insipidus.
Methods
We recruited a development cohort (cohort 1, $N=52$) and a validation cohort (cohort 2, $N=44$) including patients with central diabetes insipidus (total $N=38$) and with primary polydipsia (total $N=58$). All patients and 92 healthy controls underwent arginine stimulation with 0.5 g L-Arginin-Hydrochlorid/kg body weight, infused over 30 minutes. Copeptin levels were measured at baseline and 30, 45, 60, 90, 120 minutes after arginine infusion. The primary objective in the first cohort was the diagnostic accuracy of copeptin levels at each measurement after stimulation whereas the second cohort should validate these results.
Results
Arginine infusion stimulated median [IQR] copeptin levels in healthy controls and in patients with primary polydipsia (3.6 pM/L [2.4, 5.7] to 7.9 pM/L [5.1, 11.8]), but not in patients with diabetes insipidus (2.1 pM/L [1.9, 2.7] to 2.5 pM/L [1.9, 3.1]). In the first cohort, a cutoff of 3.5 pM/L at 60 minutes provided the highest diagnostic accuracy to discriminate between diabetes insipidus and

primary polydipsia: 0.94 [95% CI] [0.84, 0.98], sensitivity 91%, specificity 97%. The diagnostic accuracy of this cutoff in the second cohort was 0.86 [0.73, 0.94]. By pooling the data of both cohorts an optimal diagnostic accuracy was reached for a cutoff of 3.8 pM/L at 60 minutes: 0.93 [0.86, 0.97], (sensitivity 93%, specificity 92%). The test was safe and well tolerated: the test burden (median value on a visual analogue scale from 0 [no discomfort] to 10 [maximal discomfort]) was rated 3.5 and 3 in patients with diabetes insipidus and primary polydipsia and 1 in healthy controls.

Conclusion

Arginine is a potent stimulus of the neurohypophysis. Arginine-stimulated copeptin measurements are an innovative tool to discriminate between central diabetes insipidus and primary polydipsia with high diagnostic accuracy.

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OC13.2

Empagliflozin increases sodium-levels in patients with the syndrome of inappropriate antidiuretic hormone secretion – a randomized, double-blind, placebo-controlled trial

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Introduction

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the predominant cause of hyponatremia but the available treatment options are unsatisfying and often of little efficiency. The selective sodium-glucose co-transporter 2 inhibitor empagliflozin promotes osmotic diuresis due to glucosuria and might be a novel treatment option for SIADH.

Material and methods

From September 2016 through December 2018 we randomly assigned 88 hospitalized patients with hyponatremia below 130 mmol/l due to SIADH to receive either 25 mg of empagliflozin or placebo once daily in addition to standard fluid restriction. The primary endpoint was defined as absolute change in plasma sodium concentration after four days of treatment.

Results

In total, 84 patients completed the trial of whom 40 (48%) received treatment with empagliflozin and 44 (52%) were allocated to placebo. There were no significant between-group differences among main baseline characteristics, showing an elderly study population with a median age of 80 years (IQR 65–84) in the empagliflozin and 78 years (IQR 73–85) in the placebo group. Baseline median plasma sodium concentrations were 126 mmol/l (IQR 122–127) and 126 mmol/l (IQR 123–127), respectively. The most common cause of SIADH was drug-induced. Treatment with empagliflozin resulted in a significantly higher increase of median plasma sodium concentration of 10 mmol/l (IQR 5–13) compared to placebo with 7 mmol/l (IQR 3–11), $P=0.039$. Sodium overcorrection, defined as an increase of more than 12 mmol/l per day, occurred in one patient per group.

Conclusion

In patients with SIADH, empagliflozin in addition to fluid restriction leads to a higher increase in plasma sodium levels compared to placebo and therefore is a promising new treatment option.

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OC13.3

Pituitary tumour-derived chemokines modulate immune cell infiltrates in the tumour microenvironment leading to aggressive phenotype

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Introduction

Tumour microenvironment (TME) is determined by non-tumoral cells, including immune, stromal or endothelial cells, and influences tumorigenesis, proliferation, invasiveness and angiogenesis. Little is known about TME in pituitary adenomas (PAs). We aimed to characterise the TME of PAs and its role in their aggressiveness, focusing on PA-infiltrating immune cells and cytokine network.

Methods

Cytokine secretome from 24 human PAs (16NFPAs, 8GHomas) was assessed on primary culture supernatants using a multiplex immunoassay panel with 42 cytokines. These data were compared to immunohistochemical analysis of the same tumours assessing endothelial cells (CD31), macrophages (CD68), 'M2'-macrophages (CD163), 'M1'-macrophages (HLA-DR), cytotoxic T lymphocytes (CD8), T helper lymphocytes (CD4), T regulatory cells (FOXP3), B cells (CD20) and neutrophils (neutrophil elastase), and 5 normal pituitaries were studied for comparison.

Results

The cytokine array identified IL-8, CCL2, CCL3, CCL4, CXCL10, CCL22 and CXCL1 as the main PA-derived cytokines. PAs with increased macrophage and neutrophil content had higher IL-8, CCL2, CCL3, CCL4 and CXCL1 levels, while CD8+T lymphocyte PA-infiltration was associated with higher CCL2, CCL4 and VEGF-A levels. No significant associations between PA-derived cytokines and CD4+T, FOXP3+ and B cells were noted. PA immune cell infiltrates differ from normal pituitary: PAs contained more CD68-macrophages (4.6 ± 0.4 vs $1.2\pm0.2\%$, $P<0.001$), with a 3-fold increased M2:M1 macrophage ratio, more CD4+T cells (1.0 ± 0.1 vs $0.6\pm0.1\%$, $P=0.005$), but fewer neutrophils (0.7 ± 0.2 vs $1.4\pm0.1\%$, $P=0.047$) and a trend for fewer CD8+T cells (1.8 ± 0.2 vs $2.6\pm0.3\%$, $P=0.077$) with a 2-fold decreased CD8:CD4 T cell ratio. NFPAs had significantly more neutrophils than GHomas (0.9 ± 0.1 vs $0.1\pm0.1\%$, $P=0.002$), but there were no differences regarding other immune cell subpopulations. PA-infiltrating immune cells did not correlate with the respective serum immune cell subpopulations, suggesting differential recruitment into the PA rather than altered bone marrow production. PAs with higher Ki67 had a higher amount of FOXP3+T cells, as well as lower CD68:FOXP3, CD8:CD4 and CD8:FOXP3 cell ratios. All PAs with deleterious immune infiltrate phenotype ($CD68^{hi}CD4^{hi}FOXP3^{hi}CD20^{hi}$) had $Ki67\geq3\%$. M2:M1 ratio was positively correlated with microvessel density ($P=0.015$) and area ($P<0.001$).

Conclusions

PAs are primarily infiltrated by macrophages with an increased M2:M1 ratio compared with normal pituitary, but also have reduced CD8:CD4 and CD8:FOXP3 T cell ratios. PA-derived chemokines (IL-8, CCL2, CCL3, CCL4 and CXCL1) facilitate macrophage, neutrophil and T cell recruitment into the tumour, and our data suggest that this modulation of immune cell infiltrates in the TME determines increased aggressiveness.

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OC13.4

Pharmacokinetics of somapacitan in individuals with hepatic impairment: an open-label, parallel group, phase 1 study

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Background

Somapacitan is a reversible albumin-binding growth hormone (GH) derivative developed for once-weekly administration. Non-covalent binding to endogenous albumin delays somapacitan elimination, prolonging its half-life and duration of action. Somapacitan is not cleared by a specific organ, but impaired hepatic function may affect its pharmacokinetics. We report data from an open-label, parallel group, phase I trial (NCT03212131) investigating the pharmacokinetic and pharmacodynamic properties, and safety of somapacitan in individuals with mild and moderate hepatic impairment, and normal hepatic function.

Methods

Participants were enrolled in a 16:9:9 ratio to normal hepatic function, mild hepatic impairment, and moderate hepatic impairment, respectively. Participants received a total of three somapacitan administrations (0.08 mg/kg), one per week for 3 weeks.

Results

Thirty-four participants were included: normal function, $n=16$; mild impairment, $n=9$; moderate impairment, $n=9$. Somapacitan AUC_{0-168h} was higher in the moderate impairment group (estimated ratio [ER]=4.69; 90% confidence

interval [CI]: 2.92–7.52) and similar in the mild impairment group (ER = 1.08; 90% CI: 0.66–1.75), versus the normal function group. C_{max} had a similar pattern to $AUC_{0\text{-}168h}$. Median t_{max} was longer for the moderate impairment group (15.8 hours), versus the mild impairment (11.8 hours) and normal function groups (11.9 hours). $AUC_{0\text{-}168h}$ of IGF-I and IGFBP-3 were similar in the mild and moderate impairment groups, but lower than the normal function group ($AUC_{IGF\text{-}I,0\text{-}168h}$ ER = 0.85 [90% CI: 0.67–1.08] and 0.75 [90% CI: 0.60–0.95], respectively). Lower levels of IGF-I and IGFBP-3 were noted at baseline in both impairment groups compared with the normal function group. Albumin values were within normal range for all but two moderate impairment group participants. No unexpected safety signals were reported.

Conclusions

Despite greater exposure to somapacitan, individuals with hepatic impairment exhibited a decreased IGF-I and IGFBP-3 response. GH resistance associated with hepatic impairment may potentially explain the lower response. The increased exposure may indicate that liver GH receptors are either reduced in number, creating a saturation effect for elimination, or not fully functioning after GH binding, slowing elimination. Since albumin concentrations were mostly within normal range, and somapacitan occupancy of albumin is very low (< 0.0005%), it is highly unlikely that decreased albumin concentrations caused increased exposure. Despite the higher exposure in individuals with moderate hepatic impairment, adequate treatment response may require higher somapacitan doses owing to the reduced IGF-I response. However, as somapacitan is planned to be individually dose-titrated, no specific adjustments to the dosing recommendations are relevant.

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OC13.5

Pan-genomic classification of pituitary adenomas

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Pituitary adenomas, now called pituitary neuroendocrine tumors (PitNETs), vary in histological type, secretion, invasion and growth speed. A World Health Organization (WHO) histo-prognostic classification was released in 2017. Pituitary tumorigenesis is largely unexplained. Rare germline mutations (*MENIN, AIP*), and common somatic mutations in somatotroph (*GNAS*) and corticotroph (*USP8*) are reported. Recently, genomic analyses have been reported. Yet, driver genes and pathways remain to be fully identified, as well as a comprehensive view of omics in the different subtypes of PitNETs.

Aim

To provide a genomic unbiased classification of PitNETs.

Methods

A clinical, histological and genomic characterization of 134 PitNETs of all subtypes was performed, combining exome, RNA and miRNA sequencing, SNP array and methylation array. Unsupervised classifications were generated (non-negative matrix factorization and hierarchical clustering).

Results

Median somatic mutation rate was 95, mainly C > T substitutions belonging to 'signature 1' trinucleotide signature. No difference was observed between histotypes. Only GNAS and USP8 presented > 5% mutations. Three chromosome alteration profiles were identified: extended losses, 'quiet' profiles, and extended gains. Gonadotroph and silent corticotroph were mainly 'quiet'. Chromosomal alterations were not related to aggressiveness. Epigenomic classifications (miRnome and methylome) were strongly associated with PitNETs histological type and secretion (χ^2 $P < 10–18$). Especially, PitNETs from POU1F1 (Pit1) lineage (lacto-, thyro- and somatotroph) showed diffuse DNA hypomethylation. Hypomethylation was correlated with genomic instability (correlation coefficient: 0.4). Unsupervised transcriptome classification revealed 6 groups, associated with histotype and secretion (χ^2 $P < 10–59$), with four noticeable discrepancies compared to WHO2017 classification: « null-cells » were not distinct from gonadotroph; silent corticotroph PitNETs fell apart from overt Cushing corticotroph PitNETs; 5/8 sparsely granulated somatotroph PitNETs were grouped with thyrotroph and PIT1 plurihormonal PitNETs; lactotroph PitNETs were distinct from mixed GH-PRL and somatotroph PitNETs. USP8 and GNAS mutations formed specific homogeneous subgroups. Silent corticotroph and gonadotroph shared a common gonadotroph signature.

Conclusion

This genomic study unravels important new aspects of PitNETs biology. Mainly:
- DNA hypomethylation and chromosomal instability of PitNETs of the Pit1 lineage, suggesting that Pit1 differentiation may induce chromatin opening, with subsequent genome instability.
- A specific molecular signature of sparsely granulated somatotroph PitNETs, which may help to better understand and predict resistance to somatostatin analogues. - Silent corticotroph PitNETs combine corticotroph and gonadotroph differentiation signatures.

This genomic classification of PitNETs supports the importance of pituitary lineage in pituitary tumorigenesis, and proposes a first robust and unbiased classification based on tumor biology.

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Sex Hormones

OC14.1

Testosterone replacement therapy is able to reduce prostate inflammation in men with BPH, metabolic syndrome and hypogonadism: preliminary results from a randomized placebo-controlled clinical trial

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Objectives

BPH is characterised by prostate inflammation, which frequently occurs in men with metabolic syndrome (MetS). MetS is often associated with low testosterone (T). Recent evidence shows that low, rather than high, T is associated with BPH/lower urinary tract symptoms (LUTS). To evaluate if T replacement therapy (TRT) for 6 months in BPH men with MetS and low T, is able to improve LUTS and prostate inflammation.

Methods

120 men in waiting list for BPH surgery and diagnosed with MetS were enrolled in the trial. According to total T (TT) and calculated free T (cFT), they were categorized into eugonadal (TT ≥ 12 nmol/L and cFT ≥ 225 pmol/L; $n = 48$) and hypogonadal men (TT < 12 nmol/L and/or cFT < 225 pmol/L; $n = 72$). Hypogonadal men randomly received T gel 2% (5 g/daily) or placebo for 6 months. At baseline and follow-up visit (after 6 months), all men filled-out the IPSS and NIH-CSPI questionnaires and underwent a transrectal prostatic ultrasound. After surgery, prostate tissue was collected for the assessment of gene expression, by RT-PCR, and of the histopathologic inflammatory score.

Results

After adjusting for the baseline value, age, TT and waist circumference, NIH-CSPI total score significantly decreased in both the groups ($P < 0.001$ vs. baseline), whereas IPSS total score did not change in any of the groups. IPSS bother score significantly decreased only in T-treated ($P = 0.042$ vs. baseline). Although a significant increase in total prostate and adenoma volume occurred in T-treated (both $P < 0.05$ vs. baseline), TRT arm was characterised by a significant decrease in ultrasound markers of prostate inflammation, including arterial velocity and acceleration (both $P < 0.01$ vs. baseline value). The assessment of the gene expression showed that several markers of inflammation (COX2, MCP1, RORγt and IP10) and metabolic-induced inflammation (LDLoxR, RAGE and IRS1), were significantly down-regulated in T-treated men as compared with placebo arm (all $P < 0.05$) and, in some cases, TRT was even able to decrease the gene expression below the values of eugonadal men (MCP1, IP10 and IL12) (all $P < 0.05$). In a subset of men (23 eugonadal, 8 placebo-treated and 9 TRT), TRT showed a trend towards a lower histopathological inflammatory score as compared with eugonadal and placebo-treated men (analyses ongoing).

Conclusions

Six-month treatment with T gel 2% in hypogonadal men with BPH and MetS is able to improve several clinical, ultrasound and molecular proxies of prostate inflammation. This results into a moderate improvement in symptoms, particularly bother for LUTS.

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OC14.2

The effect of testosterone therapy on serum oestradiol levels in transgender men

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Background
Testosterone therapy in transgender men (TM) is aimed at achieving serum testosterone levels in the male reference range. It remains unknown if serum oestradiol levels in TM should be evaluated and/or adjusted. Although reported serum oestradiol levels in TM are variable in the current literature, these values may be affected through two possible mechanisms: serum oestradiol levels may increase through aromatization of exogenous testosterone, while the effects of exogenous testosterone on endogenous oestradiol and gonadotropins remain unknown.
Methods
This prospective cohort study was part of the European Network for the Investigation of Gender Incongruence (ENIGI). Serum levels of sex steroids, gonadotropins and body composition were prospectively assessed in 746 TM during a three-year follow-up period, starting at the initiation of testosterone. BMI, body fat%, sex steroids, gonadotrophines were measured at each visit. Data were analyzed cross-sectionally and prospectively (Δ).
Results
Testosterone therapy resulted in a decrease in oestradiol levels over thirty-six months (−34.2, 95% CI −41.1 – −27.3, $P<0.001$), and this was already apparent after the first three months (−17.13, 95% CI −23.82 – −10.56, $P<0.001$). Serum LH levels did not change over the course of testosterone therapy ($P=1.000$), although serum FSH levels remained stable over the first nine months ($P=0.997$), with an increase between nine and thirty-six months (+12.1, 95% CI 4.3 – 19.9). Mean BMI values increased during the first year (+0.744, 95% CI 0.1 – 1.3, $P=0.024$), returning to values comparable to baseline at 18 months ($P=0.880$), and remaining stable thereafter ($P=0.557$). Mean total body fat percentage decreased over the first two years (−11.6, 95% CI −14.3 – −8.8, $P<0.001$), remaining stable thereafter ($P=0.618$). Δ (serum oestradiol) was positively correlated to Δ (serum LH) ($\rho=0.107$, $P< 0.001$) and negatively to Δ (serum FSH) ($\rho=-0.167$, $P<0.001$) and Δ (BMI) ($\rho=-0.082$, $P<0.001$) over the entire follow-up period. Δ (serum oestradiol) was not correlated to Δ (serum testosterone) ($P=0.973$) nor to Δ (total body fat percentage) ($P=0.688$).
Conclusions
Testosterone administration in TM is associated with a decrease in serum oestradiol levels, already apparent at three months follow-up. The observed decrease could not be explained by changes in serum gonadotropins nor by changes in body composition. It remains to be determined to which extent the observed decrease is due to suppression of endogenous oestradiol production and/or decreased aromatase activity. As serum oestradiol levels decrease in TM, we do not suggest monitoring and/or adjusting oestradiol levels for clinical practice.

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OC14.3

First identification of bone morphogenic protein receptor variants as a cause of primary ovarian insufficiency

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Bone morphogenetic proteins (BMPs) exhibit broad spectrum of biological activities in various tissues, including bone, cartilage, blood vessels, heart, kidney, neurons, liver and lung. BMPs are members of the transforming growth factor-β (TGF-β) family that bind to type II and type I serine-threonine kinase receptors, and transduce signals through Smad and non-Smad signalling pathways. BMPs together with other intraovarian growth factors are intimately involved in regulation of ovarian follicle recruitment, dominant follicle selection, ovulation, and atresia. We conducted a Whole Exome Sequencing on 69 Caucasian women with sporadic primary ovarian insufficiency (POI) and performed a bioinformatics analysis on a specific subset of 420 coherent candidate genes[1]. We found heterozygous variants in genes encoding *BMP* Receptors (*BMPR1A* and BMPR1B) in three POI women. POI is a major cause of infertility and is characterized by amenorrhea with an increase in gonadotropin levels and affects 1% of women before the age of 40. This disease may be the result of a variety of disorders caused by two main mechanisms: abnormal follicular development and follicle depletion due to a defect in their formation or an aberrantly rapid depletion of the stock. Although the majority of cases are idiopathic, POI can be triggered by autoimmune disease, infectious agents, iatrogenic effects, or genetic causes. It may also be part of syndromic diseases such as Turner, Fragile-X or Blepharophimosis Ptosis Epicanthus Inversus syndrome. The identified missense variants were located in the kinase domain of both receptors 1A and 1B and predicted to be deleterious *in silico*. We studied the signaling pathway of these receptors, Smad proteins phosphorylation, transcriptional activity and expression of *Id1* and *Smad7* target genes. We showed that these variants impaired the activity of the proteins. Consisting with these results, *Bmpr1a* −/− and *Bmpr1b* −/− mouse models develop infertility due to a reduced spontaneous ovulation and compromised cumulus expansion respectively. Altogether, our study describes the first BMPR1A and 1B mutations associated with isolated POI and increases the number of genes formally implicated as being responsible for this condition.

Reference
1. Patiño LC *et al*. Hum Reprod. 2017; 32(7):1512–1520.

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OC14.4

Thyroid diseases in danish women with polycystic ovary syndrome

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Background
Polycystic ovary syndrome (PCOS) could be associated with increased risk of thyroid disorders. Possible associations between TSH and cardio-metabolic risk in PCOS are debated.
Methods
National Register-based study on women with PCOS in Denmark. 18,476 women had a diagnosis of PCOS in the Danish National Patient Register. PCOS Odense University Hospital (OUH, $N=1,146$) was an embedded cohort including premenopausal women with PCOS and clinical and biochemical examination. Three age-matched controls were included per patient in PCOS Denmark ($N=54,757$). The main study outcome was thyroid disease (myxedema, struma, Graves disease, thyroiditis) defined according to nationwide in- and outpatient hospital contact diagnosis codes and/or inferred from filled medicine prescriptions. A possible link between baseline TSH and development of cardio-metabolic disease (ICD10 codes and/or medical treatment for diabetes and cardiovascular disease including hypertension) was examined in PCOS OUH.
Results
The age at inclusion was median (quartiles) 29 (23–35) years and follow up was 11.1 (6.9–16.0) years. The Hazard ratio (95% CI) for development of thyroid disease was 2.5 (2.3; 2.7) ($P<0.001$) and the total event rate of thyroid disease was 6.0 per 1,000 patient years in PCOS Denmark vs. 2.4 per 1,000 patient years in controls ($P<0.001$). Women in PCOS OUH with TSH ≥2.5 mU/L ($n=133$) had higher BMI (median 29 vs. 27 kg/m^2), higher waist, higher triglycerides, and higher free testosterone by the time of PCOS diagnosis compared to women in PCOS OUH with TSH <2.5 mU/L ($n=588$). Baseline TSH did not predict later development of cardio-metabolic diseases in PCOS OUH.
Conclusion
The event rate of thyroid disease was higher in women with PCOS compared to controls. Baseline TSH was associated with PCOS metabolic phenotype, but did not predict development of cardio-metabolic disease.

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OC14.5

The pattern of cancer occurrence in Turner syndrome

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Background
Studies have shown that the overall risk of cancer is not increased in Turner syndrome (TS). However, the pattern of cancer occurrence may be different than in the background population.
Aim
To describe the cancer morbidity pattern in TS.
Design
Nationwide epidemiological study using Danish registries on morbidity.
Methods
1,156 Females with TS diagnosed during 1960–2014 were identified using The Danish Cytogenetic Central Registry. Subsequently they were linked with personal-level data from the Danish National Patient Registry. Statistics Denmark randomly identified 115,578 controls matched on sex and age. Stratified Cox regression were used to analyze cancer morbidity, computing proportional hazard ratios (HR).
Results
The overall risk of cancer was not elevated with a HR of 1.04 (Table 1). We observed an increased risk of skin cancer, but not melanoma. In addition, we also observed an increased risk benign skin neoplasms. We also observed a decreased risk of breast cancer, while all remaining cancer types occurred with a frequency equal to that observed in the background population.
Conclusion
In this large cohort of females with TS, we confirm that cancer is not seen more frequently, but that the pattern of cancer occurrence is different from what is observed in the general population. The risk of breast cancer is lower than in the general population. Whether this is due to insufficient treatment with female sex hormone replacement therapy or specific characteristics of females with TS remains to be determined.

Table 1

	All karyotypes		
Neoplasm	Cases n (%)	Controls n (%)	HR (95%CI)
All cancers	67	7,876	1.04 (0.80–1.36)
All benign neoplasms	164	16,318	1.09 (0.91–1.30)
Lip, oral cavity and pharynx cancer	3	168	1.69 (0.42–6.84)
Cancer of the digestive tract	13	1,163	1.58 (0.89–2.80)
Cancer of respiratory organs	4	849	0.63 (0.24–1.70)
Bone cancer	0	22	NA
Melanoma of the skin	4	626	0.67 (0.22–2.09)
Skin cancer	12	682	**2.23 (1.19–4.17)**
Benign skin neoplasm	36	2231	**2.03 (1.43–2.90)**
Malignant mesothelial neoplasms	1	29	5.51 (0.73-41.44)
Benign mesothelial neoplasm	0	19	NA
Breast cancer	11	2518	**0.44 (0.22–0.88)**
Female genitalia	13	1299	1.53 (0.88–2.64)
Uterus cancer	7	855	1.25 (0.59–2.64)
Ovarian cancer	4	545	1.08 (0.40–2.89)
Urinary tract cancers	5	253	1.70 (0.54–5.35)
Malignant CNS tumors	2	212	1.12 (0.28–4.52)
Benign CNS tumors	7	455	1.48 (0.55–3.97)
Cancers of endocrine glands	0	139	NA

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Guided Posters

Adrenal and Neuroendocrine - Tumour

GP1

^{68}Ga-exendin-4 PET/CT detects insulinomas in patients with hypoglycemia in multiple endocrine neoplasia type 1

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Context
Surgical intervention is advised in patients with multiple endocrine neoplasia type-1 (MEN-1) with non-functioning pancreatic neuroendocrine tumors (PanNET) and a size $\geq$20 mm. However, functioning PanNET such as patients with endogenous hyperinsulinemic hypoglycemia (EHH) due to (one or multiple) insulinomas should be treated surgically independent of size. Reliable preoperative localization of insulinomas is critical for surgical strategy.
Objective
To evaluate feasibility and sensitivity of ^{68}Ga-exendin-4 PET/CT in the detection of relevant lesions in *MEN-1* patients with EHH in comparison with magnet resonance imaging (MRI).
Design
Post-hoc subgroup-analysis of a larger prospective imaging study with 52 EHH patients.
Patients
Six of 52 consecutive patients with EHH and genetically proven *MEN-1* mutation were included.
Interventions
All patients received one ^{68}Ga-exendin-4 PET/CT and one MRI scan within 3-4 days. Thereafter, surgery was performed based on all imaging results.
Main Outcome Measures
Lesion-based sensitivity of PET/CT and MRI were calculated. Readers were unaware of other results when reading the scans. Reference standard was surgery with histology and treatment outcome. True positive was defined as PanNET $\geq$20 mm or insulinoma (=relevant lesions).
Results
In six patients, 37 PanNET were confirmed by histopathology. Sensitivity (95% confidence interval) for combined PET/CT + MRI, MRI and PET/CT was 92.3% (64%–99.8%), 38.5% (13.9–68.4%) and 84.6% (54.6–98.1%), respectively (*P*-value = 0.014 for the comparison of PET/CT + MRI versus MRI). After surgery, EHH resolved in all patients.
Conclusion
^{68}Ga-exendin-4 PET/CT is feasible in *MEN-1* patients with EHH. The combination with MRI is superior to MRI alone in the detection of insulinomas and may guide the surgical strategy.

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GP2

Lanreotide therapy vs wait-and-see in patients with pancreatic neuroendocrine tumors

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Background & Aim
Pancreatic neuroendocrine tumors (pNETs) are detected in >80% of MEN1 patients. MEN1 pNETs are well differentiated G1-G2 NETs. They are usually not surged unless a size >1–2 cm or a growth rate >0.5 cm per year. Somatostatin analogues represent one of the main therapeutic option in patients affected with G1-G2 NETs. However, neither somatostatin analogues nor other therapies have been prospectively evaluated in clinical trials specifically focusing on MEN1-related pNETs. The aim of this study was to prospectively evaluate the effectiveness of lanreotide in patients with MEN1-related pNETs <2 cm.
Patients & Methods
From 1 January 2012 to 30 December 2018, all MEN1 patients admitted to the Federico II NET Unit of Naples who were diagnosed with one or more pNETs <2 cm of maximal diameter, were considered for this study. Study design was prospective observational, with comparison of patients treated with lanreotide autogel 120 mg every 28 days (LAN group) and patients not receiving any therapy (Follow-up group). All PNETs $\geq$10 mm by CT scan or MRI were taken in account as target lesions. Median PFS was evaluated according to Recist 1.1 criteria. All patients were radiologically evaluated every 6 months. A written informed consent was signed from all participants. The study was approved by the local Ethic Committee.
Results
Forty-two patients (19 M and 23 F, mean age 42.7 years, range 20–65 years) were enrolled. LAN group included 23 patients and Follow-up group included 19 patients. Median follow-up was 66.5 months. As a whole, 49 pNETs $\geq$10 mm were identified. In the LAN group, 19 patients had stable disease at the last follow-up, while 4 had tumor progression (size increase in three and increased number of lesions in one). In the Follow-up group, 13 patients had pNET progression (size increase in ten, increased number of lesions in three, both in two), while 6 were stable. The median PFS was significantly longer in LAN group than in Follow-up group (median not reached vs 40 months, $P<0.001$).
Conclusions
This is the first prospective study evaluating the efficacy of somatostatin analogues in MEN1 patients with pNETs. These findings highlight that lanreotide autogel is effective as anti-proliferative therapy in MEN1-related pNETs <2 cm, suggesting the use of these compounds to arrest the development of tumor lesions as well as to delay or avoid pancreatic surgery.

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GP3

ProGRP is an effective marker for disease monitoring in lung carcinoids with non-informative chromogranin A: Lessons from clinical practice

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Introduction
The histologic classification of lung carcinoids (LCs) as typical (TCs) and atypical (ACs) highlights its role as major prognostic factor for these patients. However, in the absence of sensitive biomarkers to effectively predict tumor behavior, long-term imaging surveillance is recommended for disease monitoring. Limited data suggest that progastrin-releasing peptide (ProGRP) may have diagnostic & monitoring utility in LCs.
Aim(s)
To evaluate the possible role of ProGRP, in addition to chromogranin A (CgA), as a biomarker for LCs surveillance.
Materials and methods
Retrospective analysis of consecutive LCs patients treated in an ENETS Center of Excellence with regard to clinico-pathological parameters, treatment outcomes and their correlation with ProGRP and CgA.
Results
Thrity-five patients (pts) were studied (23 women; median age of 62y with a median follow up of 47 m). TCs and ACs were diagnosed in 43 and 57% of pts, respectively. 9 pts (26%) were defined as DIPNECH. The disease was localized in 31% & metastatic in 69% of cases. 71% of pts were already pretreated at the time of the first ProGRP evaluation. Disease status at first ProGRP measurement was: no evidence of disease (NED, 20%), stable disease (SD, 23%), progressive disease (PD, 57%). The NED group had normal ProGRP & CgA. In the SD group, ProGRP was increased in 62% vs 38% increase in CgA, while in the PD group 70% had increased ProGRP vs 35% with elevated CgA. Overall, ProGRP was increased in 50% of pts with evidence of disease, all with normal CgA.
Conclusion
ProGRP seems to be a valuable biomarker for monitoring patients with LCs, mainly when CgA is non-informative. Larger series including prospective long-term follow-up are needed to establish ProGRP's specific role in monitoring disease activity in LCs pts.
Keywords: progrp, lung carcinoids, biomarkers.
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GP4

Two cases of pseudopheochromocytoma due to Obstructive sleep apnea: which mechanisms?

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Introduction
The obstructive sleep apnea syndrome (OSAS) has a well-documented association with increase cardiovascular morbidity and mortality. The patients with OSAS have a high prevalence of hypertension and the OSAS may present similar to a pseudo-pheochromocytoma (PPH). We report two cases with PPH caused by OSAS; a common medical condition which is less recognized as a cause of raised catecholamines.
Observations
Case 1: 54 year-old man had a history of recent poorly controlled hypertension and obesity. He had a history of fatigue and drowsiness. Laboratory evaluation was elevated 24-h urinary catecholamine levels (UC) (3.2 times the upper normal levels).
Case 2: 52 year-old woman with a history of poorly controlled resistant hypertension was admitted to our hospital with severe hypertension. She had a history of fatigue and intermittent episodes of palpitations. Laboratory evaluation was significant for elevated UC (3.5 times the upper normal levels).
These patients were previously healthy without any medication and denied any alcohol or illicit drug abuse. Other causes of secondary hypertension such as primary hyperaldosteronism, hyperthyroidism, hypercorticism, and endocrine neoplasms were excluded by hormonal explorations. Computed Tomography-scan showed kidneys with normal size, good cortical index, and normal vessels. In addition, MIBG scintigraphy did not detected any catecholamine-producing tumor. The OSAS was established. Following 4 weeks of overnight continuous positive airway pressure (CPAP) therapy, blood pressure were at 130/80 mm of Hg. Three months later, UC were normalized and symptoms were gone.
Discussion
Twenty-four-hour UC were initially found to be increased in patients with untreated OSAS compared with those with narcolepsy. Evidence is accumulating to suggest a role for sympathetic overactivity in the pathophysiology of these observations. OSAS, however, is not the only cause of PPH as they could be showed in other causes, notably physiological stress, antipsychotic drugs, anti-parkinson drugs, etc. None of these conditions were found in our patients. Mechanisms by which chemoreflex dysfunction may contribute to chronically elevated sympathetic tone and hypertension are discussed.
Conclusion
Finally this cases represent two patients with untreated OSAS and difficult to control HTA, with clinical and biochemical evidence of increased sympathetic activity mimicking a pheochromocytoma. Nasal CPAP therapy allows improvement of hypertension with catecholamine hypersecretion and distinction of this condition from pheochromocytoma. We suggest that a diagnosis of OSAS should be considered in patients with clinical and biochemical evidence of catecholamine excess in whom a catecholamine producing tumor cannot be identified.

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GP5

Pheochromocytoma's of MENX rats belong to the pseudo-hypoxia cluster

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Pheochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumors derived from chromaffin cells of the adrenal medulla and paraganglia of the autonomic nervous system, respectively. Despite a common origin, these tumors are quite heterogeneous in terms of driver mutations, copy number alterations and activated downstream-signaling pathways. Genome wide expression analysis has identified at least three main tumor clusters: a pseudo-hypoxic cluster, one with activation of wnt-signaling and one with enhanced kinase-signaling. Further subgrouping has been suggested according to molecular, clinical and pathological phenotypes. Tumors in the pseudo-hypoxic Cluster 1 present a marked increase in cell proliferation and activation of angiogenesis pathways. Several genes predispose to Cluster 1 tumors, including *VHL*, *EPAS1, FH* and *SDHx*, but for some patients the underlying genetic mutation could not be identified. Surprisingly, targeting these genes in mice did not lead to the development of PPGLs. Our unique MENX rat model, carries a germline mutation in *Cdkn1b*, coding for a highly unstable variant of the cell cycle inhibitor p27. MENX rats develop bilateral pheochromocytomas with 100% penetrance: at 8–10 months of age the homozygous mutant; >15 months the heterozygotes. Following genome-wide transcriptomic analyses and candidate gene profiling we observed that the rat tumors display expression signatures characteristic of Cluster 1 human pheochromocytomas. These include increased expression of angiogenesis markers like *VEGF* and *ANGPT2* and pseudohypoxic markers as *HIF2a*. Moreover, lack of PNMT expression and catecholamine secretion in these rats are also in line with a pseudo-hypoxic phenotype. We therefore hypothesize that in MENX rats defective p27 function predisposes to the development of pheochromocytomas resembling human Cluster 1 tumors. Thus, these rats might lead to new insights into the pathomechanism of Cluster 1 tumor formation. Moreover, they offer a unique opportunity to preclinically evaluate drugs for efficacy against this specific subset of PPGLs.

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GP6

Cellular modelling of SDH-associated pathomechanism of pheochromocytomas and paragangliomas

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Introduction
The capability of cancer to accommodate to special metabolic circumstances is a hallmark of it's existence. Pheochromocytoma/paragangliomas (Pheo/PGL) are rare neuroendocrine tumors with strong and specific metabolic phenotype due to mutations of genes encoding succinate dehydrogenase (SDH) subunits. In this study our aim was to evaluate the expression of glutaminase-1 in hereditary Pheo/PGL tissues and to inhibit SDH activity via pharmacological treatments and gene silencing in order to identify an *in vitro* model useful for the evaluation of metabolic consequences of SDH inhibition.
Materials and methods
Immunohistochemistry was performed on 15 Pheo/PGL tumor tissue blocks obtained from 9 patients with hereditary Pheo/PGL. *SDHB* silencing was carried out using siRNA on PC12 cells. Itaconic acid (Ita) and atpenin A5 (AA5) were used as pharmacological inhibitors of SDH enzyme on PC12, HeLa and H295R cells. Metabolite profiles were assessed with liquid chromatography-mass spectrometry (LC-MS), data were normalized to DNA concentrations. Cellular viability was assessed with alamarBlue.
Results
The expression of glutaminase-1 (GLS-1) by immunohistochemistry positively correlated with malignancy in Pheo/PGL tumors. All SDH inhibiting treatments significantly increased the succinate/fumarate ratio in all cell lines compared to control. *SDHB* siRNA transfection significantly increased the cell viability of PC12 cells. Itaconate significantly increased the viability of PC12 cells but significantly decreased HeLa and H295R cells' viability. Atpenin significantly decreased viability of H295R cells, and significantly increased HeLa cell line's viability, while no effect in PC12 cells was observed. SDH inhibition had significant effects on the metabolite profiles, depending on the inhibition method and cell type. In PC12 cells glutamate levels showed significant decrease without lactate accumulation after Ita or *SDHB* siRNA treatments. siRNA inhibition resulted in decreased malate and aspartate levels. HeLa and H295R cells showed significantly higher lactate and glutamate and decreased aspartate concentrations upon Ita treatment, while malate concentrations only increased in HeLa cells. AA5 treatment didn't yield cell specific results: all cell lines exhibited significantly increased lactate and decreased glutamate, malate and aspartate levels compared to controls.
Conclusion
Increased GLS-1 expression in malignant samples points to the importance of glutamine/glutamate metabolism in Pheo/PGL. Ita treatment of PC12 cells mimics the phenotype observed in *SDHB* mutated Pheo/PGL tissues. Dissecting

SDH inhibition (Ita) from electron-transport chain blockage (AA5) caused cell type specific effects. Targeting glutamine metabolism might yield a novel therapeutic target for malignant Pheo/PGL.

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GP7

Parafibromin is regulated by ubiquitin specific protease 37 (USP37) and the c-terminus of USP37 interacts with the beta-catenin binding region of *CDC73* in hyperparathyroidism-jaw tumor syndrome

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CDC73 *(also known as HRPT2*) encodes parafibromin and is known to be the causative gene of hyperparathyroidism-jaw tumor (HPT-JT) syndrome. There is no known ubiquitination of parafibromin, and the deubiquitinating enzyme (DUB) for parafibromin has not been identified to date. Full-length DUB cDNAs encoding 58 family members of ubiquitin specific proteases (USPs) were subcloned. The DUB cDNA was used to identify parafibromin interacting by yeast two-hybrid screening. We investigated biochemical interactions between specific DUBs and parafibromin to confirm their binding and to investigate whether specific DUBs deconjugate ubiquitin from parafibromin by GST pull-down and immunoprecipitation analysis, respectively. And we examined the binding region of USP37 and parafibromin, and vice versa. Parafibromin was polyubiquitinated, especially in mutant forms. In yeast two-hybrid assays, USP37 was found to be a DUB interacting with parafibromin. GST pull-down analysis confirmed that parafibromin binds to USP37. We have shown that parafibromin can bind directly to USP37 and have demonstrated that USP37 specifically controls K48-linked polyubiquitination and stabilizes parafibromin. To determine the correct binding site, full length and deletion constructs were generated for both USP37 and *CDC73*. Simultaneous immunoprecipitation analysis betweenthe USP37 full length and *CDC73* deletion constructs and the *CDC73* full length and USP deletion constructs was performed. The analysis revealed that the c-terminus of USP37 interacted with the beta-catenin binding region of *CDC73*. Our results suggest that USP37 is a novel regulator of parafibromin stability in HPT-JT syndrome.

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GP8

Pheochromocytoma: Positive predictive values of mildly-elevated urinary fractionated metanephrines in a large cohort of community-dwelling patients

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Introduction
The importance of highly sensitive screening tests for pheochromocytoma/paragnaglioma (PPGL) is clear. However, a low level of specificity may lead to unnecessary biochemical and imaging investigations and even to needless surgical procedures. Therefore, in patients with elevated values of metanephrines, it is essential to establish a rational threshold for performing prompt thorough diagnostic investigations rather than opting for active surveillance.
Objective
This study sought to investigate the positive predictive value (PPV) of different thresholds of elevated urinary fractionated metanephrines (UFM) and to analyze current features of PPGL in a large cohort of community-dwelling patients.
Methods
The study was conducted at a large publicly-funded health maintenance organization (HMO) in Israel insuring approximately two million residents. We reviewed the computerized files of all patients who performed UFM tests in 2012–2017 and their levels of metanephrines and/or normetanephrines were $\geq$1.5x the upper normal limit (UNL). Clinical, biochemical and imaging data were retrospectively analyzed.
Results
Of the 10164 subjects referred to UFM testing, levels of $>$1.5xUNL and $\geq$2xUNL were found in 264 (2.6%) and 143 (1.4%), respectively. Sixty patients were subsequently diagnosed with PPGL (mean age 51.8$\pm$14.3, 65% females). Of these, 59 (98.3%) had UFM $\geq 2\times$UNL, yielding a positive predictive value (PPV) of 41.3% (59/143) for this threshold. A diagnosis of PPGL was established in only one out of 121 individuals with UFM level of 1.5–2$\times$UNL (PPV$=$0.8%), in 7 out of 45 individuals with UFM level of 2–2.5$\times$UNL (PPV$=$15.6%), and in 7 of 28 with UFM of 2.5–3$\times$UNL (PPV$=$25%). The main reason for UFM screening, in 51.7% (31/60) of PPGL patients, was adrenal incidentaloma. Median metanephrines/normetanephrines levels were 2.9xUNL and 2.5$\times$UNL, respectively (mean: 6.6$\pm$9$\times$UNL and 6.1$\pm$8.9$\times$UNL, respectively). Extra-adrenal tumor was detected in 6 patients (10%); bilateral masses and malignant PPGL in one patient, each. The classical triad of pheochromocytoma (headaches, sweating, tachycardia) was present in only one patient and 34 (56.7%) had none of these symptoms.
Conclusions
Most PPGL patients are currently diagnosed due to the detection of an adrenal incidentaloma. While in patients with UFM $\geq\times$2UNL the PPV for PGGL justifies a thorough diagnostic assessment, in patients with milder elevations the probability of PPGL diagnosis is very low.

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GP9

IGF-1 splice variants' expression in adrenal gland neoplasms- Possible role in adrenal tumorigenesis

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Introduction
IGF-1 overexpression has been associated with tumorigenesis. IGF-1Ea, IGF-1Eb and IGF-1Ec isoforms were shown to be regulated differently in cancer. IGF-1Ec and IGF-1Eb overexpression has been positively associated with cell survival and proliferation in various tumors. Elevated IGF1Eb/IGF-1Ea ratio has been suggested as a biomarker of cervical cancer prognosis. Herein, we aimed to examine the expression of IGF-1 isoforms in human adrenocortical carcinomas (ACCs), adrenocortical adenomas (ACAs), pheochromocytomas (Pheo) and compare to normal adrenal gland (NAG). Additionally, we investigated the role of IGF1-Ec and IGF1-Eb peptides in proliferation and migration of adrenal cortex carcinoma cell lines elucidating the underlying mechanism.
Methods
mRNA levels of the isoforms were evaluated by qPCR in fresh frozen tissues (ACA$=$8, ACC$=$6, Pheo$=$11). Immunohistochemical (IHC) analysis (ACA$=$15, ACC$=$13, Pheo$=$8, NAG$=$5) was performed using IGF-1Ec, IGF-1Eb and IGF-1Ea antibodies. SW$-$13 and H295R adrenal cortex carcinoma cells were

incubated with IGF-1Ec and IGF-1Eb peptides at various concentrations alone or in combination with ERK inhibitor. XTT cell proliferation assay and scratching assay were also performed.
Results
IGF-1Ec, IGF-1Eb, IGF-1Ea mRNA levels were increased in adrenal cortex neoplasms (ACC + ACA) compared to medulla (Pheo). Additionally, the mRNA levels of IGF-1Ec and IGF-1Eb were significantly higher in ACCs as compared to ACAs. These findings were confirmed at protein level, since 100% of ACCs (IRS = 6.62) and 73.3% of ACAs (IRS = 3.6) expressed IGF-1Ec, 67% of ACCs (IRS = 5.57) and 25% of ACAs (IRS = 1.25) expressed IGF-1Eb and 58% of ACCs (IRS = 4.5) and 66% of ACAs (IRS = 3.1) expressed IGF-1Ea. More importantly, protein expression of IGF-1Eb (IRS = 6.4) was higher while IGF-Ec expression was attenuated in NAG (IRS = 4.42) compared to ACCs. Interestingly, no expression of any isoform was detected in the Pheo group. A borderline negative correlation between IGF-1Eb ($P = 0.03$) levels as well as IGF-1Eb/IGF-1Ea ratio and Ki-67 ($P = 0.07$) was observed in ACC group. Incubation of SW-13 and H295R cells with IGF-1Ec resulted in significantly increased cell proliferation and migration compared to untreated cells, while ERK inhibitor attenuated this effect, indicating the involvement of ERK1/2 pathway.
Conclusion
Higher expression of IGF-1Ec and IGF-1Eb is linked to increased malignant potential of adrenal neoplasms. IGF-1Ec may play a causative role in ACC tumorigenesis acting -at least in part- through activation of ERK1/2 pathway, while higher expression of IGF-Eb may have a protective effect. Further studies are warranted in order to address the possible prognostic role and/or the use of IGf-1Ec and IGF-1Eb as therapeutic targets.

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GP10

Brown fat proliferation- A rare complication of Phaeochromocytoma

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Phaeochromocytoma is a catecholamine producing tumour arising from the adrenomedullary chromaffin cells. It produces hormones such as epinephrine, norepinephrine, catecholamine and dopamine. (1) There have been some case reports describing an association between Brown adipose tissue (BAT) accumulation due to catecholamine excess caused by a phaeochromocytoma. We present a similar case in this abstract. A 77 year old lady was referred to the community geriatricians with symptoms of profuse sweating, difficulty walking, increase in abdominal girth, weight loss of 4–5 stones over the previous 4 months, abdominal pain, poor appetite and insomnia. Past medical history included bronchiectasis, Type 2 Diabetes, previous neck of humerus fracture, and pulmonary embolism. A CT chest, abdomen and pelvis showed an ill-defined heterogenous right peri-renal/retroperitoneal mass of fat and soft tissue density, and a 3.2 cm left adrenal enhancing mass. Urine normetadrenaline was raised at 11.21 umol/24hours (Normal Range <3). She was discussed in Urology and adrenal MDTs who felt there was a high likelihood of abdominal malignancy. Subsequently, a core biopsy of the right retroperitoneal mass was carried out to further classify it. She was treated with an alpha-blocker and this dramatically improved her symptoms but the abdominal discomfort remained. She then underwent an ultrasound guided biopsy of this mass. Histology showed adipocytes with multi-vacuolated cytoplasm and central nuclei consistent with brown fat. She subsequently underwent an elective laparoscopic adrenalectomy. A left adrenal mass was localised and removed. Histology of this lesion confirmed a phaeochromocytoma with positive immunohistochemical staining for CD56, chromogranin and synaptophysin with a maximum PASS score of 2. She made an unremarkable recovery post operatively. Her catecholamine levels and her blood pressure normalised post-surgery. A subsequent CT done eight week post-operatively showed a dramatic generalised reduction in the bulk, vascularity and density of the retroperitoneal brown fat with no local recurrence. The patient has reported a dramatic improvement in both her generalised and abdominal symptoms. Her diabetes has also resolved postoperatively. In summary, this case highlights the association between BAT and phaeochromocytoma. It has been hypothesized that catecholamine excess leads to a proliferation of BAT. The presence of clinical symptoms of tachycardia, weight loss, persistent sweats should prompt investigations for an underlying phaeochromocytoma. However, the presence of co-existent abdominal masses on imaging may suggest the possibility of excess BAT accumulation and should not be automatically assumed to be a primary or secondary malignancy.
Reference
1. https://academic.oup.com/jcem/article/99/6/1915/2537399

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GP11

Corticotropinoma as the underlying cause of intermittent Cushing's syndrome in a patient previously diagnosed with primary pigmented adrenocortical disease (PPNAD) – a case report

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Background
The diagnostic process to unveil the underlying cause of endogenous Cushing's syndrome (CS) is often challenging. Sometimes, atypical manifestation of the disease or only periodic hypercortisolaemia with spontaneous resolutions are observed and make the diagnosis even more difficult. Although it is common in primary pigmented nodular adrenocortical disease (PPNAD), pituitary corticotroph adenoma can manifest itself as cyclic Cushing's syndrome as well.
Case description
We present the difficulties that came with the patient with previously diagnosed primary pigmented nodular adrenal disease (PPNAD) and conflicting hormonal and radiological findings a few years later. A 33-year-old female with almost 10-year-long history of intermittent Cushing's syndrome and no family history was first admitted for endocrinological evaluation in 2010. As a result, she underwent unilateral adrenalectomy because of an overt, apparently ACTH-independent, Cushing's syndrome with hyperandrogenism and left adrenal hyperplasia. Histological examination revealed the diagnosis of PPNAD. Although being scheduled for right adrenalectomy, she moved on without any additional treatment. Despite repeated search, no other components of Carney's complex had ever been discovered. Since 2015, cushingoid features had been getting more florid. Meanwhile, she gave birth to three healthy children from untreated pregnancies, while single pregnancy ended in miscarriage in 12 Hbd. Finally being able to undergo concluding hormonal evaluation, laboratory and radiological findings were consistent with ACTH-dependent excessive cortisol production this time. Pituitary MRI showed a lesion of <3 mm on the left side of adenohypophysis (suggesting microadenoma) and bilateral inferior petrosal sinus sampling (BIPSS) confirmed this suspicion. The patient underwent effective transsphenoid resection of the tumor and is now eucortisolaemic after one year since the operation. The genetic testing for PRKAR1A mutations was negative and the second histopathological evaluation raised considerable doubts whether the diagnosis of PPNAD was stated correctly.
Conclusions
This case illustrates that careful evaluation of hypercortisolic patients is always crucial before moving on to definite treatment. BIPSS is the procedure of significant value in patients with misleading hormonal tests' results and uncertain source of cortisol. Isolated, non-familiar PPNAD has been very rarely reported. Pituitary lesion as the component of Carney's complex may comprise hormonally active GH/prolactin adenoma or inactive incidentaloma, although single cases of corticotropinoma have also been described. However, genetic testing is helpful to state the diagnosis in many cases.

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GP12

Functional mixed oncocytic adrenocortical neoplasm presenting as an asymptomatic adrenal mass

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Oncocytic adrenocortical neoplasm (OAN) represents a rare variant of adrenocortical carcinoma (ACC) with less than 150 cases reported in the literature. OANs account for 1.8% of adrenal masses, predominantly in adults and usually presenting as large tumors featuring hormonal secretion in 20% of cases. Accurate histological characterization of OANs is crucial as this subtype is believed to be more indolent in clinical behavior. There are 3 categories of OANs: pure oncocytic, mixed oncocytic and ordinary adrenocortical with focal oncocytic changes. The Weiss scoring system used for ACC overestimates malignancy in OANs, therefore alternatives like the Lin-Weiss-Bisceglia (LWB) system need to be used for proper diagnosis and subsequent evaluation of malignant potential. We report the case of a 63-year-old menopaused female with medical history of well controlled type 2 diabetes and hypertension addressed by her GP for exploration of a large adrenal mass neglected by the patient for four years. On interrogation, the patient was completely asymptomatic. Clinical examination revealed a large palpable mass in the left abdomen, normal BMI, no Cushing or virilization syndrome. Hormonal workup showed important elevation of 17OHprogesterone and DHEAS, increased D4Androstendione and total testosterone. The rest of the hormonal workup was in the normal range. Whole body CT scan was consistent with a left heterogeneous adrenal mass of 14×13.6×11 cm, 42HU spontaneous density with calcifications and necrotic areas and no adenopathy or distant metastasis. Open surgery was performed and excised a 15 cm mass weighing 1140 g. Histologic diagnosis was challenging and demanded a second opinion to finally conclude in favor of a mixed OAN with three major criteria and two minor criteria according to the LWB scoring system and a prognosis of malignant evolution. Adjuvant Mitotane treatment was started after discussion in multidisciplinary meeting. Very close clinical, hormonal and imaging follow-up is required for a minimum of 5 years. Although rare entities, OANs should be considered in the differential diagnosis of large adrenal masses. Histological examination by experienced pathologists using the LWB scoring system is of major importance in order to establish the tumor's biologic potential and the patient's prognosis.

Keywords: oncocytic adrenocortical neoplasm, adrenal mass

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GP13

KCTD20, a new gene in cortisol-secreting adrenocortical tumors related to inactivating mutations of the Carney Complex gene (PRKAR1A)

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Introduction

Adrenal Cushing due to bilateral multiple adrenal tumors known as Primary Pigmented Nodular Adrenocortical Disease (PPNAD) can be observed in the multiple neoplasia syndrome Carney Complex or as an isolated disease. In both situations germline inactivating mutations of PRKAR1A (regulatory subunit R1A of PKA) can be observed. The loss of *PKA R1A* results in an increased PKA activity. Comparison of the transcriptome of PPNAD and stably transfected H295R adrenal cortical cells with and without inactivation of *PRKAR1A* (H295R/TR/shPRKAR1A) identified a gene whose expression is decreased following the loss of *PRKAR1A* expression: *KCTD20* (potassium channel tetramerization domain containing). This work aims to understand the role of KCTD20 in endocrine hyperactivity and tumor development of PPNADs and Carney Complex.

Methods

H295R, HEK293 cells and PPNAD primary cell culture, were used. The transcriptional regulation of *KCTD20* by PKA R1A (siRNA interference) (RNA, protein) was analysed. The role of *KCTD20* was evaluated through its inactivation by silencing RNA (siKCTD20) and its overexpression (vector-KCTD20) to investigate the effects on PKA R1A alteration concerning cell proliferation/apoptosis (MTT/annexin V, flow cytometer), cell signalling pathways (PKA, AKT, intracellular calcium), and steroidogenesis. KCTD20 intracellular localisation was analysed by immunofluorescence. KCTD20 protein contains a BTB domain. The immunoprecipitation of KCTD20 and mass spectrometry analyses was used to identify the partners of KCTD20 and to precise its role.

Results

In H295R, the decrease in KCTD20 expression after *PRKAR1A* invalidation is independent of PKA activity. Overexpression of KCTD20 increases apoptosis and decreases cell proliferation. Invalidation of *KCTD20* protects against apoptosis ($P<0.01$), increases the activity of the Star-Luc reporter ($P<0.001$), the expression of *Star* ($P=0.01$) and *CYP11B1* genes ($P=0.05$), and cortisol production in H295R cells ($P<0.05$). These effects seem independent of PKA activity. Invalidation of *KCTD20* results in membrane depolarization in response to KCL and increases intracellular calcium ($P<0.001$). Flag-KCTD20 exhibited a cytosolic and spot-like distribution in transiently transfected H295R and Hela cells. Culline 3 was identified as a potential partner of KCTD20. In PPNAD from patients with *PRKAR1A* mutations in primary cell culture, the overexpression of KCTD20 decreases the *CYP11B1* gene (RT/PCR).

Conclusion

PKA R1A acts on KCTD20 via a PKA independent pathway. KCTD20 may play a role in adrenal Cushing by mechanisms independent of PKA activity.

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GP14

Endoscopic ultrasound guided radiofrequency ablation (EUS-RFA) as a novel therapeutic approach in highly-selected pancreatic functioning and non-functioning neuroendocrine neoplasms (pNENs) patients: Preliminary report

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Introduction

EUS-RFA is rapidly emerging as a possible treatment alternative for patients with pNENs who are poor surgical candidates.

Aim(s)

To summarize our experience in terms of feasibility, safety and efficacy of EUS-RFA in a cohort of patients with functional and non-functional pNENs.

Materials and methods

Retrospective case series of pNENs patients treated with EUS-RFA at two tertiary referral centers in Israel between March 2017 and October 2018.

Results

Eighteen consecutive pNENs patients that underwent EUS-RFA have been included (11 males, median age of 62.5 (range 28 – 82)). A total of 27 lesions with a median size of 13 mm (range 4.5–29) were treated. The location of the target lesion was: head ($n=10$), body ($n=8$), uncinate process ($n=5$) and tail ($n=2$); in two patients, synchronous liver and lymph node metastasis underwent RFA. Functionally, the tumors were non-functional pNENs and insulinomas in 11 and 7 patients respectively. All tumors were well-differentiated based on Ki-67. Technical success, defined as post RFA changes in tumor vascularity and/or tumor necrosis on surveillance imaging was reported in 26/27 lesions. Normalization of glucose levels was observed in all (7/7) insulinomas within 24 h. There were no major complications 48 h post-RFA. Two patients developed mild pancreatitis post-RFA that resolved within 72 hours. No recurrences were observed during a median follow up of 6 months (range 1–20 m).

Conclusion

EUS-RFA for highly selected pNENs patients who cannot or do not want to undergo surgical resection appears to be safe and feasible. Prospective studies comparing RFA with surgical excision, including larger cohorts of patients and longer follow-up periods, are warranted to establish the role of EUS-RFA in the treatment algorithm for pNENs.

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Calcium and Bone 1

GP15

Recombinant human parathyroid hormone 1–84 for the treatment of adults with chronic hypoparathyroidism: Six-year safety and efficacy results of the RACE study

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Background
RACE is an open-label study that assessed the long-term safety and efficacy of recombinant human parathyroid hormone 1–84 (rhPTH[1–84]) for the treatment of hypoparathyroidism in adults (ClinicalTrials.gov identifier NCT01297309). Here, we present 6-year safety and efficacy data.
Methods
Patients initially received 25 or 50 μg of rhPTH(1–84) subcutaneously, once daily, with stepwise dose adjustments of 25 μg (up or down) to a maximum of 100 μg/day. rhPTH(1–84) could be titrated and oral calcium (Ca) and calcitriol doses adjusted at any time during the study to maintain albumin-corrected serum Ca levels in the target range (2.0–2.25 mmol/L). A composite efficacy endpoint was the proportion of patients who achieved at least a 50% reduction from baseline (BL) in oral Ca dose (or Ca $\leq$500 mg/day) and at least a 50% reduction from BL in calcitriol dose (or calcitriol $\leq$0.25 μg/day), while normalising or maintaining albumin-corrected serum Ca compared with BL value and not exceeding the upper limit of normal for the central laboratory. Data are summarised with descriptive statistics (mean $\pm$ SD).
Results
The study cohort consisted of 49 patients enrolled at 12 US centres (mean age, 48.1 $\pm$ 9.78 years; 81.6% female); data from 34 patients (69.4%) who completed 72 months (M72) of treatment with rhPTH(1–84) as of July 17, 2018, are presented here. Oral Ca and calcitriol doses were reduced by 40.4% and 72.2% at M72, respectively, and albumin-corrected serum Ca levels were maintained within the target range (BL, 2.1 $\pm$ 0.17 mmol/L; M72, 2.1 $\pm$ 0.17 mmol/L). At M72, 22 of 34 patients (64.7%) achieved the composite efficacy endpoint. Urinary Ca excretion declined from above normal at BL to within the normal range (BL, 8.9 $\pm$ 5.01 mmol/d; M72, 5.3 $\pm$ 3.22 mmol/d). Mean serum creatinine levels remained stable (BL, 84.7 $\pm$ 18.16 μmol/L; M72, 79.7 $\pm$ 18.76 μmol/L), as did estimated glomerular filtration rate (BL, 77.7 $\pm$ 17.67 mL/min/1.73 m^2; M72, 79.4 $\pm$ 18.39 mL/min/1.73 m^2). Serum phosphorus levels declined from above normal at BL to within normal range (BL, 1.6 $\pm$ 0.19 mmol/L; M72, 1.3 $\pm$ 0.20 mmol/L); calcium-phosphorus product levels also declined (BL, 3.4 $\pm$ 0.51 $mmol^2/L^2$; M72, 2.7 $\pm$ 0.40 $mmol^2/L^2$). Treatment-emergent adverse events and treatment-emergent serious adverse events were reported in 98.0% and 26.5% of patients, respectively; no new safety concerns were identified.
Conclusions
Continuous use of rhPTH(1–84) over 6 years resulted in a favourable safety profile, was effective, and improved key measurements of mineral homeostasis, notably normalisation of urinary calcium.

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GP16

The effect of parathyroidectomy on glucose homeostasis and incretin hormone release in patients with primary hyperparathyroidism: a pilot study

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Background
Primary hyperparathyroidism (PHPT) has been linked to glucose homeostasis disorders, leading to insulin resistance and type 2 diabetes mellitus. Previous small studies evaluating the effect of parathyroidectomy (PTX) on various parameters of glucose metabolism have produced conflicting results. The impact of PTX on incretin hormone levels has not been studied yet. The aim of this pilot study was to investigate the effect of PTX on markers of glucose metabolism and insulin resistance, as well as on incretin hormone levels in patients with PHPT.
Methods
Fourteen non-diabetic patients with PHPT were included in this study. All patients were scheduled for a curative PTX. Preoperatively, fasting plasma glucose(FPG), fasting insulin(I), gastric inhibitory polypeptide(GIP), glucagon-like peptide-1(GLP-1), calcium, phosphorus, parathyroid hormone (PTH) and 25-hydroxyvitamin-D [25(OH)D] were measured. Homeostasis Model Assessment (HOMA2) was used for estimating insulin resistance (HOMA2-IR), β-cell function (HOMA2-B) and insulin sensitivity (HOMA2-S). QUICKI index for insulin sensitivity was also calculated. A 75g oral glucose tolerance test (OGTT) was performed to further evaluate glucose, insulin and incretin response as well as insulin sensitivity using the Matsuda Index. All measurements and calculations were repeated 6 weeks post-PTX.
Results
Patients had a mean age of 52.9 $\pm$ 10 years (female:male ratio = 12:2). Preoperatively, PTH was positively correlated with HOMA2-B (r = 0.74, P = 0.002) and GLP-1 (r = 0.79, P = 0.02). After PTX, calcium and PTH levels were normalized and phosphorus was increased. Body mass index also increased slightly (P = 0.02). A significant increase was observed in GLP-1 response during OGTT after PTX (in 60 min: 55.2 (79.8) vs 91.5 (74.4) pg/ml, P = 0.05 and in 120 minutes: 71.3 (51.3) vs 91.3 (74.0) pg/ml, P = 0.03). GIP response was not significantly altered. Postoperatively, the correlation between HOMA2-B and PTH remained significant (r = 0.55, P = 0.04), whereas PTH was also associated positively with HOMA2-IR (r = 0.56, P = 0.04) and negatively with Matsuda index (r = −0.58, P = 0.03) and QUICKI (r = −0.41, P = 0.04).
Conclusion
To our knowledge, this is the first study investigating the effect of PTX on incretin hormone levels in PHPT patients. The increase of the GLP-1 response observed after curative surgery may potentially reflect the partial recovery of glucose homeostasis. Additional findings of this pilot study indicate a correlation between PTH and indices of β-cell function in PHPT patients. Larger studies are needed to clarify the pathophysiology background behind PHPT and glucose metabolism and to evaluate the impact of PTX on this association.

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GP17

Utility of a second technecium99mMIBI-SPECT imaging before re-operating in patients with persistent sporadic primary hyperparathyroidism: results of a retrospective multicentric study

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Introduction
Persistent primary hyperparathyroidism (pHPT) occurs in 2.5 to 15% of cases after parathyroidectomy. Pre-operative localization studies (usually ^{99m}Tc-MIBI and cervical ultrasonography (US)) allow focused surgical approach (unilateral neck exploration or minimally invasive parathyroidectomy). Few studies have evaluated the best pre-reoperative approaches in case of persistent sporadic

pHPT. The aim of our study is to evaluate the value of a second pre-operative ^{99m}Tc-MIBI in persistent sporadic pHPT and the interest of the adjunction of US.
Patients and Methods
Fifty patients operated on between 2006 and 2016 in three French University Hospitals (Nantes, La Pitié Salpêtrière, Paris and Angers) were included in this study. All patients had a persistent sporadic pHPT after a first surgery and have been re-operated on.A ^{99m}Tc-MIBI was performed in each case before the first and the second operation. US was always performed before the first operation and in 43 patients before re-operation. The cure rate (following second ^{99m}Tc-MIBI and second surgery), the number of new pathologic localized glands, and the intrinsic properties of second ^{99m}Tc-MIBI to localize the side of an abnormal parathyroid gland were evaluated. Intrinsic properties of ^{99m}Tc-MIBI and US were also evaluated.
Results
Forty-two patients (84%) were cured after the second surgery. Among these, 31 (62% of the patients) had a gland removed on the area identified by second-MIBI. Twenty-six new pathologic glands (52%) were identified by second-MIBI, including 18 patients (36%) with a multiglandular disease and 8 patients (16%) with a negative first-MIBI. Overall intrinsic properties of the second-MIBI are 67% sensitivity (se), 91% specificity (sp), 82% positive predictive value (PPV) and 81% negative predictive value (NPV). Performing the second-MIBI one year or more after the first -MIBI provided important sp: 97% vs 86% when second-MIBI was performed in the first year, and PPV: 93% vs 77%, but with a decreased sensitivity (59% vs 71%) and NPV (79% vs 82%). Concordant second-MIBI and US (17 patients) had the better se (77%), 85% sp, 77% PPV and 85% NPV.
Conclusion
Performing a second ^{99m}Tc-MIBI leads to find new pathologic glands in more than 50% of the cases in sporadic pHPT, especially in multiglandular disease. The concordant couple ^{99m}Tc-MIBI and US is the most accurate examination to localize the side of an abnormal parathyroid gland before re-operation. When discordant, the ^{99m}Tc-MIBI performed more than one year after the first-MIBI has the best specificity and NPV.

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GP18

Calcium to Phosphorus (Ca/P) ratio as an accurate index for the diagnosis of primary hyperparathyroidism (PHPT) and hypoparathyroidism (HypoPT)

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Background
The diagnosis of PHPT and chronic HypoPT is still challenging, mainly due to the wide spectrum of clinical and biochemical presentation and the lack of validated diagnostic index in literature. The serum Ca/P ratio has been proposed as an accurate tool to diagnose PHPT in a small sample of patients, while no data is available about its possible application for HypoPT.
Aim
To validate the serum Ca/P ratio as a diagnostic index for PHPT and to investigate its diagnostic performance in the diagnosis of HypoPT by analyzing a large series of data coming from a multicenter study.
Methods
Multicenter, retrospective, case-control study, including 432 PHPT patients and 217 HypoPT patients, compared with 389 controls. Main outcomes: serum Ca, P, albumin, creatinine, parathyroid hormone (PTH) and 25-OH vitamin D (only for controls and PHPT). *Statistical analysis:* Comparisons among groups were performed by the nonparametric Kruskal-Wallis, followed by the Dunn's post hoc test. The diagnostic accuracy of Ca/P ratio was investigated by receiver operator characteristics (ROC) curves in order to define cut-off points (with the highest sensitivity and specificity).
Results
The Ca/P ratio was significantly different among groups, resulting higher in PHPT and lower in HypoPT patients than controls ($P<0.0001$). At ROC curve analysis, the Ca/P ratio above 3.3 was defined for the diagnosis of PHPT (sensitivity 85.7%, specificity 85.3%), while the Ca/P ratio below 2.3 for the diagnosis of HypoPT (sensitivity 88.2%, specificity 87.9%). Considering the PHPT group, the cut-off of 3.1 for Ca/P was able to specifically identify patients with normocalcemic PHPT (sensitivity 80.3%, specificity 80.2%).
Conclusions
This study further validates the serum Ca/P ratio as a highly accurate diagnostic index for PHPT, defined by Ca/P above 3.3. For the first time, a Ca/P ratio below 2.3 is proposed to identify HypoPT patients. Our findings confirm the reliability of this index to screen and/or rule out disorders of Ca-P metabolism.

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GP19

18F-Fluorocholine PET/CT in patients with primary Hyperparathyroidism and negative or inconclusive 99mTc-MIBI parathyroid scan: clinico-pathological correlations

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Introduction
The gold standard for evaluating Occult Parathyroid Adenomas (OPa) in patients with biochemical pattern of primary hyperparathyroidism (PHPT) is the 99mTc-MIBI parathyroid scan. 18F-Fluorocholine (18F-FCH) PET/CT has been proposed as a potential technique for detection and localization of OPa when 99mTc-MIBI scan is negative or inconclusive.
Aims
To evaluate sensitivity and positive predictive value of 18F-Fluorocholine PET/CT in patients with biochemical PHPT with negative or inconclusive 99mTc-MIBI scan. To correlate 18F-FCH PET/CT findings with clinical and surgical characteristics.
Methods
We analyzed all subjects with biochemical PHPT attended in our department (January–December 2018) with a negative/inconclusive 99mTc-MIBI in which 18F-FCH PET/CT was performed. Patient characteristics, time of diagnosis of PHPT, serum calcium and parathyroid hormone (PTH) levels were recorded. In those patients who underwent parathyroidectomy, affected glands, type of surgery, postoperative serum calcium, PTH levels and pathological features were correlated with 18F-FCH PET/CT findings. Differences were considered significant for a*p value* <0.05. SPSS Statistics package was used for statistical analysis (Mann-Whitney, Chi-square and T student tests).
Results
A total of 23 subjects with biochemical PHPT with negative ($n=19$) or inconclusive ($n=4$) 99mTc-MIBI scan were included (74.47% female, 61.4 ± 14.7 years, time since diagnosis 24.7 ± 30 months, 17.4% with previous unsuccessful surgery, calcium 2.69 ± 0.18 mmol/l, PTH 21.75 ± 28 pmol/l, 3 subjects with MEN1 and 1 with familiar PHPT). 18F-FCH PET/CT was positive in 18 patients, negative in 4 and inconclusive in 1. No differences were found between subjects with positive and negative 18F-FCH PET/CT in the analyzed variables (a tendency to higher PTH was observed in subjects with positive 18F-FCH PET/CT ($P=0.057$)). Parathyroidectomy was performed in 12 patients (11 patients are pending of surgery), resulting in 10 cases a solitary OPa by pathology. OPa were located 6 in the left upper gland, 2 in the left lower gland and 2 in the right lower gland. 18F-FCH PET/CT localization was concordant with the excised OPa in all patients except for one case. In one case of failed surgery PET indicated an ectopic gland and in the other case a left low gland. Moreover, elevated preoperative PTH and serum calcium decreased 10 minutes after surgery.
Conclusions
In our series of patients with biochemical PHPT and negative/inconclusive 99mTc-MIBI parathyroid scan, 18F-FCH PET/CT offers greater sensitivity and precision during performance of parathyroidectomy (sensitivity 78.2%, positive predictive value 83.3%). No clinical or biochemical data was associated with PET positivity.

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GP20

Clinical, biochemical and radiological profile of normocalcaemic hyperparathyroidism: a multicentric cross-sectional evaluation

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Background
The normocalcaemic hyperparathyroidism (NHPT) has been defined as a condition with persistently normal total and ionized calcium levels in the presence of high levels of PTH. The clinical aspects of NHPT have been evaluated in different cohorts but the interpretation of these findings is confounded by differing methods used to rule out secondary hyperparathyroidism and by the small number of NHPT subjects enrolled. Up to now, there is no information available that could determine the optimal management of this condition.
Objective
To evaluate the clinical, biochemical and radiological profile of NHPT in comparison with PHPT and control subjects.
Methods
We designed a multicentric cross-sectional study and we enrolled patients with NHPT and primary hyperparathyroidism (PHPT) diagnosed according to criteria of the 'Fourth International Workshop of Asymptomatic Hyperparathyroidism'. Body mass index (BMI) and age matched control subjects were consecutively recruited from outpatient clinic of endocrinology at Campus Bio-Medico. All patients underwent a biochemical examination including calcium-phosphorus metabolism and bone turnover markers. We evaluated the lumbar spine (L1–L4), total hip, femoral neck, and non-dominant forearm bone mineral density (BMD) and the trabecular bone score (TBS). Morphometric vertebral fracture (VF) were assessed by DXA scan.
Results
From December 2016 to July 2018, we identified 47 patients with NHPT, 41 with PHPT and 39 control subjects. All study groups had no significant differences in terms of age, BMI and kidney function. NHPT and PHPT patients had significantly higher PTH and 25(OH) Vitamin D levels ($P<0.001$) and lower Ca*P ($P<0.001$) compared to controls. NHPT has lower CTX levels compared to PHPT ($P=0.039$) and no differences were recorded compared to controls. In NHPT group, P1NP resulted not different when compared to controls and PHPT subjects. Compared to controls, NHPT ($P=0.035$) and PHPT ($P=0.003$) group have lower total hip BMD; NHPT showed higher non-dominant forearm BMD than PHPT subjects ($P=0.017$), while compared to controls presented similar values. No significant differences in TBS between the three groups have been founded. After adjustment for confounding factors, only PHPT group had an increased risk of VF compared to controls (OR:5.10, 95% CI:1.34 to 21.58). 31% of NHPT and 12% of PHPT patients fulfilled the criteria for asymptomatic hyperparathyroidism.
Conclusion
Up to now, our study described the biochemical and radiological profile of the largest cohort of NHPT subjects. Our findings suggest that the profile of NHPT subjects is closer to control one.

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GP21

The long-term outcomes of chronic post-surgical hypoparathyroidism

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Hypoparathyroidism (HP) is a rare disease characterized by an absence or inappropriately low concentrations of circulating parathyroid hormone, leading to hypocalcaemia, hypophosphatemia and elevated urinary calcium excretion.
Aim
To determine complications in chronic post-surgical HP patients.
Material and methods
We have analyzed the data from 76 patients (71 women and 5 men; median age 51.8 years (range 18–77)) with chronic post-surgical HP reviewed during 2017–2019. We present the main characteristics of patients including a volume of surgery, disease duration, biochemical parameters, treatment modalities and disease-associated complications.
Results
The average HP duration in group was 8.7 years (2–32). In most cases HP developed after total thyroidectomy for nontoxic unilateral/multinodular goiter and well-differentiated thyroid carcinoma (38.2% and 30.3% respectively). Other reasons included diffuse toxic goiter (14.5%), thyroid malignancy with central neck dissection (10.5%) and primary hyperparathyroidism due solitary adenoma (6.6%). 15 patients (19.7%) were diagnosed with HP after the reoperation on neck region. The median levels of serum Ca and albumin-adjusted serum Ca on conditional therapy were 2.03 mmol/l (1.83; 2.24) and 1.97 mmol/l (1.78; 2.15) respectively. Patients required alfacalcidol in medium doses of 1.5 mcg/day (min 0.25; max 6.0) and calcium carbonate in medium doses of 1875 mg/day (min 250; max 4500). 12 patients received thiazide diuretics in doses 25–75 mg/day to control the hypercalciuria. We did not reveal hypomagnesaemia (0.76 mmol/l (0.71; 0.8)) and vitamin D deficiency (32.75 ng/ml (28.1; 42.9)) in study group. The following complications were identified: decrease of estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 in 9 patients (11%); nephrocalcinosis and kidney stones in 4 (5%) and 17 (22%) patients respectively. A diagnosis of hypoparathyroid-caused cataract was confirmed in 5 (6.5%). 5 patients suffered from central nervous system calcifications (Fahr's syndrome) detected by CT scan results. An electrocardiogram showed HP-associated cardiac arrhythmias and prolongation of the corrected QT interval in 5 patients (6.5%). Symptoms of myopathy with increased serum levels of creatine phosphokinase and ossification of longitudinal spine ligament were identified in 8 (10%) and 4 (5%) respectively.
Conclusion
Chronic HP and its treatment may lead to long-term complications affecting various organ systems and consequently the quality of life thus active screening of these patients is strongly recommended. The longitudinal studies and further research are required to develop the new effective strategies in prevention of long-term HP complications.

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GP22

OFELIA – Prevalence of osteoporosis in fragility fracture patients

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Worldwide, a care gap has been recognized between presenting with a fragility fracture and prevention of the next fracture. Fracture Liaison Service is the most cost-effective method to close this gap, but its implementation is sparse in many countries. To assess the need for a subsequent fracture prevention program in Denmark, we conducted a cross-sectional study – named OFELIA - aiming to estimate the prevalence of osteoporosis in a Danish cohort of fragility fracture patients aged 18+ years. Over at 12 month period, patients were consecutively identified when treated for fragility fractures at Aarhus University Hospital. Patients were informed about bone health and asked to participate in the study meaning accepting a DXA and answering questions about risk factors. Of 1164 identified patients, 832 were included and 794 (70% women, 66% aged $\geq$50 years) patients completed the investigation. The overall prevalence of osteoporosis in this cohort according to WHO's criteria of a T-score at hip or spine below -2.5 was 14.9% (118 patients, of these 20 patients knew their diagnose on forehand), increasing to 20.3% in patients $\geq$50 years (22.9% in women, 9.6% in men). In addition to age above 50 years, female sex, low BMI, and early menopause were significantly associated with osteoporosis. At 3-years follow-up we performed interviews in 93 out of 98 patients diagnosed with osteoporosis according to OFELIA. Of these, a total of 75 patients (81%) received anti-osteoporosis treatment initiated by their GP as a result of the DXA result and 71 (95%) were still – after three years - adherent to treatment. In the group of 93 interviewed patients ten had experienced a subsequent (minor) fracture and 84 patients supplied their daily intake of calcium and D-vitamin. Control DXA after 2–3 years performed in 56 patients showed increasing bone mineral density in 49 (87.5%) patients. Given that osteoporosis was demonstrated in one of five patients aged 50 years or older treated for a fracture at AUH, OFELIA stresses the need for implementation of a program aiming to secure appropriate investigation and treatment in patients presenting a fragility fracture. A suggested high adherence to initiated treatment in patients diagnosed with osteoporosis after a fracture indicates a beneficial outcome of FLS.

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GP23

Study of hsa-miR-30e miRNA as a biomarker in identifying multiple gland disease in sporadic primary hyperparathyroidism: Is it time for individualized molecular-based surgery?

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Introduction
Sporadic primary hyperparathyroidism (sporadic PHPT) is a common endocrine disorder, usually caused by a single parathyroid adenoma. However, up to 15% of patients present with multiple gland disease (MGD), which cannot be always diagnosed preoperatively, raising serious management problems. No predictive genetic screening tests are currently available to distinguishing adenomas from MGD in sporadic PHPT. MiRNAs are widely established as genetic molecules that have unique features suitable for biomarker use, as they display an exceptional stability against degradation and are easily extracted from various specimens including peripheral blood. The aim of this study was to investigate differential expression of hsa-miR-30e miRNA in patients with adenomas or MGD, as well as the association between the single nucleotide polymorphisms (SNP-ss178077483 and rs7556088) found in hsa-miR-30e and their possible role in sporadic PHPT tumorigenesis.
Methods
120 patients with sporadic PHPT were genotyped, 77 presenting with a single adenoma and 43 with MGD. 54 healthy adults served as controls. Patients with secondary hyperparathyroidism or patients with genetic syndromes involving PHPT, familiar hereditary disease or history of other malignancies were excluded. Patients with single adenomas were included only if they were followed-up for at least 2 years and confirmed to be disease free. The control group was tested and found to be negative for PHPT. Clinical data was collected from both Institutions' databases. Polymorphisms were identified using allele specific polymerase chain reaction technique. Hsa-miR-30e expression in samples was detected by real-time quantitative reverse transcriptase PCR.
Results
When comparing patients with adenomas and MGD, there was no significant difference in clinical and biochemical parameters. There was also no difference between weight and size of the resected glands in these two groups. Hsa-miR-30e expression was found to be significantly higher in patients with MGD compared to patients with single adenomas ($P=0.0019$). The genotype frequencies for ss178077483 and rs7556088 were found to differ significantly between patients with sporadic PHPT and healthy controls, but not between patients with adenomas and MGD. Furthermore, no significant differences were found in hsa-miR-30e expression levels regarding to specific genotype carriers.
Conclusions
Although SNPs do not seem to serve as possible genetic biomarkers for the preoperative differential diagnosis of MGD, hsa-miR-30e expression could potentially serve as a marker for this purpose.

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GP24

The impact of impaired calcium-phosphorus metabolism on the renin-angiotensin-aldosterone system in patients with primary hyperparathyroidism

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Objective
Primary hyperparathyroidism (PHPT) is associated with increased cardiovascular morbidity including hypertension with a prevalence ranging from 40 to 65%. The renin-angiotensin-aldosterone system (RAAS) is a key system in the regulation of sodium/potassium balance, volume homeostasis as well as blood pressure. There is increasing evidence of interactions between calcium and calcium-regulatory hormones with the RAAS. The aim of this study was to investigate the association between impaired calcium-phosphorus metabolism and the RAAS in PHPT patients.
Material and methods
We examined 57 patients with confirmed PHPT (48 women, 9 men, median age 49 years (Q1 = 39; Q3 = 56)). All patients underwent biochemical evaluation with monitoring blood pressure. Standardized blood sampling was performed before and in 3 days after surgical treatment for PHPT. The exclusion criteria were the glomerular filtration rate <75 ml/min/1.73 m^2, severe cardiovascular pathology, obesity, diabetes mellitus and treatment with drugs affected calcium balance.
Results
All cases presented symptomatic PHPT (median serum calcium level 2.73 mmol/l (Q1 = 2.61; Q3 = 2.98), PTH 122.7 pg/ml (Q1 = 94.0; Q3 = 203.0)). 38.6% of patients had mild and moderate hypertension that was corrected with antihypertensive therapy. Median levels of the RAAS components before and after surgery were: plasma renin activity (PRA) 0.42 (Q1 = 0.20; Q3 = 1.47) and 0.29 (Q1 = 0.08; Q3 = 1.16) ng/ml*h, aldosterone 108.2 (Q1 = 88.8; Q3 = 131.7) and 97.9 (Q1 = 77.7; Q3 = 126.8) pg/ml, angiotensin II 19.2 (Q1 = 16.3; Q3 = 21.1) and 20.2 (Q1 = 16.9; Q3 = 22.8) pg/ml respectively. No patients had deviations of serum aldosterone and angiotensin II levels, but slightly elevated PRA levels were defined in 10.5% of them. At the 3-rd day after surgery the biochemical evaluation revealed a significant decrease in PRA ($P=0.019$) and serum aldosterone levels ($P=0.005$). We found a significant positive correlation between intact PTH and PRA ($P=0.009$) as well as serum calcium and PRA levels ($P=0.001$) before parathyroidectomy. Serum calcium was also positively correlated with aldosterone ($P=0.018$) before surgery. In the early postoperative period PTH correlated only with angiotensin II level ($P=0.012$).
Conclusion
The study showed the significant changes of the RAAS activity after parathyroidectomy even in the early postoperative period. Further investigation with a long observation period is required to clarify these findings.

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GP25

Impact of chronic hypoparathyroidism on health-related quality of life, symptoms, employment, and relationships: findings from a 13-country patient survey

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Significant knowledge gaps exist regarding the humanistic effects of hypoparathyroidism, a rare, debilitating disorder. We report results from a global survey to characterise the burden of hypoparathyroidism from the patient perspective. An anonymous survey was conducted in patients with uncontrolled chronic hypoparathyroidism (as determined by patients' report of persistent symptoms and/or poorly controlled calcium levels as told by their physician) despite receiving conventional therapy. Patients currently or previously treated with parathyroid hormone were excluded. Health-related quality of life (HRQoL) and health status were evaluated using 2 validated instruments, SF-36 and EQ-5D-5L. Hypoparathyroidism-associated symptoms were assessed through the disease-specific Hypoparathyroidism Symptom Diary (7 days recall). Levels of work productivity and impairment were evaluated using the WPAI tool. All analyses were descriptive. The survey was conducted October 2017–March 2018 in 398 patients. Patients were asked to rate their self-perceived overall symptom severity level given the scale of no symptoms (3%), mild (32%), moderate (53%), or severe (12%). Mean SF-36 summary scores (0–100) were 45.4/44.6/37.1/28.7 (physical component summary) and 53.2/44.9/35.2/31.6 (mental health component summary) for patients reporting no/mild/moderate/severe hypoparathyroidism symptoms, respectively. Mean EQ-5D-5L utility scores (0–1) were 0.9/0.8/0.7/0.4 and EQ-5D-5L visual analogue scale scores (0–100) were 86.9/72.5/57.7/41.1 for patients reporting no/mild/moderate/severe hypoparathyroidism symptoms, respectively. Per the Hypoparathyroidism Symptom Diary, patients reported moderate/severe/very severe physical symptoms of physical fatigue (39%/25%/9%), muscle cramps (38%/12%/4%), and heaviness

in limbs (37%/14%/4%). Moderate/severe/very severe cognitive symptoms (slow/confused thinking) were reported by 28%/13%/6% of patients. Moderate/severe/very severe mood symptoms of anxiety and sadness/depression were reported by 29%/14%/3% and 28%/10%/4% of patients, respectively. The percentages of patients reporting an impact on family relationships, work, sleep, and ability to exercise were 63%, 75%, 78%, and 84%, respectively. 50% of patients were currently employed. WPAI scores showed patients working at 59% of their full capacity. Overall work impairment increased with self-perceived symptom severity: 18%/28%/49%/68% for patients reporting no/mild/moderate/severe hypoparathyroidism symptoms, respectively. Change of employment resulting from hypoparathyroidism was reported by 0%/29%/67%/83% of patients reporting no/mild/moderate/severe symptoms, respectively. The percentages of patients reporting 'a major impact' on relationships also rose with symptom severity: spouse/partner (0%/14%/33%/55%), family (0%/13%/34%/61%), and friends (0%/16%/45%/65%), for patients reporting no/mild/moderate/severe symptoms, respectively. Findings from this global survey demonstrated substantial burdens associated with uncontrolled chronic hypoparathyroidism with respect to HRQoL, disease-related symptoms, employment status, productivity, and relationships. The degree of burden corresponds with the severity of hypoparathyroidism-related symptoms reported by patients.

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Diabetes and Cardiovascular Disease

GP26

Association of MR-proANP with cardiovascular risk factors in middle aged patients with diabetes mellitus type 2 and non-diabetic controls

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Aim
To explore if MR-proANP is associated with cardio-metabolic risk factors in patients with med type 2 diabetes mellitus (T2D) and non-diabetic controls.
Methods
MR-proANP was analyzed in 761 middle-aged (54–66years) patients with type 2 diabetes and 184 non-diabetic controls and related cardio-metabolic conventional risk factors as age, sex, previous cardiovascular diseases (atrial fibrillation, myocardial infraction), glucose, LDL cholesterol, mean systolic blood pressure, active smoking, BMI, left ventricular mass index (LVMI), toe pressure index (TBI).
Results
Lower levels of MR-proANP were found in patients with T2D compared to non-diabetic controls (73 ± 38.5 vs. 80.3 ± 31.2 pmol/l, $P=0.03$). In T2D and non-diabetes group MR-proANP was positively correlated to age ($r=0.2$, $P<0.001$ and $r=0.4$, $P<0.001$, respectively) and LVMI ($r=0.1$, $P=0.003$ and $r=0.2$, $P=0.03$, respectively) and negatively to blood glucose ($r=-0.7$, $P=0.05$ and $r=-0.1$, $P=0.03$, respectively) and LDL-cholesterol ($r=-0.01$, $P=0.6$ and $r=-0.1$, $P=0.02$ respectively). For T2D patients linear regression analysis adjusted model for cardio-metabolic risk factors MR-proANP showed an significant association to gender (B = 0.04, 95% CI 0.02–0.06, $P<0.001$), age (B = 0.009, 95% CI 0.005–0.01, $P<0.001$), previous atrial fibrillation (B = 0.09, 95% CI 0.009–0.1, $P=0.03$), BMI (B = 0.005, 95% CI 0.001–0.009, $P=0.03$), systolic blood pressure (B = 0.001, 95% CI 0.001–0.001, $P=0.02$), active smoking (B = 0.04, 95% CI 0.01–0.07, $P=0.001$) and abdominal circumference (B = 0.002, 95% CI 0.001–0.004, $P=0.005$). For non-diabetic controls MR-proANP was associated to gender (B = 0.06, 95% CI 0.01–0.1, $P=0.1$), age (B = 0.004, 95% CI 0.001–0.008, $P=0.03$) and abdominal circumference (B = 0.005, 95% CI 0.001–0.01, $P=0.03$).
Conclusion
Lower levels of MR-proANP in T2D compared to non-diabetic controls showed significant association with cardio-metabolic risk factors. Our results suggest that ANP could have metabolic actions and may be implication in the pathophysiology of T2D.

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GP27

Serum insulin levels are associated with vulnerable plaque components in the carotid artery

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Background
Impaired insulin and glucose levels are implicated in the etiology of cardiovascular disease, however, their influence on the formation and composition of atherosclerotic plaque remains unclear.
Purpose
To investigate the association between fasting serum insulin and glucose levels with atherosclerotic plaque composition in the carotid artery.
Methods
In 1740 participants (mean age 72.9 years, 46% women, 14.4% diabetes mellitus) from the population-based Rotterdam Study, we performed carotid MRI to evaluate the presence of calcification, lipid core, and intraplaque hemorrhage in carotid atherosclerosis. All participants also underwent blood sampling to obtain information on serum insulin and glucose levels. Using logistic regression models, we assessed the association of serum insulin and glucose levels (per standard deviation (SD) and in tertiles) with the different plaque components, while adjusting for sex, age, intima-media thickness, and cardiovascular risk factors.
Results
High serum insulin levels were associated with the presence of intraplaque hemorrhage [adjusted odds ratio (OR) per 1-SD increase: 1.32 (95% confidence interval (CI) 1.01–1.75)] and with a lower frequency of lipid core [adjusted OR: 0.61 (95% CI: 0.54–0.88)]. We found no association with the presence of calcification. Sensitivity analyses restricted to individuals without diabetes mellitus yielded similar results. No associations were found between serum glucose levels and any of the plaque components.
Conclusions
Higher serum insulin levels are associated with the presence of intraplaque hemorrhage, and with a lower frequency of lipid core in carotid atherosclerosis. These findings suggest a complex role for serum insulin in the pathophysiology of carotid plaque vulnerability.

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GP28

The synergistic impact of apolipoprotein B/ A-1 and lipoprotein (a) on coronary artery calcification

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Objective
Apolipoprotein B/Apolipoprotein A-1 ratio (Apo B/Apo A-1) and lipoprotein (a) (Lp(a)) are known to be associated with atherosclerotic vascular disease. We investigated the influence of Apo B/Apo A-1 and Lp(a) on coronary artery calcification (CAC) among healthy Korean adults.
Methods
A total of 1081 participants underwent cardiac computed tomography in health promotion center were enrolled. Anthropometric profiles and multiple cardiovascular risk factors, including Apo B, Apo A-1, and Lp(a) were measured were measured. Multi-detector CT was used to measure coronary artery calcium score (CACS) and CACS > 0 was defined as the presence of CAC. Adjusted Odds ratios for the presence of CAC according to Lp(a) and Apo B/Apo A-1 tertiles were estimated using logistic regression.
Results
Subjects were grouped according to Lp(a) and Apo B/Apo A-1 levels. There were significant differences in cardiovascular parameters among the groups and the prevalence of CAC significantly increased with Lp(a) and Apo B/Apo A-1 levels. In the logistic regression analysis adjusted for multiple risk factors, odds ratio (95% CI) for the prevalence of CAC comparing the lowest Lp(a) and Apo B/Apo A-1 group to the highest group was 2.554 (1.256–5.201) ($P<0.05$).
Conclusion
These results show that Apo B/Apo A-1 and Lp(a) have a synergistic impact on prevalence of CAC, which suggests that individuals with elevated Lp(a) and Apo

B/Apo A-1, should be more closely monitored to allow a better risk assessment for subclinical atherosclerosis.

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GP29

Systematic screening of masked hypertension in normotensive type 2 diabetic patients

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Introduction
Masked hypertension (MH) is a relatively recent description leading to a similar cardiovascular risk as permanent hypertension. Masked hypertension is more common among diabetic patients.
Methods
This was a case-control study. We performed 24-hour ambulatory BP in 53 type 2 diabetic patients normotensive in clinical measurement. We compared both Masked Hypertension and Normotensive groups according to clinical/laboratory parameters and target organ damage, and identify MH predictor risk factors among diabetic population.
Results
We recruited 53 patients whose mean age was 55.3 ± 8.4 years (range 35–72 years) with a sex ratio (H/F) equal to 0.89. The mean age of diabetes was 8.7 ± 3.9 years with extremes between 2 and 17 years old. The mean BMI of our patients was 28.2 ± 5.3 kg/m^2. Overweight was found in almost half of our patients (47.2%). Obesity was found in 32.1% of cases. Metabolic syndrome was found in 64.2% of patients. In our study, the prevalence of HTAM in type 2 diabetics was 64%. Our study also found that this HTAM was more often nocturnal (58.5%), occurred in predominantly non-dippers. Left ventricular hypertrophy, micro-albuminuria and documented arterial stiffness by pulsed pressure greater than 60mm Hg in were more common in the group of HTAM. For the predictive factors of HTAM, we were able to collect in univariate analysis the factors age of diabetes, fasting blood glucose, body weight and microalbuminuria. In multi-variate analysis, the predictive factors that emerged in our study are: the bad glycemic control (HbA1c $\geq$7%), elevated BMI and duration of diabetes.
Conclusion
The masked hypertension should be evaluated in diabetic patients because it helps to better assess cardiovascular risk in particular by identifying affected target organs.

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GP30

Cardiovascular risk factors in patients with type 2 diabetes and non-alcoholic fat liver disease

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Background and aims
To investigate the level of lipoprotein associated phospholipase A2 (LpPLA2), nitrogen oxide (NO) in patients with type 2 diabetes (DM2) and nonalcoholic fatty liver disease (NAFLD) against a variety of hypoglycemic therapies (HT).
Materials and methods
A one-stage examination of 90 patients with DM 2 and NAFLD was carried out. Men ratio 37.8%, women ratio 62.2%, mean age 57.3 ± 11.6 years. Mean HbAlc 7.4 ± 1.82%. According to the HT conducted, the patients were divided into groups: 1) monotherapy with metformin (MF); 2) sulfonylurea preparations (SU) + MF; 3) insulin therapy IT + MF; 4) IT + (SU). The cytolysis parameters (ALT, AST), systemic inflammations (LpPLA2, NO) were evaluated. All the patients underwent liver elastography.
Results
The group average BMI 33.7 ± 3.48 kg^2, waist circumference 118.6 ± 38.4 cm. The highest ALT level (56.35 ± 38.6 u/l), AST (38.6 ± 14.4 u/l) was noted in the group of patients receiving MF. In the group of patients receiving SU, both in combination with MF and with insulin, the concentration of LpPLA2 was significantly higher than in the other groups (562.6 ± 97.8 ng/ml and 672.7 ± 173.08 ng/ml, respectively). The NO level was elevated in all groups, an average of 85.08 ± 40.58 μmol/l. The highest level of NO was recorded in the group of patients receiving insulin. In patients with DM 2 and NAFLD, the most common change in the liver according to elastometry is steatosis (77%). In 33% of the patients fibrosis (F) was detected. The highest F rates were noted in the group of patients on IT (11.8 ± 9.38 kr), with this group having a longer duration of the disease (9.7 ± 4.59 years).
Conclusion
It was found that the patients with DM2 and NAFLD have an increased level of LpPLA2, with its highest rate in patients receiving SU, both in combination with MF and with continuous-acting insulin, that may indicate a higher cardiometabolic risk in this group of patients. Regardless of the variant of hypoglycemic therapy, all the patients had an increase in NO level. The most common change in the liver in combination with NAFLD and DM 2 is steatosis (77%), one in three patients showed signs of liver fibrosis.

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GP31

Abstract Unavailable.

GP32

Breastfeeding is inversely associated with subclinical atherosclerosis in postmenopausal women

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Introduction
The aim of this study was to evaluate the association between a personal history of lactation and indices of subclinical atherosclerosis and arterial stiffness in postmenopausal women.
Patients and methods
This cross-sectional study included 283 postmenopausal women. Sonographically assessed indices of vascular function [pulse wave velocity (PWV)] and vascular structure [intima-media thickness (IMT), atherosclerotic plaque presence] were tested for possible association with the history of lactation.
Results
The duration of lactation ranged between 1 and 80 months. PWV was negatively associated with the duration of lactation (b-coefficient = −0.127, P value = 0.038), independently of age, BMI, LDL-cholesterol levels, smoking and arterial pressure. Subclinical atherosclerosis was associated with lactation (OR = 0.958, P value = 0.042), age, BMI and arterial pressure. Women who had lactated for more than 6 months presented significantly decreased mean common carotid IMT compared with women who had lactated for 1 to 6 months (0.72 + 0.13 mm vs 0.68 + 0.13 mm, F = 4.267, P value = 0.041), independently of other traditional cardiovascular risk factors.
Conclusions
Postmenopausal women with a personal history of breastfeeding present decreased arterial stiffness and atherosclerosis, even after adjustment for traditional cardiovascular risk factors. If causality is confirmed, these findings may indicate a protective effect of lactation against subclinical atherosclerosis in later life.

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GP33

Application of 3D skin culture model as a tool to study the role of immune mechanisms in chronic diabetic foot ulcers pathogenesis

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The aim
To test cytotoxic effects of immune factors of patients with chronic diabetic foot ulcers on keratinocytes and fibroblasts in a 3D skin culture system.
Materials and methods
In this study a multilayer 3D human skin model comprising of keratinocytes, fibroblasts and dendritic cells in an agarose-fibronectin gel was used. 20% serum of 13 patients with chronic noninfected diabetic foot ulcers, 13 diabetic type 2 patients and 13 healthy people and lymphocyte/monocyte mixture of the same groups of patients were added to the culture model. The system was also tested with standard irritants – dimethyl sulfoxide, Lipopolysaccharide. Cell viability and growth of fibroblasts and keratinocytes was measured using the resazurin reduction assay.
Results
Decreased fibroblasts viability was seen in the presence of blood components of patients with chronic diabetic foot ulcers (blood serum and lymphocyte/monocyte mixture). At the same time, the cytoinhibitory effect was observed mainly in the presence of lymphocyte/monocyte mixture of these patients (Table 1).

Table 1 Results of 3D culture model testing.

	Control (standard irritants only, no serum + lymph/monocyte)		Healthy people (20% serum + lymph/monocyte)	
Irritant	Keratinocytes (%)	Fibroblasts (%)	Keratinocytes (% to control)	Fibroblasts (% to control)
Control	100	100	-	-
DMSO, (100 mM)	101.1 [98.7;103.5]	104.8 [101.1;108.2]	103.0 [98.7;107.1]	99.8 [98.3;101.1]
SCS, (5 μg/ml)	94.4 [90.1;99.2]	97.1 [93.6;100.3]	103.8 [102.9;104.2]	99.8 [99.1;103.1]
LPS, (10 μg/ml)	108.0 [103.1;112.6]	97.1 [92.1;101.3]	95.5 [92.1;99.2]	76.8 [69.7;87.2]
DMSO + LPS	87.6 [83.3;91.2]	105.1 [102.1;108.6]	84.0 [79.1;89.1]	90.8 [82.3;96.8]
Only 20% serum	-	-	104 [96.7;110.3]	98.3 [96.9;99.7]
Only lymph/monocyte	-	-		

Table 1 Continued.

	Diabetic patients (20%serum + lymph/monocyte)		Diabetic foot ulcers patients (20%serum + lymph/monocyte)	
Irritant	Keratinocytes (% to control)	Fibroblasts (% to control)	Keratinocytes (% to control)	Fibroblasts (% to control)
Control	-	-	-	-
DMSO, (100 mM)	96.8 [90.4;96.7]	89.6 [82.4;93.1]	92.6 [90.3;95.3]	76.8* [72.3;81.3]
SCS, (5 μg/ml)	92.5 [85.7;99.8]	84.1 [79.3;88.1]	88.7 [85.2;101.1]	70.0* [64.3;78.1]
LPS, (10 μg/ml)	91.7 [76.3;92.4]	77.2 [67.1;82.3]	71.2** [64.8;75.9]	67.8* [62.5;70.6]
DMSO + LPS	86.1 [78.4;92.6]	82.6 [77.4;91.2]	84.2 [76.4;91.2]	66.1* [61.4;69.6]
Only 20% serum	98.8 [86.7;100.2]	95.8 [87.2;101.2]	94.7 [84.8;99.6]	93.2 [88.1;96.2]
Only lymph/monocyte	93.6 [85.8;98.1]	89.1 [74.2;95.3]	87.1** [83.2;91.4]	64.7* [59.8;67.9]

*Significant difference vs diabetic, healthy group and control, $P<0.05$;
**Significant difference vs healthy group and control, $P<0.05$.

Conclusion
3D skin culture model can be used to study *in vitro* the role of immune factors in pathogenesis of chronic diabetic foot ulcers.

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GP34

Stroke in diabetic patients and cardiovascular risk factors control

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Introduction
Strokes are common diabetes macrovascular complications. A good control of cardiovascular risk factors such as glycemic control has been proven to reduce the risk of its appearance. *Aim:* Describe diabetes prevalence in patients admitted to hospital because of a stroke, as well as their treatment and metabolic control.
Patients and methods
Observational retrospective study of patients admitted to the Neurology section because of a stroke between 2016 and 2017. Statistical analysis performed with SPSS (22th version).
Results
611 patients recruited. Age: 65.13 ± 12.72 years. 32.7% women. Mean of HbA1c 6.75 ± 1.54%. 28 patients died during their hospital stay, 35.7% of which had a previous diabetes story. ($P=0.55$). Prior DM history in 187 patients (30.6%): 0.5% LADA, 1.1% DM1 and 97.9% DM2. 55.9% were treated with antidiabetic drugs, 18.4% with insulin, 12.8% with both and in 12.8% the treatment was unknown. HbA1c was requested in 72.2% of people with diabetes with a HbA1c of 7.71 ± 1.72%. 51.9% of them met their glycemic target. In 53.2% non-diabetic people HbA1c was requested: 20 patients (4.1%) were diagnosed with diabetes (Mean HbA1c 7.06 ± 0.72%) and 85 with prediabetes (34.7%, Mean HbA1c 5.94 ± 0.20%). 23 patients with diabetes (12.3%) and 3 (15%) newly diagnosed were evaluated by an endocrinologist. Treatment at discharge was modified in 22.5% of patients with prior DM history (42.9% by endocrinologists and 57.1% by neurologists) and in 25% of newly diagnosed diabetic patients (40% by endocrinologists and 60% by neurologists). Most patients (68.1%) improved their ambulatory glycemic control with a mean HbA1c reduction of 0.75 ± 1.61% (in 5.48 ± 2.68 months). 19 patients had a worse ambulatory glycemic control and only 2 of these had been evaluated by endocrinologists.
Conclusions
1) Diabetes prevalence in patients with stroke is high in our series, in spite of which HbA1c is not routinely evaluated.
2) Almost a half of diabetic patients (48.1%) do not meet their glycemic goal at admission. However only a small percentage (12.3%) of them are evaluated by an endocrinologist and after this evaluation most of them improve their glycemic target.

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GP35

Cardiovascular biomarkers and calculated risks - an association study

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The identification of type 2 diabetes patients at particularly high risk for cardiovascular events might be facilitated by the use of specific risk calculators or by measurements of serum biomarkers.
Objectives
To correlate the levels of cardiovascular biomarkers – assymetric dymethylarginine (ADMA), endothelin 1 (ET-1), N-terminal brain natriuretic pro-peptide (NT-proBNP) and placental growth factor (PIGF-1), with calculated cardiovascular risks using three different risk engines.
Material and methods
102 women and 67 men with type 2 diabetes on oral antidiabetic drugs agreed to participate in this cross-sectional study (mean age – 60.3 ± 9.6 years; mean diabetes duration – 7.6 years). Fasting morning blood and urine samples were collected and the glycemic and metabolic parameters were assessed by routine laboratory (glycated hemoglobin A1c, lipid profiles, creatinine, microalbuminuria etc.). Serum levels of NT-proBNP and PIGF-1 were measured by electro-hemiluminescence (Elecsys 2010, Roche Diagnostics) while enzymatic immunoassays were used for ADMA (BioVendor) and ET-1 (IBL International GMBH). Cardiovascular risks were calculated using the Framingham Risk Score (FRS), the UKPDS version 2.0 and the ADVANCE risk engines. Correlation and regression analysis were performed on an IBM SPSS 19.0 for Windows platform (SPSS Corp., Chicago, IL).
Results
ADMA levels were above the upper normal limit in 11.0% of the participants, ET-1 levels - in 20.4%, and NT-proBNP - in 33.5%. Based on the ADVANCE risk calculator 10.8% of the participants had a 4-yr risk for CV events ≥ 8.0%. The FRS based 10-yr risk was very high (> 20%) in 8.0% of the participants, and moderate (15 – 30%) – in 12.1%. The UKPDS-based risk was very high (>30%) in less than 20% of the participants. Levels of PIGF-1 showed no correlation with the calculated CV risks, the same was true for levels of ADMA, except for UKPDS-based 10-yr risk for stroke. Plasma levels of endothelin-1 were correlated only with the UKPDS-based 10-yr risk for stroke and fatal stroke, while NT-proBNP levels were highly and significantly correlated with all possible CV risk calculations. The curve estimations within the regression analyses produced similar results.

Conclusion
Serum levels of ADMA and PIGF-1 do not seem related to calculated cardiovascular risks. ET-1 is linked to risk for stroke, while NT-proBNP - to both cardio- and cerebrovascular risk estimations.

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GP36

Family education, quality of life and glycosylated haemoglobin control among Nigerian diabetics: a quasi-experimental study

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Glycaemic control remains poor among individuals with diabetes mellitus (DM) in Nigeria and is linked to a non-supportive family environment. Family-Integrated Diabetes Education (FIDE) has been shown to improve glycaemic control in studies among Hispanics and Caucasians. However, there is dearth of literature on its effectiveness among Africans; despite the close-knit nature of many African families. The study aimed at determining the effects of FIDE on glycosylated haemoglobin (HbA1c) and Quality of Life (QoL) of type 2 diabetes patients in Nigeria; with the overarching goal of improving diabetes-education policy/operating procedure in Nigerian hospitals. Quasi-experimental design involving two teaching hospitals was utilized. There were 88 patients in Control-Group (CG) and 82 in Intervention-Group (IG), with a corresponding number of family members. Patients' diabetes knowledge, QoL and HbA1c were determined. Family members completed a questionnaire on diabetes-knowledge. IG received FIDE and patients and family were assessed for immediate post-intervention knowledge. HbA1c, and QoL were reassessed at three and six-month post-intervention. Data was analyzed using independent t-test, paired t-test and repeated-measures ANOVA, at $P < 0.05$. One hundred and fifty-two (152) patients completed the study – 78 in CG and 74 in IG. 55.3% being $\geq$60 years. Duration of DM was $<$ 20 years in 88.3%. Family members were mostly female (62.9%) with 52.8% aged $\leq$ 40 years. Knowledge of family members in IG was significantly higher than that of CG post-intervention ($8.6 \pm 3.0/5.8 \pm 2.2$, $P < 0.01$). HbA1c reduced significantly in IG by third month (8.9%/7.8%; $P < 0.01$), but did not in CG. QoL of IG improved significantly between third and sixth month ($51.4 \pm 8.8/56.2 \pm 11.9$; $P = 0.001$). Family Integrated Diabetes Education (FIDE) improved glycaemic control and quality of life of diabetes patients. It is recommended that family members be formally included in diabetes-education in all Nigerian hospitals. It is hoped that results of this study will drive policy change in Nigerian hospitals in the near future towards improving diabetes care.

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Metabolic Syndrome and Hypoglycaemia

GP37

Abstract Unavailable.

GP38

Beta cell senescence: effect of glucotoxicity and glucolipotoxicity

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Pancreatic beta cell senescence is one of the recent explanations for theincreased prevalence of type 2 diabetes in the elderly. Aging may exert a distinct influence on pancreatic β cell turnover, regeneration capacity and function. Oxidative stresses induced by metabolic stresses reduce pancreatic beta cell mass and secretion. We investigated how metabolic stresses effect on pancreatic beta cell senescence. INS-1 cells were exposed to 33mM glucose (glucotoxicity: high glucose (HG)) or 33 mM glucose with palmitate 200 uM (glucolipotoxicity: HG + palmitate (HGP)). Cell viability and apoptosis were assessed by MTT assay and Annexin V staining. We compared senescence β-Galactosidase (SA-β-Gal) staining and p16INK4aimmunostaining between high glucose (HG) and HG + palmitate (HGP). We assessed phospho-p38 MAPK, Sirt1 and p16 protein expression with metabolic stresses. CDK4 protein and antioxidant enzyme were assessed in both conditions. INS-1 cell viability was decreased and apoptosis was increased in both HG and HGP. SA-β-Gal and p16INK4a immunostaining were significantly increased in both stresses compared to control. HG and HGP decreased phospho-p38 MAPK and increased p16INK4aprotein expression. HG and HGP decreased CDK4 and catalase expression. In conclusion, we found metabolic stresses like glucotoxicity and glucolipotoxicity increased beta cell senescence. Beta cell aging induced metabolic stress may related to phospho-p38 MAPK and p16INK4apathway, beta cell cycle and anti-oxidant system.

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GP39

Generalized lipodystrophy associated with delayed neuro-somatic development and multiple dysmorphisms in a neonate with a compound heterozygous missense mutation in the SYNE2 gene

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Generalized lipodystrophies are extremely rare diseases. Despite remarkable progress in identifying genes responsible for the most common forms of genetic lipodystrophies, the molecular basis of disease in some patients with distinctive phenotypes remains unclear. We herein describe the case of a male patient born from non-consanguineous parent affected by a syndrome characterized by generalized lipodystrophy, psycho-somatic growth retardation, cleft palate, macroglossia, right cryptorchidism, fingers with extended base and short femurs. In the third month of life, an abnormally increased appetite, the lack of weight growth and the dystrophic appearance became very evident. Moreover the ultrasound analysis revealed hepatic steatosis and blood test howed high triglyceride values (up to 1577 mg/dl), low serum leptin levels (0.1 ng/ml). Based on patient's clinical features, instrumental and laboratory results, Berardinelli-Seip syndrome was initially hypothesized. The entire coding region of candidate genes involved in congenital generalized lipodystrophy (BSCL1, AGPAT2, CAV1, PTRF) and other forms of lipodystrophy (LMNA) were sequenced by Sanger method but no mutations were found. To have a better insight on the possible genetic alterations causing the disease, we performed exome sequencing using Illumina NextSeq500. After data filtering and segregation analysis, we identified compound heterozygous missense variants in the spectrin repeat containing nuclear envelope protein 2 gene (SYNE2):c.18632C$>$ T (p.T89M) and c.20410G$>$ A (p.D326N). The first genetic variant is shared with the father, the second one with the mother. The mutation p.T89M is classified as patogenetic for Emery-Dreyfuss muscular dystrophy (EDMD) in ClinVar Database, and it was previously reported in two families with EDMD. In conclusion we describe a likely novel syndrome characterized by generalized lipodystrophy, severe delayed psycho somatic development and multiple dysmorphisms, possibly related to a compound heterozygous missense mutation in the SYNE2 gene.

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GP40

Long-term administration of Empagliflozin may promote hepatic and renal lipid accumulation, and inflammation in the APOE knockout model

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Introduction
Metabolic disorders characterized by insulin resistance/hyperinsulinemia, such as metabolic syndrome and T2DM, are associated with Non-Alcoholic Fatty Liver Disease (NAFLD). SGLT-2i reduce reabsorption of glucose from the kidneys thereby promoting glucosuria, while their beneficial effects on insulin resistance have been recently recognized. In this study, we aimed to investigate the effect of Empagliflozin, in *de novo* triglyceride synthesis and beta-oxidation as well as high-fat diet (HFD)-induced inflammation in the liver and kidneys of ApoE (−/−) male mice.
Methods
At the age of 5 weeks, mice were switched from normal to HFD. After 5 weeks, they were divided into Control-group (9 mice) and Empa-group (9 mice: empagliflozin 10 mg/kg per day). After 10 weeks, animals were culled and liver and kidneys were harvested. Biochemical markers were measured at the onset and at the end of the intervention. The mRNA levels of enzymes contributing in *de novo* triglyceride synthesis including GPAT1, GPAT3, GPAT4, AGPAT2, DGAT1, DGAT2 and beta oxidation (AMPKa 1 and 2) were measured by qPCR. Liver and kidney sections were stained with H&E and histomorphometric analysis was performed. Immunohistochemical staining with anti-MCP-1 and anti-CD-68 was also conducted to assess inflammation.
Results
Empa-group mice had lower glucose and HDL-cholesterol levels ($P \leq 0.01$), while total-cholesterol, LDL and triglycerides did not change significantly compared to control group. Histomorphometry indicated that Empagliflozin significantly induced lipid accumulation and infammation in both liver and kidney, compared to Control-group. Immunohistochemistry staining revealed an increase in CD68 and MCP-1 expression in the Empa-group compared to Control-group in both kidney and liver. GPAT3, AGPAT2 mRNA levels were increased in Empa-group compared to Control-group in both kidney and liver ($P < 0.05$). Empagliflozin also increased GPAT4, DGAT1 and DGAT2 mRNA levels in both kidney and liver approaching statistical significance ($P \leq 0.09$). AMPKa2 expression was up-regulated in the kidney of the Empa-group compared to the Control-group ($P \leq 0.01$) while no significant difference was observed in AMPKa 1 and 2 expression in the liver.
Conclusions
Our study revealed that long-term administration of Empagliflozin in ApoE (−/−) atherosclerosis mouse model, promotes NAFLD and induces lipid accumulation and inflammation in the kidney, at least partially via inducing the expression of enzymes involved in *de novo* synthesis of triglycerides and inflammatory process.

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GP41

Applying the Bradford Hill criteria to evaluate the association between hypoglycaemia and cardiovascular events/mortality (CVEM) [Data from meta-analysis (MA), Randomized Controlled Trials (RCTs), and observational outcome studies (OBS)]

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Background
The association between hypoglycaemia and CVEM is controversial. It is not ethical or practical to design RCTs to study this association as the primary clinical outcome measure. Therefore, utilization of epidemiological principles to study this association is essential.
Objective
To systematically explore the data from MA, RCTs and OBS on hypoglycaemia and CVEM applying Bradford Hill criteria [strength, consistency, dose response or biological gradient, specificity, temporality, biological plausibility, coherence, experimental evidence, and analogy].
Methods
A systematic literature search was performed using PubMed database, with several combinations of MeSH terms. Bibliography mining was also done on relevant articles to be as inclusive as possible.
Results
Strength: Three MAs demonstrated significant increase in CVEM; data driven from RCTs and OBS illustrated Hazard Ratio (HR) of 2.0 and 4.0, respectively. Consistency: Four RCTs and two OBS with entirely different populations illustrated increase in CVEM related to hypoglycaemia. Dose response or biological gradient: One MA demonstrated HR of 1.6 for mild hypoglycaemia versus 2.3 for severe hypoglycaemia. Specificity, temporality, biological plausibility and coherence: Not possible to assess directly through studies with CVEM measures; these criteria can be fulfilled by biological and physiological studies; hypoglycemia leads to abnormalities in myocardial perfusion, thrombotic process, cardiac repolarization; these abnormalities could potentially lead to increased risk of CVEM. Temporality has been shown with studies that utilized continuous glucose monitoring and ECG, simultaneously. Experimental evidence: Evidence exists from both interventional and observational studies with hard and surrogate outcomes. Analogy: Collectively the data from biological, physiological and outcome studies for heart disease such as heart failure illustrated increase in CVEM in population without and with diabetes through same pathways that have been observed for hypoglycaemia.
Conclusion
Available data from literature collectively illustrates that the association between hypoglycaemia and cardiovascular events fulfil Bradford Hill criteria for association.

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GP42

Magnitude of effects of testosterone replacement therapy on testosterone normalization, parameters of metabolic syndrome and vascular function and morphology in obese hypogonadal patients with type 2 diabetes – the SETH2 study

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Background
The association between testosterone deficiency, metabolic syndrome (MetS) and type 2 diabetes (T2DM) is well established. Male hypogonadism is related to an increase in glycometabolic and cardiometabolic complications.
Objective
To evaluate magnitude of effects of testosterone replacement therapy (TRT) on testosterone normalization, parameters of the MetS and vascular function and morphology in obese hypogonadal male patients with T2DM.
Study design
SETH2 was a randomized, double blind, placebo-controlled clinical study of 55 obese diabetic males not treated with insulin, with confirmed late-onset hypogonadism. Two study groups were formed. Group T patients ($n = 28$) were treated with testosterone undecanoate (1000 mg depot injection administered i.m. at first visit, with second injection following six weeks later and the remaining ones every 10 weeks following the previous) while group P patients ($n = 27$) received placebo.
Methods
Ultrasound assessment of endothelial function – flow mediated dilatation (FMD) of brachial artery and vascular morphology of carotid artery (intima media thickness - IMT), biochemical and hormonal blood sample analyses were performed at baseline and after one year. Effect size was assessed using Cohen's d (with 95% confidence interval for Cohen's d).
Results
TRT resulted in a statistically significant decrease of fasting plasma glucose (1.23 ± 1.25 mmol/l, $P < 0.001$; d = 1.07, 95% CI: 0.51 – 1.64), HbA1c (0.94 ± 0.88% points, $P < 0.001$; d = 1.03, 95% CI: 0.47 – 1.59), HOMA-IR (4.64 ± 4.25, $P < 0.001$; d = 1.23, 95% CI: 0.66 – 1.81) and an increase in total (9.80 ± 3.59 nmol/l, $P < 0.001$; d = 2.78, 95% CI: −3.62 – −2.12), calculated bioavailable (5.76 ± 2.16 nmol/l, $P < 0.001$; d = 2.79, 95% CI: −3.53 – −2.05) and calculated free testosterone (248.29 ± 99.45 pmol/l, $P < 0.001$; d = 2.61, 95% CI: −3.33 – −1.89) and FMD (2.40 ± 4.16% points, $P = 0.005$; d = 0.66, 95% CI: −1.20 – −0.12). IMT has decreased in both groups; by 0.10 ± 0.06 mm ($P < 0.001$) in group T and by 0.05 ± 0.09 mm ($P = 0.006$) in group P; d = 0.66, 95% CI: 0.11 – 1.20. No statistically significant effects were observed on other parameters of MetS.

Conclusion
TRT exerted very large effects on levels of testosterone (d ranging from 2.61 to 2.78) and on some parameters of MetS (d ranging from 1.03 to 1.25) with moderate effect on vascular function (d = 0.65) and morphology (d = 0.66).

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GP43

The elevated chemerin plasma concentrations in men diagnosed with metabolic syndrome are correlated with markers of low-grade state inflammation but not with SHBG serum levels and accompanying hypoandrogenemia.

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Background
Chemerin (CHEM) is a newly-discovered adipokine involved in the immune, metabolic and reproductive processes. Low-grade state inflammation (LGSI) is a key element in the pathogenesis of metabolic syndrome (MS).
Objectives
The aim of the study was to assess the effect of age on MS prevalence, androgenic status as well as on selected inflammatory indices and CHEM plasma concentrations. Additionally we investigated correlations between CHEM and age-dependent serum androgen changes in addition to LGSI parameters in males diagnosed with MS compared to healthy subjects.
Materials and methods
For the study 149 men aged 40 to 70 years were enrolled. They were divided into four equal numbers groups. Measurement of anthropometric indices, blood pressure and laboratory tests included fasting plasma glucose, lipids, CHEM, selected androgens, IL–18, hs-CRP and SHBG were carried out.
Results
The criteria for diagnosis of MS were fulfilled a total of 67 men (45%). The incidence on MS did not increase with age ($P = 0.533$). Both adrenal androgens decreased with age (DHEA: $P = 0.0042$; DHEAS: $P < 0.0001$), as opposed to total ($P = 0.955$) and free testosterone ($P = 0.526$) as well as SHBG ($P = 0.074$). CHEM concentrations increased with age ($P = 0.0089$) and were higher in men diagnosed with MS compared to healthy subjects: 90.18 (53.7–190.61) vs. 73.64 (15.58–236.55) ng/mL; $P = 0.0002$. Men diagnosed with MS revealed a significantly lower total testosterone serum level: 5.3 (2.0–15.2) vs. 6.3 (2.3–34.2) ng/mL; $P = 0.0004$ and SHBG: 45.62 (17.17–120.31) vs. 71.97 (24.83–193.31) nM/L; $P < 0.000001$. Furthermore, elevated LGSI indices have been demonstrated in men suffering from MS, as opposed to healthy ones [IL-18: 530.64 (261.46–944.97) vs. 418.85 (200.54–791.08) pg/mL; $P = 0.000045$ and hs-CRP: 2.03 (0.31–38.0) vs.0.97 (0.08–90.3) ng/mL; $P = 0.0016$)]. CHEM plasma concentrations were correlated with some components of MS (systolic blood pressure, HDL-cholesterol, triglycerides and waist circumference). Additionally, CHEM serum levels were clearly correlated with LGSI indices: hs-CRP ($R = 0.265$; $P = 0.001$) and IL-18 ($R = 0.375$; $P = 0.000009$)- regardless of age, smoking, metabolic status and androgenemia. In contrast, CHEM plasma levels revealed no statistically significant relationships with androgenemia and SHBG plasma levels.
Conclusions
The elevated CHEM plasma concentrations detected in obese men diagnosed with MS are closely related to accompanying LGSI than to androgen deficiency.

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GP44

Effects of anti-inflammatory treatment on fibroblast growth factor-21 in obesity and metabolic syndrome

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Background
Fibroblast growth factor-21 (FGF21), which has recently been identified as a central regulator of metabolism, is known to be increased in conditions of obesity, insulin resistance, and fatty liver. Likewise, there is evidence that FGF21 increases with systemic inflammation. The aim of this study was to evaluate whether chronic low-grade inflammation might be the underlying mechanism and whether an anti-inflammatory treatment decreases FGF21 levels in metabolic disorders.
Methods
This is a secondary analysis of two interventional studies of treatment with an Interleukin-1 (IL-1)-receptor antagonist anakinra (Kineret®) in patients with obesity and features of the metabolic syndrome. The CortIL trial was a prospective interventional trial ($n = 61$) investigating short-term effects of anakinra and dexamethasone in metabolic syndrome. The TestIL trial was a placebo controlled, double-blinded interventional trial ($n = 67$) investigating longer-term effects of anakinra in metabolic syndrome versus placebo. FGF21 was measured at baseline, at day 2 and at 4 weeks of treatment with anakinra. Furthermore, FGF21 levels were measured after dexamethasone suppression test.
Results
Mean age of all includes patients ($n = 140$) was 54 years (SD 12.1), 26% were female and the mean body mass index (BMI) was 37 kg/m2 (SD 4.8). Almost half of the patients were diabetic (45%) and had slightly increased c-reactive protein levels of 4.7 mg/L (SD 5.4), mirroring a state of chronic low-grade inflammation. FGF21 levels highly positively correlated with fasting glucose levels, HOMA-index, c-peptide levels, HbA1c and BMI. Treatment with anakinra led to a short-term reduction of FGF21 levels by 49.0 pg/mL (95% CI, (−205.9) – 107.9); $P = 0.064$; however, this effect was no longer visible at 4 weeks (between-group difference: −8.8 pg/mL (95% CI, (−130.9) – 113.3); $P = 0.89$. Short-term treatment with dexamethasone was associated with profound reduction of FGF21 by 174.5 pg/mL (95% CI, (−235.8) – (−113.2)); $P < 0.001$.
Conclusions
Anti-inflammatory treatment led to a reduction of FGF21 levels in individuals with obesity and features of the metabolic syndrome. Chronic low-grade inflammation may be one of the key mediators for increased FGF21 in metabolic disorders.

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GP45

Hypoglycemia and dementia risk in older patients with type 2 diabetes: a propensity-score matched analysis of a population-based cohort study

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Background
Type 2 diabetes mellitus (T2DM) is associated with an increased risk for dementia. The effects of hypoglycemia on dementia are controversial. Thus, we evaluated whether hypoglycemia increases the risk for dementia in senior patients with T2DM.
Methods
We used the Korean National Health Insurance Service Senior cohort, which includes >10% of the entire senior population of South Korea. In total, 7,752 patients who had ever experienced hypoglycemia were matched with those who had not, using propensity score matching. Forty-eight confounding variables, including age, socioeconomic status, medication use, and underlying diseases, which may affect dementia, were corrected for propensity score matching. The risk of dementia was assessed through a survival analysis of matched pairs.
Results
Patients with underlying hypoglycemic events had an increased risk for all-cause dementia, Alzheimer's dementia (AD), and vascular dementia (VaD) compared with those who had not experienced a hypoglycemic event (hazard ratio [HR] 1.254, 95% confidence interval [CI] 1.166–1.349, $P < 0.001$ for all-cause dementia; HR 1.264, 95% CI 1.162–1.375, $P < 0.001$ for AD; HR 1.286, 95% CI 1.110–1.490, $P < 0.001$ for VaD). In the subgroup analysis, hypoglycemia was associated with an increased risk for dementia in both sexes with or without T2DM microvascular or macrovascular complications.
Conclusions
Our findings suggest that patients with a history of hypoglycemia have a higher risk for dementia. This trend was similar for AD and VaD, the two most important subtypes of dementia.

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GP46

Characteristics and management of Type 1 diabetes mellitus patients with diabetic ketoacidosis

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Background & Objectives
Type 1 diabetes mellitus (T1DM) is a complex disease with both genetic and environmental factors in its pathophysiology. Higher risks of diabetic emergencies such as diabetic ketoacidosis (DKA) confers a greater difficulty in its management than Type 2 diabetes. This study aims to describe and compare the characteristics, management and outcomes of T1DM patients with and without complication of DKA.
Methods
A total of 333 T1DM patients who visited a tertiary hospital for clinic follow-up of T1DM in Singapore from May 2017 to October 2017 was studied. Patients were then stratified based on presence or absence of DKA after the initial diagnosis. Relevant demographics, pharmacological and non-pharmacological management and outcomes were analysed.
Results
Amongst the T1DM patients, 133 (39.9%) had at least one subsequent DKA episode while 200 patients (60.1%) did not. Greater proportion of patients with subsequent DKA episodes first presented with DKA before diagnosis of T1DM (DKA 62.7% vs No DKA 34.2%, $P<0.01$). Average HbA1c over the last 1-year was higher in patients with DKA than those without DKA (DKA 9.52 ± 1.85% vs. No DKA 8.55 ± 1.72%, $P<0.01$). Incidence of microvascular complications were higher in patients with DKA (50.0% vs 33.5%, $P<0.01$) while incidence of macrovascular complications was similar in both groups (12.9% vs 14.5%, $P=0.70$). Furthermore, hypoglycemic admissions were more common in patients with DKA (24.8% vs 10.0%, $P<0.01$). In terms of non-pharmacological management, compliance to self-blood glucose monitoring (59.4% vs 73.9%, $P<0.01$) and DM education class uptake (7.5% vs 22.6%, $P<0.01$) was poorer in patients with DKA than those without DKA. However, there was no significant difference seen in use of continuous glucose monitoring (DKA: 15.8% vs no DKA: 22.6%, $P=0.13$) or use of insulin pumps (4.0% vs 2.3%, $P=0.54$).
Conclusion
This study highlights the differences in characteristics, complications and management of T1DM with and without subsequent DKA episodes. It suggests that increased emphasis on educating management of hypoglycaemia and DM education classes would be beneficial for the control of T1DM. Moreover, importance of compliance to self-blood glucose monitoring should also be reinforced. Further studies will be required to optimise management of T1DM patients and to prevent future diabetic emergencies in these patients.

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GP47

Awareness, treatment rates and compliance to treatment in patients with serum LDL cholesterol higher than 250 mg/dL, and possible, probable and definite familial hypercholesterolemia

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Aim
Familial hypercholesterolemia (FH) is an autosomal dominant genetic disease characterized by increased levels of low density lipoprotein cholesterol (LDL-chol). Despite relatively high prevalance and significant association with increased mortality, the awareness of physicians and patients is low and it is an underdiagnosed and undertreated disease. We aimed to detect patients with FH and determine treatment status and compliance.
Materials and methods
Patients >18 years old and have a serum LDL-chol $\geq$250 mg/dL between January 2010-December 2016 were identified from the database of our hospital. A survey was performed by reaching patients via phone. Demographic features, smoking status, use of alcohol, exercise, presence of cardiovascular disease (CVD), use of medication for dyslipidemia, CVD and high cholesterol levels in the family were questioned. Patients with a serum thyrotrophin $\geq$10 mIU/mL, patients with glomerulonephritis and nephrotic syndrome, patients with high liver enzymes and patients with serum triglyceride >400 mg/dL were excluded. DUTCH lipid diagnostic criteria was used to classify patients.
Results
LDL-chol was $\geq$250 mg/dL in 1918 measurements. When repeated measurements were excluded, 1365 patients were identified. Patients that could not be reached by phone and who refused to interview were excluded and data of 367 patients were analyzed. There were 248 (67.6%) female and 119 (32.4%) male patients and mean age was 50.5 ± 11.66. LDL-chol was $\geq$330 mg/dL in 50 (13.6%) and 250–329 mg/dL in 317 (86.4%) patients. Mean DUTCH score was 6.36 ± 1.63. 40 (10.9%) patients were classified as definite, 181 (49.3%) as probable and 146 (39.8%) as possible FH. Among patients with definite or probable FH, 84 (38.0%) had CVD. DUTCH scores were 8.09 ± 1.54 and 6.74 ± 1.31 in patients with and without CVD, respectively. Considering all patients, 42% were taking medication for dyslipidemia. Among 213 patients that were not on antilipidemic treatment, 162 (76.1%) stated that medication was never recommended previously, 30 (14.1%) had stopped medication him/herself and 21 (9.8%) had stopped medication with the advice of the physician. 49 (58.3%) definite or probable FH patients with CVD was taking antilipidemic treatment.
Conclusion
A significant proportion of patients with LDL-chol $\geq$250 mg/dL were not taking antilipidemic drugs and other cardiovascular risk factors were not under control. Similar with many other countries, diagnosis and treatment rates of FH patients were very low in our country. Further national studies are required to increase awareness of the disease in both physicians and patients.

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Acromegaly and GH

GP48

Prolonged diagnostic delay in acromegaly is associated with long-term morbidity and excess mortality: data from a nationwide study

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Background
Clinical features of acromegaly develop insidiously and the diagnosis is often delayed. However, diagnostic delay (DD) in acromegaly has not been systematically investigated. Our primary aim was to investigate DD in a nationwide cohort of patients with acromegaly. Secondary aim was to study the impact of DD on morbidity and mortality.
Methods
Adult patients diagnosed with acromegaly between 2001 and 2013 were identified in the Swedish National Patient Registry. Forty-four diagnostic codes for predefined comorbidities associated with acromegaly, registered from 1987 to 2013, were recorded. The DD was calculated as the time between the first registered comorbidity and the diagnosis of acromegaly.
Results
A total of 603 patients with acromegaly (mean age at diagnosis: 51.8 ± 15.3 years) were included (280 men, 323 women). The mean DD was 5.5 ± 6.2 years (median 3.3; range 0.0–9.4), with a tendency towards a longer DD in women than in men [median 4.1 (0.1–10.6) *vs* 2.7 (0.0–8.0); $P=0.055$]. DD was 1–<5 years in 23% patients; 5–<10 years in 17%; and $\geq$10 years in 24%. Patients without comorbidities and those with comorbidities identified within a year before the acromegaly diagnosis, or later, were analysed as a single group, named *patients without DD* (36%). Of 603 patients, 579 (96%) had comorbidities at any time during the study period. The median number of comorbidities was 4.0 (2.0–5.0), and was significantly higher in patients with longer DD ($P<0.0001$). The most frequent comorbidities were neoplasms, excluding pituitary tumours (61%), cardiovascular (57%), and musculoskeletal (51%) diseases, with a higher frequency in patients with longer DD ($P<0.0001$). The longest DD was found for neurological-psychiatric symptoms (4.6 ± 6.3 years) and the shortest for local effects; *e.g.* symptoms due to tumor compression of surrounding structures (1.7 ± 3.4 years). DD for cardiovascular, musculoskeletal disorders, and neoplasms was 2.6 ± 4.5, 3.4 ± 4.9, and 3.7 ± 5.4 years, respectively. The observed number of deaths was 61, and expected number 42.2, resulting in a standardized mortality ratio of 1.45, 95% CI 1.11–1.86. Excess mortality was only found in patients with *DD* $\geq$*10 years* (1.76, 95% CI 1.12–2.65) whereas mortality was similar to the general population in the groups with shorter DD [*1–<5 years*, 1.32 (95% CI 0.68–2.31); *5–<10 years* 1.54 (95% CI 0.74–2.83)] as well as in patients *without DD* (1.18; 95% CI 0.68–1.92).

Conclusions
Our findings suggest that diagnosis of acromegaly is delayed in a substantial number of patients. The delay of the acromegaly diagnosis is associated with excess morbidity and mortality.

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GP49

Pharmacokinetics of somapacitan in individuals with renal impairment: an open-label, parallel group, phase 1 study

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Background
Somapacitan is a reversible albumin-binding growth hormone (GH) derivative developed for once-weekly administration that acts directly or indirectly via insulin-like growth factor I (IGF-I). As renal impairment may affect drug metabolism and excretion, we report data from an open-label, parallel group, phase I trial (NCT03186495) investigating the pharmacokinetic and pharmacodynamic properties, and safety of somapacitan in individuals with varying degrees of impaired renal function or normal renal function classified by glomerular filtration rate (GFR).
Methods
Participants were enrolled in five renal function groups in a planned ratio of 16:8:8:8:8 corresponding to normal renal function, mild renal impairment, moderate renal impairment, severe renal impairment, and requiring haemodialysis treatment, respectively. Participants received a total of three somapacitan administrations (0.08 mg/kg), one per week for 3 weeks.
Results
Forty-four participants were included: normal function, $n=15$; mild impairment, $n=8$; moderate impairment, $n=8$; severe impairment, $n=5$; requiring haemodialysis, $n=8$. Reported data are estimated ratios [90% CI]. Compared with the normal function group, steady-state exposure ($AUC_{0–168h}$) was higher for the severe renal impairment (1.75 [1.00;3.06]) and requiring haemodialysis (1.63 [1.01;2.61]) groups, and similar for the mild (1.25 [0.74;2.11]) and moderate renal impairment (1.27 [0.77;2.07]) groups. C_{max} was similar for all groups (mild impairment, 1.31 [0.71;2.39]; moderate impairment, 1.40 [0.79;2.47]; severe impairment, 1.47 [0.77;2.81]; requiring haemodialysis, 1.34 [0.77;2.32]) compared to the normal renal function group. $AUC_{IGF\text{-}I,0–168h}$ was increased in the moderate (1.35 [1.09;1.66]) and severe renal impairment (1.40 [1.10;1.78]), and requiring haemodialysis groups (1.24 [1.01;1.52]), versus the normal function group. $AUC_{IGFBP\text{-}3,0–168h}$ increased in all renal impairment groups (mild 1.12 [0.99;1.27]; moderate 1.18 [1.06;1.32]; severe 1.36 [1.20;1.55]; requiring haemodialysis 1.53 [1.37;1.70]) versus the normal function group. No unexpected safety signals were reported.
Conclusions
Degree of renal impairment affected steady-state exposure; individuals with severe renal impairment or requiring haemodialysis had significantly higher somapacitan exposure. Increased exposure was likely related to a decreased GFR, indicating that somapacitan, at least in part, is cleared through the kidneys. Increased levels of IGF-I (in the moderate and severe renal impairment, and requiring haemodialysis groups) and IGFBP-3 (in all renal impairment groups) were likely due to increased somapacitan exposure. Patients with severe renal disease or requiring haemodialysis may require lower doses of somapacitan compared to patients with normal renal function, owing to the increased somapacitan exposure. However, as somapacitan is planned to be individually dose-titrated, no specific adjustments to the dosing recommendations are relevant.

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GP50

Sleep disorders and cognitive dysfunction in acromegaly

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Background
In the general population, sleep disorders are associated with an increased risk of cognitive impairment; moreover, people with dementia often have sleep disturbances. The prevalence of sleep disorders, such as sleep apnea, in acromegalic patients is higher than in the general population, and they may have a higher risk of cognitive impairment due to acromegaly treatment (i.e. Radiotherapy) or cardiovascular comorbidities. In the literature, data about the relationship between sleep disorders and cognitive dysfunction in acromegaly are scant.
Aim
We aim to study the relationship between sleep disturbances and cognitive dysfunction in a group of acromegalic patients.
Methods
We studied 67 consecutive acromegalic patients at different stages of the disease. We performed a neurocognitive assessment with the following tests: Babcock Story Recall Test, Digit Span Test forward and backward, Corsi Block-Tapping test forwards and backwards, Complex Figure Test, Stroop Color and Word Test, Frontal Assessment Battery, Trail Making Test, phonemic and semantic fluency. Patients also completed the Acromegaly Quality of Life Questionnaire (AcroQoL), Epworth Sleepiness Scale, and Pittsburgh Sleep Quality Index. We also collected clinical, endocrinological, and metabolic data.
Results
Of the 67 acromegaly patients in the study, 38.8% were male, median age of diagnosis was 45 years (interquartile range IQR 35, 53), median age at the neurological examination was 56 (IQR 48, 65) and mean IGF-1 was 441.88 ug/L (3 patients were first diagnosis, 4 patients had a cured disease). Most participants performed within the normal range of cognitive tests, however, approximately 6-10% were impaired, depending on the test. In linear regression models adjusted for age, sex, BMI, disease duration, and disease activity, poorer sleep quality was associated with lower global cognitive z-score ($B=-0.03$, 95% CI -0.06, -0.002). Daytime somnolence was associated with poorer physical QoL subscore ($B=-0.04$, 95% CI -0.08, -0.002). Sleep quality was associated with poorer overall QoL ($B=-0.03$, 95% CI -0.05, -0.006), physical QoL ($B=-0.04$, 95% CI -0.07, -0.005), psychological QoL ($B=-0.02$, 95% CI -0.04, -0.001), and social QoL ($B=-0.02$, 95% CI -0.04, -0.0009).
Conclusions
In acromegaly, we found that poor sleep quality is associated with lower QoL, and some evidence that is associated with lower cognitive function.

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GP51

Prognostic value of short-acting pasireotide test for response prediction to pasireotide LAR in patients with acromegaly resistant to first-generation analogs. Can a short-acting pasireotide test predict the response of long-acting pasireotide treatment in patients with acromegaly resistant to first generation somatostatin analogs?

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Introduction
The treatment of choice in acromegaly is a transsphenoidal surgery of a growth hormone (GH) - producing pituitary adenoma. In patients with persistent acromegaly after surgery medical treatment is recommended. First generation somatostatin analogs: lanreotide autogel and octreotide LAR are effective in 25% to 45% of patients depending on population and study protocol. Second-generation somatostatin analog – pasireotide LAR seems to be more effective. The possibility to indicate clinical predictive factors of pasireotide LAR response could help in selecting patients who would benefit the most from the treatment.
Aim
The aim of the study was to check if the response to short-acting pasireotide can predict the efficacy of treatment with pasireotide LAR in patients with active acromegaly resistant to first-generation somatostatin analogs.
Patients and methods
Twenty four patients with active acromegaly after surgical debulking treated with first-generation somatostatin analogs were enrolled in the prospective study. After two-month wash-out period all patients had a test with short-acting pasireotide performed (GH measurements 0, 60, 120 and 180 minutes after s.c. administration of 600 μg of short-acting pasireotide) and were then switched to pasireotide LAR 60 mg administered i.m. every 28 days for 3 months. The effects of pasireotide LAR on GH, IGF-1, insulin, glucose and HgbA1c concentrations and the predictive value of the test were analysed after 3-month treatment.

Results
After 3 months of treatment with pasireotide LAR eight patients (33%) reached GH < 1 μg/l, fifteen patients (62.5%) reached GH < 2.5 μg/l. Four patients (16.7%) reached IGF-1 < 1 × upper limits of normal (ULN), eleven patients (45.8%) IGF-1 < 1.5 × ULN. There was a significant decrease in median GH and the mean IGF-1 after pasireotide LAR treatment vs first-generation somatostatin analogs: 1.66 μg/l (IQR:0.24–12.1) vs 2.88 μg/l (IQR:0.75–9.3), $P < 0.001$ and 1.49 ± 0.582 × ULN vs 2.31 ± 0.696 × ULN, $P < 0.001$, respectively. Pasireotide LAR was well tolerated, but hyperglycemia was the most frequent adverse event. Insulin decreased: 10 (IQR:2.4–46.8) vs 7.1 μIU/ml (IQR:1.3–25) $P = 0.001$ and fasting glucose increased: 104 (IQR:84–191) vs 119 (IQR:96–453) mg/dl, $P < 0.001$) within 3 months of pasireotide treatment. We found a statistical significant correlation between a maximal GH decrease during the short-acting pasireotide test and GH and IGF-1 after 3-month treatment ($R = 0.57$, $P < 005$ and $R = 0.56$, $P < 0,05$ respectively).
Conclusions
Pasireotide LAR is more effective in decreasing GH and IGF-1 levels than first-generation somatostatin analogs in acromegalic patients after surgical debulking. Better efficacy of pasireotide LAR is correlated with higher GH decrease after administration of 600 ug short-acting pasireotide.

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GP52

Final height in childhood onset hypopituitarism

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Background
Growth hormone (GH) deficiency(GHD) in childhood is associated with impairment in linear growth. GH therapy enables the achievement of normal adult height in most cases. The response is variable and factors influencing height outcome are still not clearly defined.
Objective
To evaluate near adult height (NAH) in a single center cohort of childhood onset GHD patients treated with GH and investigate main predictors of final height (FH) .
Patients and methods
80 GHD-patients (41M-39F) followed from the diagnosis to the achievement of NAH were enrolled. Mean age at diagnosis was 9.9 ± 4.0 years. 79% of patients (63/80) had isolated GHD (IGHD), 21% (17/80) had multiple pituitary hormone deficiency(MPHD) and received hormone replacement as necessary. Structural abnormalities of the pituitary gland were detected in 40 patients. Height, Height velocity (HV) and IGF-1 were evaluated at diagnosis, at the end of the first year of treatment, at onset of puberty and at the attainment of NAH and were expressed as standard deviation score (SDS) according to reference standards. Change in HSDS (Δ) from baseline to the different end points was calculated.Multiple regression analysis was used to evaluate predictor of FH.
Results
At diagnosis HSDS (−2.53 ± 0.94), HVSDS (−2.47 ± 1.69) and IGF1SDS (−1.23 ± 1.24) were below normal ranges. After 1 year of GH, HSDS (−1.86 ± 0.84, $P < 0.0001$), HVSDS (3.03 ± 2.79, $P < 0.0001$) and IGFISDS (0.34 ± 1.24, $P < 0.0001$) significantly improved. At puberty onset, mean age of patients was 12.52 ± 1.67 years. ΔHSDS from baseline to pubertal onset was significantly higher in MPHD vs IGHD (3.03 ± 1.66 vs 0.6 ± 0.68, $P < 0.0001$) while was comparable between males and females. NAHSDS (−0.87 ± 0.98), achieved at a mean age of 16.94 ± 1.51 years, was significantly higher compared to baseline ($P < 0.0001$), and was higher in patients with MPHD vs patients with IGHD (−0.47 ± 1.15 vs −0.98 ± 0.91, $P < 0.05$). Although NAHSDS was higher in males vs females (−0.65 ± 0.9 vs −1.11 ± 1.02, $P < 0.05$), the total gain in HSDS was comparable between the two sexes (1.66 ± 0.91 vs 1.64 ± 1.09, P = ns). Multiple regression analysis showed that NAH correlated with sex ($P < 0.05$), severity of GHD ($P < 0.05$), diagnosis ($P < 0.0001$), age at diagnosis ($P < 0.0001$), HV in the 1° year of treatment ($P < 0.0001$), H at onset of puberty ($P < 0.0001$), prepubertal ΔHSDS ($P < 0.0001$) and duration of treatment ($P < 0.0001$).
Conclusion
GH treatment enables the achievement of normal NAH.Early treatment and optimization of prepubertal growth are important to obtain a better growth response. Patients with severeGHD and MPHD have a greater gain in height and NAH than patients with mildGHD and IGHD.

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GP53

Efficacy and safety of once-weekly somapacitan in adult growth hormone deficiency (AGHD) confirmed in a 53-week REAL-1 trial extension

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Background
Following the 34-week, double-blind, placebo-controlled main phase of REAL-1 (NCT02229851), this open-label trial extension evaluated efficacy and safety of somapacitan in patients aged 23–79 years with AGHD, for an additional 52 weeks (8 weeks' dose titration followed by 44 weeks' fixed dose treatment; 86 weeks' treatment in total).
Methods
Patients completing the main trial entered the extension: 1) somapacitan-treated patients continued on that treatment; 2) daily growth hormone (GH)-treated patients were re-randomised 1:1 to somapacitan or daily GH; 3) patients receiving placebo were switched to somapacitan. Starting doses were age- and gender-dependent and titrated towards a target insulin-like growth factor-I standard deviation score (IGF-I SDS) −0.5 to +1.75. Changes from the original baseline to end of extension period in body composition were evaluated by dual-energy X-ray absorptiometry (truncal fat %, truncal fat mass, visceral adipose tissue %, visceral adipose tissue, total fat mass, android fat mass, gynoid fat mass, truncal lean body mass, appendicular skeletal muscle mass, and lean body mass). IGF-I SDS and lipid profiles were also compared. Exploratory analyses on changes from baseline were based on mixed models of repeated measures, comparing somapacitan/somapacitan and daily GH/daily GH arms. 300 patients were treated in the main phase and 272 (91%) in the extension.
Results
Mean patient age was 45.1 years; 51.7% were female. Mean exposure (during the extension alone) was 355 (somapacitan/somapacitan) and 349 days (daily GH/daily GH), respectively. After 86 weeks' treatment, target IGF-I SDS were achieved in all treatment arms (mean values [SD], somapacitan/somapacitan: from −2.54 [1.26] to −0.22 [1.27]; placebo/somapacitan: −2.64 [1.28] to −0.31 [1.08]; daily GH/daily GH: −2.33 [1.28] to −0.24 [1.32]; daily GH/somapacitan: −2.75 [1.20] to −0.39 [1.12]). The beneficial effects of somapacitan on body composition observed in the main phase were maintained and did not differ statistically significantly between the somapacitan/somapacitan and daily GH/daily GH arms ($P > 0.05$). There were no statistically significant differences in IGF-I SDS or lipid parameters between the somapacitan/somapacitan and daily GH/daily GH arms. Incidence, severity and type of adverse events were similar for somapacitan and daily GH treatment. Few injection site reactions were reported and all were mild to moderate in severity. No anti-somapacitan antibodies were detected.
Conclusions
Body composition changes and IGF-I SDS observed in the main phase of REAL-1 were maintained in the trial extension. No new safety signals/tolerability issues were identified for somapacitan.

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GP54

Pharmacokinetics in patients with prolactinomas

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Introduction
Prolactinoma is the most commonly occurring hormonally active pituitary tumor. In most cases, dopamine receptor agonists (DA) as a monotherapy are effective. However, approximately 10% of patients with prolactinomas fail to achieve normalization of serum prolactin levels during treatment with DA, which indicates resistance to this group of drugs.
Aims
The goal was to study the pharmacokinetics of cabergoline in patients harboring prolactinomas sensitive and resistant to cabergoline.
Materials and methods
We evaluated the levels of cabergoline in blood plasma by tandem mass spectrometry. A single determination of the level of cabergoline in plasma during

long-term treatment was performed in 18 patients with prolactinomas, of which six were sensitive to dopamine agonist therapy, 12 were resistant. 10 patients (2 - sensitive and 8 resistant) underwent also measurement of cabergoline levels during the pharmacokinetic test (0, 30, 60, 120, 240 min after patient took 1 tablet of cabergoline (0.5 mg) orally). The test was performed 7 days after the last dose of cabergoline. To determine cabergoline in blood plasma, at 9:00 am a blood sample was taken (0 minute), then blood was taken 30, 120 and 240 minutes after taking the drug.
Results
The concentration of cabergoline in the blood plasma at the 0 minute of the test was not different in patients sensitive and resistant to DA (Mann – Whitney U-test $P=0.147$). In the group of sensitive patients a correlation was found between the level of cabergoline at 0 minute and the dose of cabergoline that the patient constantly takes for a long time ($r=0.89$, $P=0.019$). Among resistant patients this correlation was not found ($r=0.39$, $P=0.238$). The pharmacokinetic test in sensitive patients did not reveal any significant changes in the level of cabergoline during the test ($P=0.392$). In resistant patients there were significant differences in the level of cabergoline ($P=0.0119$). A comparative analysis of the data showed that the concentration of cabergoline in the blood of patients who are resistant to treatment with DA increases sharply by 120 minutes of the sample. A statistically significant difference was found comparing levels at 0 and 120 minutes by the Wilcoxon criterion, $P=0.012$.
Conclusion
Thus, the pharmacokinetics of cabergoline differ in patients sensitive and resistant to treatment with DA, thereby may contribute to the low effectiveness of treatment in patients with prolactinomas resistant to treatment with DA, and predetermine the lack of effect of dose escalation of the drug.

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GP55

Acromegaly do not increase the risk of vertebral fractures: a retrospective and prospective study on 50 patients

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Context
Previous studies suggest that patients with acromegaly were at higher risk of vertebral fractures (VFs) despite normal bone mineral density (BMD). However, these patients could have several associated endocrine deficits known to increase the fracture risk, such as hypogonadism. In addition, patients with acromegaly have radiological deformations of the spine, called Erdheim's syndrome, which can overestimate the radiological VFs.
Objective
Investigate the prevalence of VFs in a cohort of patients with acromegaly.
Methods
It was a monocentric, retrospective and prospective study. Patients with acromegaly under 80 years of age and followed at the Nantes University hospital in January 2018 were included. Patients were excluded if they had a rheumatologic or endocrine disease interfering with the results. The rheumatologic evaluation was less than 3 years for all patients. The prevalence of radiological VFs was evaluated on conventional lombar and thoracic spine radiographs using Genant's semi quantitative assessment. We studied qualitative abnormalities of the spine using three criteria: osteophytes, disc space narrowing and cuneiform aspect of vertebrae. The X-rays were read by two rheumatologists independently. We analyzed BMD at lumbar spine and total hip, endocrine status and quality of life was investigated by three questionnaires (AcroQol, specific of acromegaly; Oswestry evaluating the functional impact of pain; HAQ evaluating the functional capacity).
Results
Fifty patients (19 females, 31 males) with a median age of 53 (range 28–79) were included. The average of time between the diagnosis of acromegaly and the last rheumatologic evaluation was 9.1 years. Three patients (6.1%) had a VF: 1 grade 1 and 2 grade 2 of Genant's assessment. 28% patients were osteopenic and 12% were osteoporotic. 26% were hypogonadal (100% substituted), 16% had central adrenal insufficiency (100% substituted). 14 women were menopaused (74% of women). Thoracic spine was deformed in 31 patients (61%) and lombar spine in 21 patients (43%). Patients with spine deformation were older ($P=0.043$), with higher BMI ($P=0.004$) and had a trend to be more hypogonadal ($P=0.06$). Concerning quality of life, AcroQoL's average was 70.9% (score 0 to 100, maximal quality of life =100, range 32–98), HAQ's average was 0.18 (score 0 to 3, maximal quality of life 0, range 0–1.38) and Oswestry's average was 9.8 (score 0 to 100, maximal quality of life 0, range 0–44).
Conclusions
Acromegaly patients are not at an increased risk of vertebral fractures, but they have vertebral deformations.

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GP56

Sclerostin and fracture risk assessment in acromegaly

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Introduction
Sclerostin is well-known as an inhibitor of bone formation but also promotes bone resorption. Acromegaly is a disease characterized by increased bone turnover and higher vertebral fracture risk.
Purpose
The aim of the study was to determine sclerostin levels in acromegaly patients with regard to the disease activity. We also evaluated the associations between sclerostin and random growth hormone (GH), insulin-like growth factor 1 (IGF-I), lumbar spine (LS) bone mineral density (BMD), femoral neck (FN) BMD and fracture risk.
Material and methods
A study group consisted of 72 patients with acromegaly, and was divided into three subgroups: active acromegaly (AA), controlled acromegaly (CTA) and cured acromegaly (CA). Fifty-four age- and sex-matched subjects were enrolled to the control group (CG). Blood samples were obtained from all participants to assess sclerostin, GH, IGF-I. The patients were questioned about clinical risk factors of fracture. Dual-energy x-ray absorptiometry was performed at two sites: LS and hip. Further, we estimated the ten-year probability (10yp) of major osteoporotic and hip fractures using FRAX calculator online.
Results
The patients with acromegaly had significantly lower sclerostin levels than CG, despite of subject classification (AA vs CG; CTA vs CG; CA vs CG; AA+CTA+CA vs CG; CTA+CA vs CG; $P<0.05$). Significantly higher probability of major osteoporotic and hip fractures was observed in the following groups: AA+CTA+CA, CTA+CA, CTA compared with CG. There were no significant differences in sclerostin levels among the subgroups of patients with acromegaly. Sclerostin correlated positively with the 10yp of major osteoporotic fracture in the groups: AA+CTA+CA ($P=0.003$), CTA+CA ($P=0.013$) and with the 10 yp of hip fracture in the groups AA+CTA+CA ($P=0.001$), CTA+CA ($P=0.001$) and CTA ($P=0.007$). No significant correlations were found between sclerostin levels and GH, IGF-I, LS BMD and FN BMD.
Conclusion
Acromegaly is associated with higher fracture risk. Lower sclerostin levels in patients with acromegaly may reflect a compensatory mechanism to increased bone turnover.

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GP57

Biochemical control was sustained with long-acting pasireotide in patients with uncontrolled acromegaly over continued treatment with first-generation somatostatin analogues (SSAs): Results from the extension of phase 3b, open-label study

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Background
In a phase 3b, open-label study (NCT02354508) assessing efficacy and safety of long-acting pasireotide in patients with uncontrolled acromegaly after ≥ 3 months of treatment with first-generation SSAs, 18/123 (15%) patients achieved the primary endpoint of mean growth hormone (mGH) <1.0 µg/l and insulin-like

growth factor-1 (IGF-1) <ULN (upper limit of normal) at week 36. Here, we present the results from the extension phase of this study.
Methods
Controlled or uncontrolled patients who completed the 36-week core phase were eligible to enter the extension phase (week 36–72). Patients continued on the same pasireotide dose as in the core phase, but uncontrolled patients were allowed additional medication for acromegaly at investigator's judgement. The primary endpoint was evaluated in the core phase. In the extension phase, the secondary endpoints were the proportion of patients who achieved biochemical control: GH<1 μg/l and IGF-1<ULN, GH<1 μg/l, and IGF-1<ULN (by previous treatment, type of therapy and overall) at weeks 48, 60 and 72, toxicity, laboratory assessments and patient-reported outcomes.
Results
Eighty-eight patients (mean (s.d.) age, 43.7 (11.53) years, mean (s.d.) GH, 11.4 μg/l (25.81), and mean (s.d.) IGF-1, 666.7 μg/l (294.43)) entered the extension phase. Of them, 75 patients (85.2%) completed the additional 36 weeks; 6 patients each discontinued due to unsatisfactory therapeutic effect and physician's decision, 1 patient withdrew consent. At weeks 36, 48, 60 and 72, 14.8%, 12.5%, 14.8% and 11.4% of patients, respectively, achieved biochemical control. 21.6, 23.9, 21.6 and 20.5% had GH<1 μg/l and 34.1, 33.0, 37.5 and 33.0% had IGF-1<ULN, respectively. Suppressed levels of median GH and mean standardized IGF-1 at extension baseline (2.3 μg/l, 1.6) were maintained at week 48 (1.9, 1.6), week 60 (1.9, 1.5), and week 72 (1.7, 1.5). A higher proportion of patients with lower screening mGH levels (1.0–2.5 μg/l [$n=20$] vs >2.5 μg/l [$n=68$]) achieved biochemical control at all 4 time points 55%–65% vs 10.3%–11.8%. During overall study period ($N=123$), most frequent adverse events suspected to be drug related were hyperglycaemia (41.5%), diabetes mellitus (23.6%) and diarrhoea (11.4%).
Conclusions
In some patients with uncontrolled acromegaly, switching to long-acting pasireotide after ≥3 months of treatment with first-generation SSAs provided biochemical control, which was sustained over continued therapy until 72 weeks. Lower GH screening levels had a favourable impact on the achievement of biochemical control. The long-term safety and tolerability of pasireotide 40 and 60 mg over 72 weeks was consistent with that observed in the first 36 weeks during the core phase.

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GP58

ACROSTUDY – safety and efficacy in a cohort of 110 Naïve patients with acromegaly treated with pegvisomant

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Background
ACROSTUDY is an open-label, non-interventional post-authorization safety study that began in 2004 to evaluate safety in at least 1000 acromegaly patients treated with the GH receptor antagonist pegvisomant (PEGV). This commitment was fulfilled in Jan 2013. ACROSTUDY was later amended to enroll an additional 110 patients that were naïve/semi-naive to PEGV treatment. Semi-naïve patients are defined as not having received PEGV therapy for at least 6 months prior to enrollment.
Objectives
The primary objectives were to: i) assess the long-term safety of PEGV in real world practice; ii) assess the effect of IGF-I normalization on treatment outcomes, including safety, glucose control and patient-reported outcomes (PROs).
Patients & Methods
110 patients with Acromegaly 53.6% male, 81.8% Caucasian, median age 42.4 years at diagnosis; median age 48.9 years at PEGV start. Patients were considered 'IGF-I Controlled' if the most temporally-related IGF-I measurement was normal for that laboratory. Safety data including adverse events and liver tests were collected. IGF-I and HbA_1c were measured; PROs were evaluated using the Acromegaly Quality of Life Questionnaire (AcroQoL) and Patient-Assessed Acromegaly Symptom Questionnaire (PAQ19), stratified by IGF-I control.
Results
No new safety signals were identified in this sub-study. IGF-I SDS >2 decreased from 87% of patients at baseline to 31% at year 2 at a mean dose (±s.d.) of 10.4 (±7.45) mg/day; patients with IGF-I SDS <2 had a mean dose of 14.8(±6.7). Among IGF-I controlled patients, median (range) HbA_1c levels were 5.8% (5.4–6.1) at baseline and 5.6% (4.5–7.2) at year 2; in IGF-I uncontrolled patients, HbA_1c was 6.1% (4.9–6.6) at baseline and 6.3% (2.9–10.6) at year 2. Among IGF-I controlled patients, median (range) global AcroQoL scores were 54.6 (24–73) at baseline and 61.4 (13–86) at year 2; while in IGF-I uncontrolled patients, median global AcroQoL score was 59.7 (8–92) at baseline and 63.6 (25–76) at year 2. Among IGF-I controlled patients, median (range) total PAQ19 score was 20 (3–38) at baseline and 17.5 (1–40) at year 2; in IGF-I uncontrolled patients, median total PAQ19 score was 17 (0–44) at baseline and 14 (3–39) at year 2.
Summary
In this real-life world international study, overall biochemical control (*i.e.* normal IGF-I) was achieved with pegvisomant in 64.3% patients by year 2. Improved IGF-I control was associated with improved HbA_1c, QoL and symptoms of acromegaly. One limitation of the study was that the PEGV dose may not have been sufficiently titrated to achieve IGF-I normalization.

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GP59

Effects of pegvisomant and pasireotide LAR on incidence of vertebral fractures in patients with acromegaly resistant to treatment with first-line somatostatin analogs

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Purpose
Osteopathy is an emerging complication of acromegaly characterized by increased bone turnover, deterioration in bone microarchitecture and high risk of vertebral fractures (VFs). In somatostatin analog (SSA)-resistant patients (pts), Pegvisomant (PegV) and Pasireotide LAR (Pasi) are used for acromegaly treatment, but their effect on skeletal health is still not defined.
Methods
In a longitudinal international multicenter study, we evaluated incidence of radiological VFs in 55 pts (29F/26M), mean age 44.1 years (s.d.: 17) with acromegaly resistant to first line SSA.
Results
At the study entry, prevalent VFs (lumbar, thoracic) were identified in 23 pts (41.8%). Mean spine *Z*-score was −0.4 (−0.6 in PegV, −0.2 in Pasi group, respectively; $P=0.49$). Biochemical acromegaly control was reached in 22/31 pts on Peg-V (71%) and in 16/24 pts on Pasi (66.7%). During follow-up (mean 89.9 months for PegV group and 50.5 months for Pasi group), incident VFs (iVFs) were detected in 16 pts (29.1%). Occurrence of iVFs was associated with the presence of pre-existing VFs ($P=0.009$), persistence of active acromegaly ($P=0.009$) and higher median value of serum IGF-I during follow-up ($P=0.04$). There were no significant differences in age, gender, initial treatment choice and changes in lumbar spine BMD. iVFs occurred in 7/9 pts uncontrolled on Peg-V and 2/8 pts uncontrolled on Pasi. Among pts with active disease at last visit, iVFs occurred less frequently in pts on treatment with Pasi (25%) compared to Peg-V (77.8%), $P=0.03$, independently of the IGF-I values ($P=0.9$). In pts who reached acromegaly biochemical control, 5/17 (22.7%) on Peg-V and 2/14 (12.5%) pts on Pasi had iVFs, $P=0.4$. In pts on Peg-V, factors associated with iVFs during follow-up were persistence of active acromegaly and higher IGF-I values (median IGFxULN: 0.5 IQR:1.8 vs 2.6 IQR: 2.2 $P=0.02$). In pts treated with Pasi, we did not find any factors associated with iVFs. Furthermore, in pts with biochemically controlled acromegaly, no factor was associated with iVFs which occurred less frequently in pts treated with Pasi.
Conclusion
Our data confirm that active acromegaly is the main determinant of VFs and show for the first time that pts with biochemically active disease treated with Pasi had lower risk of incident VFs vs those treated with Peg-V. Conversely, no significant drug-related differences in iVFs in pts with controlled acromegaly were observed. Additional studies on larger populations and with longer follow-up are needed to confirm our data and disclose the mechanisms underlying our findings.

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GP60

Metabolic outcome in adolescents with growth hormone deficiency during transition phase

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Background
There is concern that adolescents with childhood-onset GHD (COGHD) and persistent GH deficiency may be exposed to multiple metabolic risks after GH treatment withdrawal at the attainment of final height (FH).
Aim
Aim of our study is to retrospectively compare growth response and metabolic profile in isolated idiopathic COGHD adolescents with permanent GH deficiency in comparison to GHD subjects who normalized their GH response at transition phase.
Patients and methods
20 subjects (12M-8F) (age 17.0±1.4 years) with persistent GHD at retesting and 20 adolescents (12M-8F) (age 16.8±1.0 years) with sufficient response to the test (GHS) were enrolled. In all patients the following parameters were evaluated at diagnosis of GHD during childhood and before and after 6 months of GH withdrawal at the attainment of FH: height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist/hip circumference (WHR), waist/height ratio (WHtR), IGF-1, blood glucose, insulin, HOMA, QUICKI index, total-, HDL- and LDL-cholesterol, triglycerides, atherogenic index (AI), fibrinogen and homocysteine. Height, weight and BMI were expressed in standard deviation score (SDS) according to reference standards.
Results
At diagnosis during childhood, young adults with GHD were younger than GHS subjects (7.0±4.4 vs 10.6±2.9 years) and had lower HSDS (−3.0±1.1 vs −2.2±0.8, $P=0.03$), HVSDS (−3.6±1.1 vs −2.2±1.5, $P=0.007$), HDL-C (47.6±12.6 vs 60.1±15.6 mg/dl, $P<0.03$) and higher levels of AI (3.6±1.1 vs 2.6±0.9, $P<0.02$), fibrinogen (300.7±46.6 vs 266.3±44.9 mg/dl, $P<0.05$) and homocysteine (11.8±3.9 vs 8.8±3.4 µmol/l, $P<0.04$). The groups became comparable for all these parameters during GH treatment. At the attainment of FH the total gain in HSDS was higher in GHD in comparison to GHS young adults (2.2±1.6 vs 1.2±0.4, $P<0.03$) while all other anthropometric and metabolic parameters were comparable between the two groups. (When subjects were evaluated) After 6 months of GH withdrawal, GHD patients showed higher BMISDS (0.30±1.15 vs −0.67±1.0, $P<0.05$), WHtR (0.50±0.06 vs 0.45±0.03, $P<0.008$), total cholesterol (157.7±22.3 vs 141±22.1, $P<0.05$), AI (3.4±0.5 vs 2.6±0.7, $P<0.002$), fibrinogen (307±45.7 vs 272.3±46.1 mg/dl, $P<0.05$) and homocysteine (12.1±4.6 vs 9.2±2.9 µmol/l, $P<0.05$) and lower levels of HDL cholesterol (47.8±8.8 vs 55.8±10.3 mg/dl, $P<0.03$) than subjects with sufficient GH secretion.
Conclusions
Discontinuation of GH therapy at attainment of FH in subjects with severe COGHD is associated to the development of metabolic abnormalities which are already evident 6 months after withdrawal thus underling the importance to limit the period of treatment discontinuation during transition phase.

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Reproductive Axis

GP61

Novel phenotype of isolated diminished ovarian reserve and new CSB-PGBD3 (ERCC6) mutations revealed by targeted next generation sequencing in a cohort of caucasian infertile women

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Primary Ovarian Insufficiency (POI) affects ∼1% of women under forty leading most often to definitive infertility. About 25% of cases seem to be of genetic origin. The recent leap due to whole exome sequencing has led to the identification of new genes involved. Up to now more than sixty genes have been implicated in POI. Diminished Ovarian Reserve (DOR) also leads to female infertility. DOR is defined by a decreased quantity or quality of follicles based on antral follicle count (AFC < 5) and anti-müllerian hormone plasma levels (AMH < 0.5–1ng/mL). However the etiologies involved remain largely unknown. Here, we studied 66 Caucasian patients with DOR or POI using targeted next generation sequencing comprising 60 genes involved in POI. We identified 3 novel heterozygous missense mutations in CSB-PGBD3. The first mutation, located in exon 5 (c.1339C>T; p.(Arg447Trp)) was identified in a 16 years old patient with DOR (FSH =8.5UI/L, E2=37pg/mL, AFC=6 and AMH=0.6 ng/ml) and irregular menses. Her dizygotic twin sister has regular menses and normal hormonal blood assays up to now (18 years old). Two other novel mutations in *CSB-PGDB3* were found in two patients with POI and secondary amenorrhea (17 and 30 years) (2/65=3%). The mutations are located in exons 2 of CSB-PGDB3 c.364C>T; p.(Arg122Cys) and exon 5: c.1389G>t; p.(Gln463His). All three mutations are predicted to be pathogenic by *in silico* predictive softwares. They involve residues highly conserved during the evolution. CSB-PGBD3, also named ERCC6, encodes a DNA-binding protein involved in repairing DNA damage. Biallelic Mutations of this gene are associated with Cockayne syndrome type B and cerebro-oculo-facio-skeletal syndrome. Heterozygous mutations with a dominant negative effect were found in a single report with a very low incidence (0.7%) in Chinese patients with POI. Our work shows for the first time the implication of a DNA repair gene defect in DOR and reveals that mutations of *CSB-PGBD3* have a high prevalence in POI in Europe (3%). It supports the study of *CSB-PGBD3* in unexplained DOR and isolated POI. An appropriate genetic counseling and management should be performed in the siblings. Fertility preservation should be performed in heterozygous carriers of mutations, since accumulation of oocyte damage will lead to complete loss of the ovarian reserve in the future. We are presently screening a large cohort of DOR to evaluate the frequency of *CSB-PGBD3* mutations.

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GP62

Hypothalamic miR-30 regulates puberty onset via repression of the puberty-suppressing factor, Mkrn3

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Mkrn3, the maternally imprinted gene encoding the makorin RING-finger protein-3, has recently emerged as putative pubertal repressor, as evidenced by central precocity caused by MKRN3 mutations in humans; yet, the molecular underpinnings of this key regulatory action remain largely unexplored. We report herein that the microRNA, miR-30, with three binding sites in a highly conserved region of its 3'-untranslated region (UTR), operates as repressor of Mkrn3 to control pubertal onset. Hypothalamic miR-30b expression increased, while Mkrn3 mRNA and protein content decreased, during rat postnatal maturation. Neonatal estrogen exposure, causing pubertal alterations, enhanced hypothalamic Mkrn3 and suppressed miR-30b expression in female rats. Functional *in vitro* analyses demonstrated a strong repressive action of miR-30b on Mkrn3 3'-UTR. Moreover, central infusion during the juvenile period of target site blockers, tailored to prevent miR-30 binding to Mkrn3 3'-UTR, reversed the prepubertal down-regulation of hypothalamic Mkrn3 protein and delayed female puberty. Collectively, our data unveil a novel hypothalamic miRNA pathway, involving miR-30, with a prominent role in the control of puberty via Mkrn3 repression. These findings expand our current understanding of the molecular basis of puberty and its disease states.

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GP63

A *KISS1R* gene variant in a pedigree with maternally inherited precocious puberty

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Background
The genetic causes of central precocious puberty (CPP) of clinical value identified to date are the paternally inherited Makorin RING-finger protein 3 (MKRN3) and Delta-like homolog 1 (DLK1) deficiencies. Given that CPP is typically maternally inherited, however, the molecular genetic background in the majority of CPP cases remains unknown. Using candidate gene approach focused on genes regulating GnRH secretion and action so far exceedingly rare patients with CPP were shown to carry mutations in kisspeptin system. KISS1 receptor gene (*KISS1R)* autosomal dominant heterozygous activating mutation p.(Arg386Pro) was reported previously in a girl with CPP by Teles MG *et al*.
Objectives
To identify genetic causes of maternally inherited CPP.
Population and methods
Whole genome sequencing of 9 family trios affected with CPP, demonstrating maternal inheritance pattern, was performed. A family trio analysis approach was utilized as a first tier analysis to generate a set of potential causative genetic variants inherited in the autosomal dominant pattern. The minor allele frequency (MAF) threshold for known variants was set at 0.2%, all variants exceeding this value were excluded from further analysis. Genetic variants with coverage $> 10\times$ were retained and analyzed with Variant Studio 3.0 software. Identified candidate variant and its family segregation were verified by Sanger sequencing. By targeted approach, coding and regulatory regions and copy number variants (CNV) of 398 genes reported to be associated with age at menarche by genome-wide association studies were analyzed for rare variants (MAF $<0.2\%$).
Results
The average coverage of each genome was $38\times$ and around 3.8M SNVs and InDels, 5k SVs and 600 CNVs were detected on average per single sample. In a single pedigree a heterozygous premature termination codon in *KISS1R* NP_115940.2:p.(Cys389Ter), segregating with CPP, was identified. The variant, with CADD score 28.7, was previously reported in a female with hypogonadotropic hypogonadism and has a frequency of 0.04% in GnomAD. The female proband had first signs of puberty at the age of 7.5 years and menarche at 9 years, marginaly advanced bone age, growth spurt at 7–8 years and increased basal and peak luteinizing hormone (LH). Her mother had menarche at 9 years.
Conclusions
To our knowledge this is the second CPP pedigree carrying a *KISS1R* gene variant. Although trunkating, this variant is considered to be of unknown significance. Functional study would be necessary to determine the implication of identified variant on KISS1R function and reproductive phenotype.

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GP64

Untargeted lipidomics profiling by high-performance liquid chromatography/time-of-flight mass spectrometry in polycystic ovary syndrome: candidate biomarkers and association to disease traits

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Background
Metabolomics profiling of bio-fluids suggests altered signatures in patients with the polycystic ovary syndrome (PCOS).
Subjects and methods
A high-performance liquid chromatography/time-of-flight mass spectrometry (HPLC/TOF-MS)-based metabolomics approach was developed to characterize the untargeted lipidomics signature associated with PCOS status in a discovery cohort of 30 plasma samples (15 PCOS, 15 controls, age-matched), followed in a second step by evaluation of another cohort of 46 samples (27 PCOS, 19 controls, age-matched). Rotterdam criteria were applied to confirm the subjects' eligibility. Of note, all patients with PCOS presented hyperandrogenic phenotypes. Blood samples were processed for extraction of lipids with Bligh & Dyer method, and subjected to HPLC-ESI(+)TOF-MS measurements. To analyze matrix data, Profile Analysis 2.0 (Bruker) and Metabolyst 4.0 bioinformatics tools were used. All participants were referred to body composition assessment by dual X-ray absorptiometry (DXA); in addition to vascular evaluation, including flow-mediated vasodilation (FMD) and arterial stiffness indices in a subset.
Results
Separation of more than 150 low-molecular-weight metabolites between groups resulted by untargeted lipidomics approach, with very good data clustering confirmed in multivariate analysis (PCA, PLS-DA, Cluster Analysis). ROC curves (AUC between 0.834–1) showed that a group of 18 lipid metabolites efficiently discriminated between controls and PCOS, among them, carnitines (decanoylcarnitine, L-octanoylcarnitine, heptadecanoylcarnitine) that presented highly significant elevated levels ($P<0.0001$), in addition to monoacylglycerols (MG20:3/0:0, MG0:0/18:0/0:0), with up to more than 5-fold higher levels ($P<0.0001$). On the contrary, lysophosphocholines were markedly decreased in women with PCOS vs. controls ($P<0.0001$). Tetranor-12R-HETE, released by endothelial cells upon stimulation and directly linked to inflammation, increased more than 3-fold in PCOS ($P<0.0001$). Furthermore, correlations were described. Decanoylcarnitine (C10:1), a fatty ester lipid molecule was strongly associated to a high number of metabolites, including monoacylglycerols and other acylcarnitines, tetranor-12R-HETE, lipoxin B4 and leukotriene. Within the PCOS group, acylcarnitines species correlated with body fat and the lipid profile ($P\leq0.01$). Moreover, an inverse association between carnitines and FMD was revealed ($P<0.05$).
Conclusion
Metabolomics is useful in identifying novel potential biomarkers of PCOS. Alterations in fatty acid metabolism, with decreased fatty acid oxidation may contribute to the cardio metabolic profile in PCOS. Candidate biomarkers are involved in specific metabolomic networks affected by pathological processes and may discriminate between healthy women and PCOS.

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GP65

Testosterone replacement therapy outcomes in subjects with Klinefelter syndrome: preliminary results from a meta-analysis study

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Background
In patients with Klinefelter syndrome (KS) morbidity and mortality seem to be higher than general population, this depending on a wide number of possible comorbidities. Impaired metabolic profile, increased risk of venous thrombosis and the consequent increase of cardiovascular diseases might play a key role in this condition as well as reduced bone mineral density and higher fracture risk.

Nowadays testosterone replacement therapy (TRT) is the first-choice treatment for this condition, but no evidence so far has been able to define its positive role in this population related to metabolic, cardiovascular and bone-related outcomes.
Objective
The aim of this study is to meta-analyze currently available data reporting about metabolic, cardiovascular and bone metabolism parameters before and after TRT in KS subjects.
Methods
An extensive Medline search was performed, including the following words: 'klinefelter' [All Fields] AND 'testosterone' [All Fields]. The search was restricted to English-language articles and studies including humans published up to December 31th, 2017. All trials reporting TRT metabolic outcomes in hypogonadal KS in comparison to healthy controls or untreated hypogonadal KS without any arbitrary restriction were included.
Results
Out of 525, 20 trials were included, enrolling 1060 KS patients and 806 age-matched controls with a mean age of 30.8 ± 4.9 years. Among the studies included, 15 reported information on body composition and/or on metabolic profile whereas only 4 and 2, included outcomes on bone and cardiovascular parameters, respectively. Meta-analysis of the data showed a significant increase of body-mass index (BMI) (mean difference 1.17 kg/m^2), body fat mass (mean difference 1.27 SD), waist circumference (mean difference 11.61 cm) and plasma fasting glucose (mean difference 0.26 mmol/L), total cholesterol (mean difference 0.22 mmol/L) and LDL cholesterol (mean difference 0.59 mmol/L) in untreated KS patients compared to age-matched controls ($P <$ 0.01, CI 95%). A significant improvement was observed for body fat mass ($P < 0.01$, CI 95%), LDL cholesterol ($P = 0.02$) and waist circumference ($P = 0.03$) but not for plasma fasting glucose ($P = 0.09$), comparing treated vs untreated KS patients. Finally, comparison of treated KS to age-matched control showed an improvement of BMI, total cholesterol and LDL cholesterol, but persistence of significant difference between two groups ($P < 0.05$). Similar results were observed when bone and cardiovascular outcomes were considered.
Conclusions
Our preliminary results suggest that TRT can only partially improve metabolic profile as well as body composition. Reduction of CV risk in treated KS patients should be confirmed through specific RCT.

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GP66

Diet patterns in patients with PCOS

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The study aimed to investigate diet patterns and its association with metabolic features in patients with PCOS.
Material and methods
116 women with PCOS (according to Rotterdam criteria) were investigated in Vilnius city (Lithuania) in 2009–2011. Information about nutrition habits was collected utilizing qualitative food frequency questionnaire. Participants were tested for total testosterone, sex hormone-binding globulin, fasting glucose, insulin and lipid profile. 2-hours oral glucose tolerance test was performed. Insulin resistance HOMA-IR index were calculated. Body weight and height were measured.
Results
Mean patients' age was 27.16 ± 3.87 years. 57.0% of women had enough knowledge about healthy diet. Mean number of daily meals was 3.31 ± 0.88. 42.2% of women declared that always have breakfast, 67.2% always have lunch and 41.4% dinner. BMI (25.88 ± 6.15 vs. 28.64 ± 7.42 kg/m^2, $P = 0.04$), insulin (9.95 ± 6.13 vs. 14.49 ± 12.18 μU/ml, $P = 0.01$), HOMA-IR (2.29 ± 1.63 vs. 3.52 ± 3.30, $P = 0.01$), triglycerides (1.00 ± 0.44 vs. 1.26 ± 0.73 mmol/l, $P = 0.02$) were lower and HDL-cholesterol (1.61 ± 0.36 vs. 1.43 ± 0.41 mmol/l, $P = 0.02$) was higher in women who always have had breakfast comparing to those who ate breakfast irregularly or never. Obese PCOS women more frequently had dinner comparing with normal weight PCOS. 30.8% of PCOS women ate whole grain bread every day. They had lower glucose after 75 g glucose load by 0.76 mmol/l (5.10 ± 1.52 vs. 5.86 ± 1.61 mmol/l, $P = 0.03$) and higher HDL-cholesterol by 0.17 mmol/l (1.63 ± 0.42 vs. 1.46 ± 0.39 mmol/l, $P = 0.04$) comparing to those who ate whole grain bread occasionally. 41.4% of women ate meat daily, their triglycerides were higher by 0.38 mmol/l (1.37 ± 0.79 vs. 0.99 ± 0.47 mmol/l, $P = 0.002$) comparing to those who did not eat meat every day.
Conclusion
Having regular breakfast, eating whole grain bread, limiting frequency of having meat are associated with better metabolic profile in patients with PCOS.

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GP67

MRI-based proton-density fat fraction measurements reveal alterations of abdominal fat, bone and muscle composition in lean women with PCOS

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Background
Proton-density fat fraction (PDFF), derived from chemical shift encoding-based water-fat magnetic resonance imaging, has emerged as an important surrogate method for calculation of fat composition in a number of tissues including liver, vertebrae and muscles. This study aims to determine whether fat composition of these tissues, as well as visceral and subcutaneous adiposity differ between women with PCOS and healthy controls.
Methods
17 lean women with PCOS (age: 21.4 ± 3.1 years, BMI: 22.1 ± 1.9 kg/m^2) and 16 healthy women who were matched for age, BMI and waist circumference ($P =$ 0.56, 0.12 and 0.11 respectively) were included. The diagnosis of PCOS was based on Rotterdam criteria. Hormonal and biochemical evaluations and MRI-based PDFF measurements were performed in all participants. Radiologists reporting MRI examinations were blinded to clinical data and patient control status.
Results
PDFF% values of liver were higher (median 4.5% vs. 3.6%, $P = 0.02$) whereas PDFF% values of both vertebrae and paraspinal muscles were lower (32.8% vs. 41.6%; and 12.8% vs 15.1%, $P < 0.05$ for both) in PCOS patients than controls. Also, subcutaneous and visceral adipose tissue areas were increased in PCOS patients compared to healthy women (median 32.8 cm^2 vs. 18.5 cm^2, and 112.9 cm^2 vs. 83.1 cm^2, $P < 0.05$ for both). Pancreas PDFF% values were similar between the groups. Visceral and subcutaneous fat area measurements were positively correlated with FAI ($r = 0.71$, $P < 0.01$ and $r = 0.49$, $P < 0.05$ respectively). Subcutaneous fat area was also positively correlated with fasting insulin ($r = 0.54$, $P < 0.05$) and 2 h insulin during OGTT ($r = 0.78$, $P < 0.01$). PDFF% of liver in PCOS did not show a correlation with insulin resistance or lipid parameters but there was a trend for positive correlation with free androgen index (FAI) ($r = 0.37$, $P = 0.08$).
Conclusions
Fat composition of liver calculated by PDFF with MRI, subcutaneous and visceral adipose areas are higher in lean PCOS patients than age, BMI and WC-matched healthy women. Biochemical androgen excess and insulin resistance are among the factors modulating intraabdominal adiposity in lean PCOS. Whether decreased PDFF measurements of vertebra and paraspinal muscles in the syndrome are related to muscle or bone strength remains to be determined.

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GP68

DHT, rather than free testosterone, influences symptoms of aging in eugonadal men

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Aim
To assess the relation between questionnaires of androgenic function (AMS and IIEF-EF scores) and sex hormones (DHT, estradiol and total and free testosterone) in men attending an outpatient clinic for endocrine and reproductive disorders.

Methods
We retrospectively reviewed all data entered in the electronic database of the Münster Center of Reproductive Medicine and Andrology (CeRA) Androbase from patients visited between January 2015 and October 2018. Multinomial ordinal logistic regression models were used to test for independent predictors of the questionnaires score in men naïve of possibly interfering treatments (androgens, aromatase inhibitors or PDE5 inhibitors).
Results
Among 4895 (mean age: 37 ± 12.7 years) subjects with a serum measurement of DHT and total and free testosterone during their first visit to the center, the AMS and IIEF (EF domain) questionnaires were completed by 635 and 574 men free of interfering medications and were included in analysis. Total and free testosterone and DHT were all found associated with IIEF and AMS in the whole group. When considering separately hypogonadal ($n = 219$) and eugonadal ($n = 416$) men, only DHT turned to be a significant predictor of AMS score with an increase of 1 ng/ml in serum DHT associated with a 46.7% decrease in the odds of having worse symptoms ($P = 0.011$) in subjects with normal T, but not in hypogonadal men. No significant effects were observed for free testosterone, BMI or age. No significant effects were observed for both free testosterone and DHT in regards to the EF domain of the IIEF questionnaire.
Discussion
Despite being of little value in hypogonadal men, DHT is significantly associated with aging male symptoms in subjects with normal serum testosterone. In the multivariate analysis, neither DHT nor free or total testosterone show significant association with impairment of erectile function as assessed via the IIEF questionnaire.
Conclusions
The present study is the first to demonstrate that, although DHT can be associated with male aging symptoms, it is of little value in hypogonadal men. DHT measurement might become an useful addition to the diagnostic workflow of symptoms of male aging in subjects with normal T, but should not be routinely included in the diagnostic process.

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GP69

Male patients with hypogonadism have an impaired lipoprotein function

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Background
Male hypogonadism is known to be associated with an increased incidence of cardiovascular (CV) events, although the underlying biochemical mechanisms are so far not fully understood. The clinical condition characterized by low levels of testosterone offers a unique model to unravel the possible role of lipoprotein-associated abnormalities in CV risk. In particular, the assessment of the functional capacities of high-density lipoproteins (HDL) may provide novel insights besides traditional risk factors.
Aim of the study
Aim of our study was to determine whether male hypogonadal patients have an impaired function of serum lipoproteins and if testosterone levels correlate with this function.
Methods
We evaluated HDL cholesterol efflux capacity (CEC, both ATP-binding cassette transporter and aqueous diffusion-mediated) and serum cholesterol loading capacity (CLC) in a series of 20 hypogonadal patients and in 17 age and body mass index (BMI) matched healthy control subjects.
Results
Hypogonadism significantly reduced the HDL ATP-binding cassette transporter A1 (ABCA1)-, ATP binding cassette transporter G1 (ABCG1) - and aqueous diffusion-mediated CEC (−19.6%, −40.9% and −12.9%, respectively), with a 16.2% decrement of total CEC. In the entire cohort, positive correlations between testosterone levels and both total HDL CEC ($r^2 = 0.359$, $P = 0.0001$) and ABCG1 HDL CEC ($r^2 = 0.367$, $P = 0.0002$) were observed. On the contrary, serum CLC, significantly raised (+43%) in hypogonadal patients, was inversely correlated with testosterone levels ($r^2 = 0.270$, $P = 0.00014$). HDL-C concentrations did not correlate with either testosterone levels, HDL CECs or serum CLC.
Conclusions
Our results show that in hypogonadal patients pro-atherogenic lipoprotein-associated changes lead to reduced cholesterol efflux and increased influx, thus suggesting a potential explanation for the increased CV risk in hypogonadal patients and a possible objective functional parameter of hormonal dysfunction.

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Thyroid Autoimmune Disorders

GP70

Serum levels of the soluble receptor for advanced glycation end products (AGEs) are reduced and AGEs increased in hashimoto's thyroiditis (HT)

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Objective
AGEs, compounds formed by the transformation of proteins, are increased in conditions of oxidative stress and promote inflammation by interacting with their receptor (RAGE) on cell membrane. By contrast, the soluble receptor for AGE (sRAGE), that is proteolytically cleaved from cell surface receptor via matrix metalloproteinases, sequester RAGE ligands and act as a cytoprotective and anti-inflammatory agent. AGEs/sRAGE interaction play a role in the pathogenesis of several diseases related to oxidative stress. Recently, increased levels of AGEs, as specific markers of oxidative stress, have been reported in HT, but no data are available on sRAGE levels in these patients.
Materials And Methods
We enrolled 50 euthyroid HT patients (5 M e 45 F, mean age 38.5 ± 12 yr) and 50 age- and sex-matched healthy controls. All subjects were eythyroid at time of recruitment (mean TSH value 1.98 ± 1.10 uIU/ml in HT *vs* 1.40 ± 0.73 mIU/ml in controls; $P = 0.689$) and none was on LT-4 therapy. Smokers, subjects with kidney failure, history of cancer or autoimmune, inflammatory and infection comorbidities were excluded. Patients did not differ significantly from controls with regard to the main metabolic and anthropometric parameters. In sera from each subject, sRAGE levels were measured by ELISA (kit sRAGE Elisa, R&D System, Minneapolis, USA; minimum detectable dose 3 pg/ml); AGEs were determined on spectrophotometric method.
Results
sRAGE levels were significantly lower in HT patients (median 424 pg/ml, *range 307–1070*) compared to controls (738 pg/ml, *365–1205*; $P = 0.001$), while AGEs levels were significantly higher in TH than in controls (median: 205 AU/g prot, range 38–463 *vs* 114 AU/g prot, range 30–325; $P = 0.0001$) and the two parameters were inversely correlated ($r = -0.377$; $P = 0.016$). The correlation analysis also showed a positive correlation between BMI and serum AGEs levels. On the contrary, the sRAGE levels showed significantly inverse correlations with BMI and anti-thyroid antibodies positivity ($r = -0.27$, $P = 0.001$). In regression analysis models, adjusted for BMI, serum Ab-TPO were the main predictors for both AGEs ($P = 0.014$) and sRAGEs ($P = 0.027$), irrespective of TSH and/or FT4 values.
Conclusion
sRAGE levels were decreased and AGEs increased in HT patients. Autoimmunity *per se* seems to play a role in AGEs/sRAGE imbalance, irrespective of thyroid function impairement. Given the protective effects of sRAGE, HT subjects may exhibit increased susceptibility to oxidative damage, even when in euthyroid status.

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GP71

The randomised probiotic trial of indigo study (investigation of novel biomarkers and definition of role of the microbiome in Graves' orbitopathy)

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Background
Changes of the gut microbiota may impact on the mechanisms of immune tolerance in Graves' disease (GD) and Graves' orbitopathy (GO). Probiotics, which contain live micro-organisms, can modify the composition of the gut microbiota.
Aims
We tested in a double-blind randomized placebo controlled trial whether the administration of a well-characterized, commercially available, probiotic would 1) modify the microbiota composition in GD/GO patients, 2) change the natural course of GD and/or GO progression, and 3) affect the systemic immunological status.
Methods
The probiotic compound LAB4 comprises 25 billion colony-forming-units/capsule of two *Lactobacillus acidophilus* strains plus *Bidifobacterium bifidum* and *Bidifobacterium animalis var.lactis*. Thirty GD patients untreated or within 4 weeks of anti-thyroid therapy (ATD) were randomized to receive LAB4 ($n=14$, 11 women and 3 men) or placebo ($n=16$, 14 women and 2 men) for 6 months orally while treated with ATD. Ten patients in each arm had mild to moderate GO. Serum concentrations of IgA, IgG, TSH, FT4, FT3, autoantibodies to the thyrotropin receptor (TRAb) and gene sequencing for 16S rRNA on fecal samples were assessed at baseline, at euthyroidism (EU) and at the end of 6 months follow-up (EFU).
Results
At EU we observed a significant reduction in counts of the Firmicutes phylum in the probiotics group compared to placebo ($P=0.033$). At EFU, 6 and 5 patients on placebo were hyperthyroid and euthyroid, respectively, compared to 3 and 8 on probiotics ($P=$NS). At EFU GD patients treated with placebo had higher FT3 concentrations than those receiving probiotics ($P<0.05$). Severity or progression of GO were not different between patients in the placebo or probiotic group. IgA and IgG levels were transiently lower (at EU) in patients treated with probiotics ($P<0.01$ and $P=0.02$, respectively), and returned to baseline levels after probiotic withdrawal. The probiotic administration did not affect TRAb levels.
Conclusions
Although these results have to be confirmed in a larger clinical trial, we suggest that probiotics are effective in modifying the microbiota composition in GD patients. GD patients on probiotics seem to relapse less at 6 months after ATD therapy, compared with those on placebo. Probiotics induce a transient, but significant decrease of both circulating IgA and IgG, suggesting a systemic effect of the treatment.

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GP72

Microarray profile of CD19+B cells from Graves' disease patients reveals potential molecular mechanisms associated with the proliferation of B cell signaling

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Background
Graves' disease (GD) is a common autoimmune disorder characterized by the production of autoantibodies targeting the thyroid, leading to hypothyroidism. It is widely accepted that B lymphocytes play a significant role in GD as they are the source of autoantibodies (TRAb) against the thyroid-stimulating hormone receptor (TSHR). Previously, we reported that B cells infiltrate the thyroid tissue of GD patients, and in this study we observed that the percentage of peripheral blood B cells of GD patients was significantly higher than that in healthy controls. However, few studies have sought to understand the role of thyroid antigen-reactive B cells during disease development.
Methods
LncRNA and mRNA microarray expression profiling were performed to identify the differentially expressed genes in purified $CD19^+B$ cells. Go and Pathway analysis showed the potential function and pathway involved in the target genes. Two independent algorithms were used to predict the lncRNAs that regulate target gene. The Protein-protein interaction (PPI) network present the underlying interaction of these differential genes.
Results
410 differentially expressed mRNAs between GD patients and controls, with 79 mRNAs being upregulated and 331 being downregulated in the B lymphocytes of GD patients as compared with controls. Quantitative real-time polymerase chain reaction (qRT-PCR) validated T-cell leukemia/lymphoma-1A (*TCL1A*) and SH2 domain containing 1A (*SH2D1A*), were upregulated and downregulated, respectively, in GD patients as compared to controls. GO and Pathway analyses revealed that *TCL1A* and *SH2D1A* genes are highly involved in B cell proliferation and survival. lncRNAs TC14001829.hg.1 and TC14002143.hg.1 are predicted to regulate *TCL1A* and lncRNA TC0X002222.hg.1 to regulate *SH2D1A*. qRT-PCR validated the upregulation of the lncRNAs TC14001829.hg.1 and TC14002143.hg.1, and the downregulation of the lncRNA TC0X002222.hg.1 in GD patients.
Conclusion
In conclusion, our study determined the expression profiles of mRNA and lncRNA in B cells of GD patients, and highlighted the changes in *TCL1A*, *SH2D1A*, and the related lncRNAs TC14002143.hg.1, TC14001829.hg.1, and TC0X00222.hg.1, which may participate in GD development by modulating B cell proliferation and survival. These genes and lncRNA could represent novel biomarkers and therapeutic targets for GD.

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GP73

Clinical experiences in autoimmune polyglandular diseases

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Introduction
The autoimmune polyglandular syndrome is a complex, heterogeneous disease in which autoimmune diseases of endocrine and non-endocrine organs can occur. There are 4 subgroups: the early-onset APS I develops due to the mutation of the gene AIRE and characterized by the presence of Addison's disease (AD), mucocutan candidiasis and hypoparathyroidism; the APS II is defined by the appearance of AD and autoimmune thyroid diseases (AITDs) and/or diabetes mellitus; in APS III the patients have AITDs and any other kind of autoimmune manifestations except AD, while APS IV consists of patients who could not be included in the previous 3 groups. The aim of this research was to characterize APS patients treated in our Department.
Patients and method
During the searching, 132 APS cases were identified in our database of 1762 patients (7.5% of this population) with autoimmune diseases.
Results
Of the affected individuals, 15 and 117 were male and female patient, respectively. Only 1 patient belonged to the APS I, while 25 to the APS II, 91 to the APS III and 15 to the APS IV subgroups. The average age at the diagnosis was 36.8 year in APS II, 32.9 year in APS III, and 37.9 year in APS IV. Seven different autoimmune manifestations affected endocrine organs; furthermore, 10 non-endocrine organ specific autoimmune disorders and six systemic autoimmune diseases were detected. APS was most common in the group of patients with Addison's disease (29%). AITDs were combined with other autoimmune manifestations in 10%. The first diagnosed autoimmune diseases were AITDs in 28%, AD in 14% and diabetes mellitus in 14%. Ninety-six cases with two, 28 with three, 7 with four and 1 with five autoimmune manifestations were found.
Conclusions
APS is not uncommon in patients with various forms of autoimmune diseases and may occur in one-third of patients with AD. The development of relevant diagnostic and screening protocols to identify these patients timely is warranted.
Keywords: autoimmune polyglandular syndrome, APS, Addison's disease, autoimmune thyroid disease, type I. diabetes mellitus

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GP74

The change of pulmonary artery pressure and serum vascular endothelial growth factor in Graves' disease before and after treatment

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Exertional symptoms, dyspnea, and impaired effort tolerance are common in patients with Graves' disease. Proposed explanations include high-output left heart failure, ineffective oxygen utilization, and respiratory muscle weakness. In addition, cases of pulmonary arterial hypertension (PAH) in patients with Graves' disease have been reported. Vascular endothelial growth factor (VEGF) is produced by thyroid follicular epithelial cells in response to stimulation of the TSH receptor. Secreted VEGF can lead to endothelial cell proliferation and a significant increase in serum VEGF levels in Graves' disease patients has been observed and the role of VEGF in PAH suggested. To evaluate the change of pulmonary artery pressure (PAP) and VEGF in Graves' disease, we performed two-dimensional and Doppler echocardiography and serum VEGF using ELISA (R&D systems) in 28 untreated Graves' disease patients before and after treatment (25 patients on propylthiouracil and 3 with RAI) and 10 normal controls. Pulmonary artery (PA) pressure was increased in patients with Graves' disease compared to normal controls (mean 23.5 vs 29.3 mmHg, $P<0.05$). 44% of Graves' disease (12 patients) showed PAH (PA > 30 mmHg) and serum TBII level was higher in Graves' disease with pulmonary arterial hypertension than normal PA ($P<0.05$). After treatment, PA was normalized and serum VEGF was decreased (from 314.8 ± 81.29 to 267.8 ± 69.15 pg/ml, $P<0.05$). In conclusion, 44% of untreated Graves' disease showed PAH and PAP was decreased after treatment. The pathogenesis of PAH in Graves' disease needs further studies.

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GP75

Grave's orbitopathy: clinical, paraclinical and therapeutic features

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Introduction
Grave's orbitopathy (GO) is the main extra-thyroid manifestation of Graves' disease (GD) and the leading cause of exophthalmia in adults. Its clinical presentation is extremely heterogeneous, ranging from mild ocular discomfort to sight-threatening disease. The aim of our study was to specify the clinical and paraclinical characteristics, as well as the therapeutic modalities of GO.
Patients and methods
Descriptive retrospective study in the period between September 2008-December 2018, including 45 patients followed for GO in Endocrinology-Diabetology department of the University Hospital of Casablanca.
Results
The average age was 45 years (19–70 years) with male predominance. The average duration of GD was 4.7 years (1 month–14 years). The GO appeared at the same time as the GD in 9 cases, before the GD in 2 cases, and after that in the rest of our patients. The time between GD and diagnosis of GO varied between 0 and 6 years. The GO was unilateral in 4 cases. GO was inactive in 33% of cases. Strabismus was noted in 6 patients, and associated with diplopia in 5 cases. Three of our patients had a complicated GO with a corneal abscess. According to the NOSPECS classification: the GO was classified as stage 1 in 27%, stage II in 25%, and stage III in 48% of cases. An orbital CT-scan was performed in 30 patients, and an MRI in 2 patients, who objected a GO grade I in 9 cases, grade II in 11 cases, and Grade III in 11 cases. The management of the GO was surgical in 3 cases, intravenous glucocorticoids in 32 cases. Selenium supplementation and general measures were the only treatment recommended in 10 patients.
Conclusion
Grave's orbitopathy is more common in the male patient. The clinical expression is variable. The evaluation of the gravity and the activity of the GO as well as the radiological exploration allow a better management. Being considered an autoimmune disorder, corticosteroid therapy is widely used in severe and malignant forms.

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GP76

Cardiovascular risk factors, autoimmunity and insulin resistance in Graves disease

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Introduction
Graves' disease is an autoimmune disease accounting for the majority of hyperthyroidism cases.
Aim
We aimed to assess the interrelationships between cardiovascular risk factors, autoimmunity, insulin resistance and treatment in Graves' disease.
Material and methods
We measured free T3 (FT3), free T4 (FT4), TSH, thyrotropin receptor antibodies (*TRAb*), anti-thyroglobulin and anti-TPO antibodies, thyroid volume (each lobe' volumes sum, given by the formula $0.479 \times depth \times$ wide $\times$ length), BMI, glucose, HbA1c, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), levels of total cholesterol (TC), HDL, LDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB), apoA1, lipoprotein(a) (Lp[a]), homocysteine, CRP (C-reactive protein), folic acid, B12 Vitamin in 85 patients with Graves' disease (89.4% female, 52.8 ± 13.4 years). Patients were divided in subgroups according to autoimmunity profile (positive TRAb (9.4%) or negative TRAb (81.2%)] and treatment [previously treated (80%) or in treatment with anti-thyroid drugs (20%)). Then, we divided the previously treated subgroup according to performed treatment [thyroidectomy (33.8%), I^{131} (13.2%) or anti-thyroid drugs (53%)]. *Pearson* correlation, t-test and Mann-Whitney test were performed for statistical analysis.
Results
Regarding TRAbs subgroups there was a positive correlation between Lp(a) and thyroid volume ($r=0.4726$, $P=0.0228$) in positive TRAb subgroup. A negative correlation between thyroid volume and FT3 ($r=-0.4710$, $P=0.0065$) was found in negative TRAb subgroup. Comparing with the previously treated subgroup, significantly higher thyroid volume (20.685 ± 9.86 ml vs 15.43 ± 1.398 ml, $P=0.0480$) and thyroglobulin (74.22 ± 35.29 ng/ml vs 16.47 ± 6.47 ng/ml, $P=0.0315$) and significantly lower TSH (0.85 ± 0.15 UI/ml, vs 2.3 ± 0.41 UI/ml, $P=0.0139$) were found in patients currently treated with antithyroid drugs. There was a positive correlation between HbA1c and thyroid volume ($r=0.4290$, $P=0.0255$), and between CRP and TC ($r=0.4362$, $P=0.0375$) in the previously treated subgroup. Regarding evaluation by performed treatment, significantly lower FT3 (2.395 ± 0.37 pg/ml, IC95 (2.231–2.560), $P=0.0319$ vs 3.02 ± 0.177 pg/ml, IC95 (2.67-3.38), $P=0.032$) was found in patients who performed thyroidectomy. In the thyroidectomy subgroup there was a positive correlation between FT3 and HOMA-IR ($r=0.5734$, $P=0.0103$). In patients without previous surgery or I^{131} treatment there was a positive correlation between age and thyroid volume ($r=0.2972$, $P=0.0425$), homocysteine and TRAb ($r=0.7911$, $P=0.0341$) and a negative correlation between thyroid volume and TRAb ($r=-0.5275$, $P=0.0358$).
Conclusion
In patients with Graves' disease, we found significant interrelationships between thyroid volume and function, autoimmunity, lipid and glycaemic profiles. These associations may contribute to the cardiovascular risk in Graves' disease.

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GP77

Lipid profile, insulin resistance and cytokines evaluation in autoimmune thyroiditis patients

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Introduction
Thyroid dysfunction has been associated with cardiovascular events since it worsens atherogenesis, insulin resistance and dyslipidemia. Thyroid hormones

and adipokines interact with each other to regulate metabolism. The impact of thyroid dysfunction on adipokines serum levels remains controversial.
Objective
To evaluate the interrelations between thyroid function and cardiovascular risk factors as insulin resistance, lipid profile, inflammatory markers and adipokines, in autoimmune thyroiditis patients.
Methods
60 patients with autoimmune thyroiditis were evaluated and tree groups were defined based on TSH level: TSH between 0.4 and 4.0 μUI/ml (50 individuals), TSH between 0.4 and 2.5 μUI/ml (29 individuals) and TSH higher than 4.0 μUI/ml and normal levels of free T4 (FT4) and free T3 (FT3) (10 individuals). We measured thyroid function and autoimmunity, lipid profile, serum homocysteine, vitamin B12, folic acid, high-sensitivity C-reactive protein, adiponectin, resistin, PAI-1 (plasminogen activator inhibitor-1), VCAM-1 (vascular cell adhesion molecule 1), ICAM-1(intercellular adhesion molecule 1), and insulin resistance markers comprising the HOMA-IR and WBISI (Whole-Body Insulin Sensitivity Index). A 75-g OGTT was performed in the morning (before 11 AM), and blood samples were obtained every 30 min for 120 min for measurements of plasma glucose, insulin, and C-peptide. Fisher's exact test, Kruskal-Wallis test, One-way ANOVA test and Pearson's correlations were performed for statistical analysis.
Results
In our sample, median age was 51.0 (32.3–59.8) years. There were no significant differences regarding median age or median BMI between groups. Patients with TSH >4.0 presented higher HOMA-IR when compared to those with patients with TSH 0.4–4.0 (2.1 (1.4–3.0) vs 1.02 (0.41–2.45), $P=0.042$) and lower WBISI (46.4 (27.7–72.7) vs 60.6 (42.8–124.3), $P=0.042$). In all sample, TSH was positively correlated with HOMA-IR ($r=0.317$, $P=0.014$) and negatively with WBISI ($r=-0.311$, $P=0.027$). We observed positive correlation with resistin and fasting C-peptid ($r=0.440$, $P=0.001$). FT3 was negatively correlated with PAI-1 ($r=-0.328$, $P=0.011$). In TSH 0.4–4.0 group, we found positive correlations between TSH and both HOMA-IR ($r=0.404$, $P=0.004$) and resistin ($r=0.420$, $P=0.002$). FT3 was negatively correlated with PAI-1 ($r=-0.311$, $P=0.030$). In TSH 0.4–2.5 group, FT3 was positively correlated with homocysteine ($r=0.441$, $P=0.021$) and negatively correlated with PAI-1 ($r=-0.440$, $P=0.019$). In TSH >0.4 group, we observed positive correlation between FT4 and HDL ($r=0.768$, $P=0.009$).
Conclusions
Autoimmune thyroiditis is associated with an increased cardiovascular risk. This association is complex and involves multiple factors. We found significant interrelationships between thyroid function, lipid profile, insulin resistance, homocysteine, resistin and PAI-1.

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GP78

Autoimmune thyroiditis, Graves' disease and adiponectin, resistin and plasminogen activator inhibitor-1 levels

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Introduction
The interrelationship between autoimmune thyroiditis, Graves' disease and plasma adipokines levels remains elusive.
Aims
We aimed to compare the levels of adiponectin, resistin and PAI-1 levels in patients with autoimmune thyroiditis and Graves' disease.
Subjects and methods
We recorded thyroid function tests, BMI, the levels of total cholesterol (TC), HDL, LDL-cholesterol, triglycerides (TG), apolipoprotein B (ApoB), ApoA1, lipoprotein(a) (Lp[a]), homocysteine, CRP (C-reactive protein), folic acid, vitamin B12, adiponectin, resistin and plasminogen activator inhibitor-1 (PAI-1) in 98 patients with autoimmune thyroid disease (75.9% woman, with a mean age of 46.7 ± 15.3 years). We considered three groups of patients based on their thyroid function: euthyroidism ($n=30$), hypothyroidism ($n=35$) or hyperthyroidism ($n=33$). Statistical analysis was performed with Mann-Whitney test and spearman correlations. The results are expressed as mean$\pm$S.D. A two-tailed $P\leq0.05$ was considered significant.
Results
BMI values were significant higher in hypothyroidism compared to hyperthyroid subjects (30.3 ± 9.3vs 25.3 ± 4.7 kg/m^2, $P=0.03$). Serum levels of CRP were significantly elevated in hyperthyroid compared to euthyroid subjects (0.56 ± 0.55 vs 0.30 ± 0.24 mg/dl, $P<0.001$). The levels of Lp(a) were significantly elevated in hypothyroid compared to hyperthyroid subjects (24.6 ± 30.1 vs 18.6 ± 17.8 mg/dl, $P<0.001$). When compared to hyperthyroid subjects, those with hypothyroidism showed higher levels of resistin (20.7 ± 22.6 vs 12.7 ± 10.9 ng/ml, $P<0.01$) and PAI-1 (27.3 ± 25.1 vs 19.9 ± 17.4 ng/ml, $P<0.01$), and lower levels of adiponectin ($21.0\pm13.$vs28.3 ± 14.7 μg/ml, $P<0.01$). In both hypothyroid and hyperthyroid states the levels adiponectin, resistin and PAI-1 were not correlated with BMI. Adiponectin levels were negatively correlated with free T3 in hyperthyroid subjects ($r=-0.35$, $P<0.05$) and with TSH in euthyroid group ($r=-0.61$, $P<0.001$). Resistin levels were not correlated with TSH, free T3 or free T4. PAI-1 levels were negatively correlated with free T3 in both hypothyroid ($r=-0.42$, $P<0.05$) and hyperthyroid subjects ($r=-0.36$, $P<0.05$).
Conclusions
Patients with hypothyroidism due to autoimmune thyroiditis present higher levels of resistin and PAI-1 and lower levels of adiponectin comparing with patients with hyperthyroidism due to Graves' disease. The interrelations between thyroid function and adiponectin, resistin and PAI-1 may be associated with the pathogenesis of autoimmune thyroid disease and may contribute to the increased cardiovascular risk observed in these patients.

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GP79

The neutrophil-to-lymphocyte ratio as a novel marker in patients with thyroid-associated orbitopathy – a preliminary study

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Introduction
Graves' orbitopathy (GO) is a rare autoimmune inflammatory disease occurring in 25–50% cases of Graves' disease (GD). It is associated with poor clinical outcomes, impaired quality of life and socio-economic status. Genetic, environmental and immunological factors are considered to play a role in the pathogenesis of GO, but the effects of neutrophil, lymphocyte counts as well as neutrophil-to-lymphocyte ratio on the pathophysiology of GO are still unknown.
Aim of the study
The aim of this retrospective study, which based on our knowledge is the first in Poland, was to explore the connection between white blood cell, neutrophil, lymphocyte counts, neutrophil-to-lymphocyte ratio (NLR) and the severity of GO compared with patients without thyroid-associated orbitopathy.
Subjects and methods
110 patients (91 female and 19 male; 82.7% vs 17.3%), mean age 49 ± 28.5 years diagnosed with GO hospitalized in the Department of Endocrinology (Lublin, Poland) in seven-year period was retrospectively analyzed. Among them 92 patients had active and 18 inactive thyroid associated-opthalmopathy. 50 patients with GD with no signs of opthalmopathy were also enrolled. The control group consisted of 50 healthy volunteers (24 female and 26 male: 48% vs 52%, aged 45 ± 27.0 years). All patients with GO were assessed for activity of the disease using clinical activity score (CAS). Active GO was defined as CAS ≥3/7. The correlation between neutrophil/lymphocyte ratio and clinical activity of GO (spontaneous retrobulbular pain, ocular pain with eye movement, redness of the eyelids, swelling of the eyelids, redness of conjunctiva, chemosis of the conjunctiva, swelling of the caruncule) were evaluated.
Results
It has been observed that the NLR values were statistically higher in patients with or without GO ($P=0.0001$ vs 0.0026) compared to controls. Moreover, the NLR, WBC and neutrophil counts were higher and the lymphocyte count was lower in patients with GO than in GD patients without thyroid orbitopathy ($P<0.1$). There was no statistically difference ($P=0.085$) between NLR and the activity of GO in the clinical scale, only one of the symptoms from CAS – redness of conjunctiva was positively correlated ($P=0.023$).
Conclusions
The results suggest that neutrophil/lymphocyte ratio may predict inflammatory process in GD patients with and without GO better than white blood cell, lymphocyte and neutrophil counts separately. However, analyzed group of patients is too small, therefore further research is needed to confirm these findings.

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GP80

Effect of nine months of vitamin D supplementation on muscle performance in Graves' disease: a double-blinded, randomized clinical trial

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Background
Vitamin D deficiency has been proposed to play a role in development and course of Graves' disease (GD). Muscle weakness and fatigue are shared features of GD and vitamin D deficiency. We aimed to investigate whether vitamin D supplementation would improve restoration of muscle performance and thyroid-related quality of life (QoL) in GD.
Methods
In a double-blinded clinical trial, hyperthyroid patients with a first time diagnosis of GD were randomized to vitamin D 70 mcg/day or matching placebo as add-on to standard antithyroid medication (ATD). At baseline and after three and nine months of intervention, we assessed isometric muscle strength, muscle function tests, postural stability, body composition, and self-reported ThyPRO Tiredness and Impaired Daily Life (0–100, higher score worse). Differences in change between groups were analyzed using linear mixed modelling. (The DAGMAR study clinicaltrials.gov ID NCT02384668).
Results
Nine months of vitamin D supplementation caused a reduced muscle strength increase at all muscle groups investigated, although only significant at knee extension 60° with a 7% (95% CI:0.3;13) lower increase in muscle strength compared with placebo. Vitamin D supplementation showed a trend towards reduced gain of lean body mass (−3.1% (95% CI: −6.5;0.4)). There was no significant difference in Tiredness or Impaired Daily Life, but improvement of Impaired Daily Life tended to be lower in the vitamin D group (10 points (95% CI: −2;22)). In the entire group of patients, all measures improved significantly in response to nine months of ATD with an improvement of 21–37% in muscle strength at the different muscle groups ($P_{all}<0.001$) and of 11% (95% CI:9;13) in lean body mass. Furthermore, performance of the repeated chair stand test and the time-up-and-go test improved by 15% (95% CI:12;18) and 2% (95% CI:0.4;5). Postural stability improved by 26–54% $P_{all}<0.001$. Large changes was observed in Tiredness and Impaired Daily Life with improvements of 22 (95% CI:19;26) and 36 (95% CI:28;45) points. In general, improvements were most marked during the first three months of ATD, but the recovery continued from three to nine months.
Conclusion
Nine months of vitamin D supplementation 70 mcg/day caused unfavorable effects on restoration of muscle performance. In contrast, ATD treatment was associated with marked improvement in all measures of muscle performance and thyroid-related QoL. In patients with newly diagnosed GD, high dose vitamin D supplementation should not be recommended to improve muscle function, but ATD therapy seems to be of major importance to alleviate muscle impairment.

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GP81

Retrospective analysis of the efficacy of three different dose regimens of rituximab in patients with active moderate-severe graves' orbitopathy

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Aim
The aim of this retrospective study was to assess the efficacy of different doses of rituximab (RTX) in patients with active moderate-severe Graves' Orbitopathy (GO).
Methods
Overall 40 patients, 5 M/35 F; mean age (± S.D.) 58±11 years were treated with RTX; 21 were smokers. The patients received the following treatment: 14 patients (group 1) a single 100 mg dose; 15 patients (group 2) a single 500 mg dose and 11 Patients (Group 3) 2 doses of 1000 mg.
Results (1)

Table 1

	Nr	GO duration (months)	Patients' age (years)	Nr. of pat. with previous steroid therapy	Baseline CAS*	12 weeks CAS*	24 weeks CAS*
Group 1	14	20	56	7/14	4.5±1	2.1±1.6	*1.1±-0.8*
Group 2	15	18	57	2/15	4.3±1	1.3±1.5	*0.1±1.1*
Group 3	11	18	63	2/11	4.4±1	1.8±1.3	*0.8±1.1*
ANOVA		n.s.	n.s.	n.s.	n.s.	n.s.	***0.04***

*values are expressed as mean ±S.D.

Results (2)
- Serum TRAb levels were significantly reduced in the in the three groups at 24 weeks (*P*-value Group 1 0.002, *P*-value Group 2 0.001, *P*-value Group 3 0.05). At 12 weeks serum TRAb levels decreased significantly only in group 2 (*P*-value 0.002)
- 13/40 patients at baseline and 14/40 at 24 weeks were persistently hyperthyroid, despite the change in serum TRAb title throughout RTX therapy.
- 2 patients of group 1 (100 mg dose) developed optic neuropathy.
- 3 patients presented major adverse reaction after only 25–75 mg of RTX: acute cytokine release syndrome, clinically manifesting with marked soft tissue edema associated with pain and transient decrease of vision.
Conclusions
1. RTX induced persistent GO inactivation in all the patients, regardless of the doses used. The higher CAS value at 24 weeks in patients treated with 100 mg compared to those treated with higher doses may be due to a lesser degree of orbital lymphocytic depletion.
2. The analysis of the quality of life questionnaire shows only a minimal improvement of the appearance but not of ocular function score.
3. The decrease of serum TRAb at 24 weeks was observed in all three groups of patients and might be due to the ongoing anti-thyroid therapy rather than to an effect of RTX.
4. Finally, the use of low dose RTX does not seem to prevent the development of adverse effects. We suggest that RTX should not be used in patients with subclinical optic neuropathy.

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Thyroid Nodules and Cancer

GP82

Coexistence of the BRAF V600E and TERT promoter mutations and their impact on response to therapy and final outcome of papillary thyroid cancer

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Introduction
Coexistence of the *BRAF* V600E and *TERT* promoter mutations may correlate with more aggressive histopathological features and worse course of the disease. According to the American Thyroid Association (ATA) dynamic risk stratification with modified initial estimated risk based on response- to-therapy and disease course allows individual risk assessment and support clinicians in the appropriate management approach to differentiated thyroid cancer (DTC).
Aim
The aim of this study was to examine the relation between the coexistence of the *BRAF* V600E and *TERT* promoter mutations in the papillary thyroid cancer (PTC) and response to therapy according to the ATA guidelines.

Participants
Unselected 568 PTC cases with known *BRAF* and *TERT* status diagnosed from 2000–2012 and actively monitored at one institution were reviewed retrospectively.
Main outcome measures
The association between the *BRAF* V600E and *TERT* promoter mutation and clinicopathological features, TNM stages, initial risk, response-to-therapy categories, follow-up, and the final outcome of the disease according to the revised 2015 ATA criteria and the 8th edition of the American Joint Committee on Cancer/Tumor-Node-Metastasis (AJCC/TNM) staging system.
Results
Any *TERT* promoter (*TERT*p) mutations were detected in 13.5% (77/568) of PTC cases with known *BRAF* status. The C228T and C250T mutations were 54 (9.5%) and 23 (4%) patients, respectively. Twenty-two additional other *TERT* alterations were found. Coexistence *BRAF* V600E and *TERT* hotspot C228T or C250T promoter mutation was found in 9.5% (54/568). Concurrent *BRAF* and *TERT*p positive status correlated significantly with older patient's age ($P=0.001$), gross extrathyroidal extension ($P=0.003$), pT3–4 tumor stage ($P=0.005$), stage II-IV according to the AJCC/TNM ($P=0.019$), and ATA intermediate or high risk according to the 2015 ATA initial risk stratification ($P=0.003$), as well as with the worse than excellent category of response to primary therapy ($P=0.045$), recurrence ($P=0.015$) and no remission in the final outcome ($P=0.014$). During a median follow-up of 120 months (10 years), 16 (29.6%) patients *BRAF* (+) and *TERT* (+) did not achieve excellent response to primary therapy, three (5.6%) were recurrent after a disease-free period and eight (14.8%) presented no remission at the end of follow-up.
Conclusions
The positive *BRAF* V600E and *TERT* mutation in patients with PTC correlate with poor prognostic initial factors and clinical course. Coexistence the *BRAF* and *TERT* status seems to be suitable for predicting a worse response-to-therapy, recurrence, and poor outcome.

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GP83

Prognostic significance of TERT promoter and BRAF mutations in cytologically suspicious or malignant thyroid nodules: a monocentric case series at a tertiary-level endocrinology unit

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Background
Follicular-derived thyroid cancers (FDTC) generally have a good prognosis. Nonetheless, a minority of them have an aggressive behavior and develop distant metastases, with increased mortality rates. Pre-surgically available prognostic markers, able to identify this group of patients are still lacking.
Materials and methods
The study involved 436 FNA samples with a malignant/suspicious cytology obtained from thyroid nodules in 436 consecutive patients referred for surgical excision from April 2007 to January 2017. Molecular analysis for somatic mutations of *TERT* promoter was retrospectively performed in all patients. 434 patients also underwent *BRAF* analysis. ^{131}I remnant ablation was performed in 387 patients (median dose: 100 mCi; range: 30–200 mCi). Follow-up was available for 384 patients (median: 59 months, range: 7-293 months).
Results
TERT promoter mutations and *BRAF* mutations were detected in 20/436 (4.6%) and in 257/434 thyroid nodules (59.2%), respectively. At the end of the follow-up, 319/384 patients (83%) had an excellent outcome, 37/384 (9.7%) had an indeterminate response and 28/384 (7.3%) had biochemical or structural persistent disease or died because of disease progression. Tumor size ($P=0.002$), presence of extrathyroidal extension ($P=0.0015$), vascular invasion ($P=0.0024$), lymph node involvement ($P=0.0001$), mostly N1b spread ($P<0.0001$), distant metastasis (DM) ($P<0.0001$), advanced stage at diagnosis ($P<0.0001$) and *TERT* promoter mutation ($P=0.0002$) were all significantly correlated with the risk of persistent/recurrent disease or disease-related death. At multivariate analysis, only cancer size (OR 1.06, 95% CI 1.01 to 1.09), the presence of N1b lymph-node metastases (OR 8.09, 95% CI 2.62 to 25.04) and DM (OR 7.32, 95% CI 1.17 to 45.81) predicted persistence disease or cancer-related death. *TERT* promoter mutations were related with older age ($P<0.0001$), largest tumor size ($P=0.0002$), higher tumor stages ($P<0.0001$), and DM ($P<0.0001$). DM was correlated with older age ($P=0.0487$), larger tumor size ($P=0.0015$), extra-thyroidal extension ($P=0.0120$), presence of N1b ($P=0.0001$) and *TERT* promoter mutation ($P<0.0001$). Presence of *BRAF* mutation was less frequent in patients with DM ($P=0.0201$). *TERT* promoter mutations (OR 40.58; 95% CI 3.06 to 539.04) and N1b (OR 40.16, 95% CI 3.48 to 463.04) were independent predictors of DM at multivariate analysis.
Conclusions
TERT promoter mutation was an independent predictor for DM, giving the clinician the possibility to individuate, already in the pre-surgical setting, many of the patients who deserve a more aggressive initial treatment and a closer follow-up.

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GP84

Polygenic susceptibility to papillary thyroid cancer: detection of the main genetic signature in Italian patients

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Introduction and aim
Thyroid cancer is the most common endocrine neoplasia affecting 0.2–1.5% of the individuals worldwide and its incidence is increasing [1]. Papillary thyroid carcinoma (PTC) is the main histotype (80–90%). PTC susceptibility is the result of genetic predisposition, environmental factors and lifestyle. We hypothesized that genetic predisposition to PTC is poligenic and characterized by a genetic signature involving combinations of genes previously found to be associated to PTC.
Methods and results
We considered all the genetic variants (SNPs) significantly associated with PTC on the PubMed literature database. 184 informative SNPs were selected after data refining considering linkage disequilibrium. Then, SNPs data were extracted from the 1,000 Genomes database (www.1000genomes.org), comprising genome of 2504 unselected individuals, collected worldwide. The combination of 184 SNPs associated with PTC was used to group individuals in different risk-clusters according to their genetic structure, calculated by Bayesian statistics, as previously successfully performed for polycystic ovary syndrome [2]. Individuals resulted to be distributed among seven groups worldwide, indicating different degree of genetic predisposition to PTC. Then, we repeated the same analyzes considering genetic data from about 1200 individuals (697 PTC *versus* 497 healthy controls) of Central/South Italian origin registered in a GWAS, specific for PTC, by the German Cancer Research Center (DKFZ) of Heidelberg [3]. This first analysis was refined using the 33 SNPs with highest odds ratio, therefore, reasonably most causative of genetic clustering. We clearly demonstrated that PTC and healthy control groups are genetically different, revealing diverse predisposition to develop cancer. Then, the genetic structure of each subject was indicated as a percentage of affinity to each risk-cluster and re-analyzed together with other risk factors: sex, BMI, area of origin and familiarity (quantified in a growing score as the degree of kinship increases). These data were analyzed together by principal component analysis (PCA) and clustering of the two groups was even more pronounced. The most contributive factors to the diversity between PTC and healthy controls were genetics and familiarity, while sex, body-mass index and area of origin were less relevant.
Conclusion
We demonstrated that PTC risk may be predicted using SNPs and risk factors data. Validation of the model in independent groups of PTC patients ($n=200$) and healthy controls ($n=130$) genotyped by iPlex assay is ongoing.
References
1. Cabanillas *et al*. Thyroid cancer. Lancet.2016;388:2783–95.
2. Casarini and Brigante. JCEM.2014;99:E2412–20.
3. Köhler *et al*. Genome-wide association study on differentiated thyroid cancer. JCEM.2013;98:E1674–81.

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GP85

Follistain-like 1 (Fstl1) may reduce metastastic activity of anaplastic thyroid cancer by increasging thyroid transcription factor 1 (TTF1) and epithelial gene markers

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Background
Although anaplastic thyroid cancer (ATC) is found in less than 2% of patients with thyroid cancer, it is the most advanced, aggressive and lethal. ATC is known to develop from well-differentiated thyroid cancers, such as follicular thyroid cancer, and it is undifferentiated itself. Among the thyroid-specific transcription factors that are critical for the function of thyroid, the expression of thyroid transcription factor 1 (TTF1), or NKX2.1, has been reported to correlate with the degree of differentiation, thus, its level is the lowest in ATC among thyroid cancers. TTF1 was reported to reduce invasion and metastasis in lung cancer; however, its regulatory effects on metastasis in ATC in unknown. The metastasis suppression effect of follistatin-like 1 (Fstl1) has been recently reported; however, the results are inconsistent. Herein, we investigated the effects of Fstl1 on metastasis of ATC cell line.
Methods
8505C cell line was maintained in EMEM containing 2 mM glutamine, 1% non-essential amino acids and 10% FBS. Human Fstl1 was treated at 200 ng/m for 24 hr, 48 hr, and 72 hr. Cell viability was measured by MTT assay. Expression of epithelial gene markers including claudin 1, claudin 4, claudin 7, and occludin and mesenchymal gene markers including vimentin and N-cadherin were confirmed by real-time quantitative PCR (qPCR). In addition, gene expression of TTF1 was also measured by qPCR. Protein expression of each marker was examined by western blot.
Results
Fstl1 did not affect cell viability. Gene expressions of claudin 1, 4 and 7 significantly increased after 24 hours compared to control while that of TTF1 significantly increased after 72 hours. However, there was no significant change in protein expression of each marker. None of mesenchymal markers were changed in response to Fstl1.
Conclusion
We demonstrated that Fstl1 increased epithelial gene markers and TTF1 in 8505C cell line. These suggest that Fstl1 can suppress metastastic activity of anaplastic thyroid cancer.

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GP86

Benefits and limitations of TKIs in patients with medullary thyroid cancer: a systematic review and meta-analysis

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Tyrosine Kinase Inhibitors (TKIs) have been used in patients with advanced Medullary Thyroid Carcinoma (MTC). However, for some compounds, data on effectiveness and safety are limited. The aim of this systematic review and meta-analysis was to document clinical response and toxicities of TKIs in advanced MTC.
Methods
A literature search in MEDLINE, EMBASE and Cochrane until May 2018 was performed for articles or abstracts on TKI use in MTC. Studies were included in the meta-analysis if they presented results on tumor response to TKIs and/or adverse events of TKI therapy in 5 or more patients with MTC. The primary endpoint was objective response rate; disease stability, median progression free survival (PFS), drug discontinuation due to adverse events and Grade ≥ 3 adverse events (G3AEs) were secondary endpoints. Pooled percentages were calculated using meta-analysis of binomial data. Direct comparisons between specific drugs were not feasible and drug-specific effect estimates are provided descriptively.
Results
Thirty-three publications met the inclusion criteria for analysis: 1 phase IV trial, 2 phase III trials evaluating vandetanib and cabozatinib respectively, 20 phase I or II studies, with the remaining 10 studies of retrospective/observational nature. In total, data on 1274 patients were evaluated, 81 in phase IV trial, 561 in phase III trials, 441 in phase I–II trials and 191 in retrospective studies. Significant heterogeneity was detected for all effect estimates. Overall, objective response (CR & PR) was documented in 23% (95% CI 17–28; $I^2=79.2\%$) of the patients, with higher rate observed with sunitinib [38% (95% CI 20–59)]. Stable disease was reported in 44% (95% CI 38–51; $I^2=71.1\%$) of patients, with higher rate observed with axitinib [58% (95% CI 38–78)]. Overall disease progression was reported in 19% (95% CI 14–25; $I^2=80.1\%$) of patients, with the lowest proportion reported in the motesanib [8% (95% CI 3–15)] patients. Overall, 33% (95% CI 23–42; $I^2=90.7\%$) of patients discontinued the drug due to toxicity or disease progression with the lowest proportion reported in the cabozantinib group 14% (95% CI 11–18). G3AEs were reported in 50% (95% CI 47.1–52.9) of patients, with the lowest proportion reported in pazopanib treated group [14.2% (95% CI 2.7–25.8)].
Conclusion
TKI treatment in MTC exhibited a significant benefit in terms of reducing progression of the disease, however, careful monitoring of patients on these drugs is important to manage AEs efficiently and proactively, and determine if the drug is no longer effective.

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GP87

Intronic RAS and PI3KCA mutations identified by Next Generation Sequencing in thyroid nodules with indeterminate cytology may associate with follicular thyroid cancer

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Introduction
Accurately discern malignant from benign nodules sometimes represents a real challenge. Fine needle aspiration (FNA) biopsy, ultrasound and The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) allow for accurate diagnosis in 60–80% of all nodules. However, 10–20% of thyroid FNAs yield an indeterminate cytology (BSRTC III and IV categories). The real malignancy rate of BSRTC III category is difficult to ascertain because histopathological analysis of the lesion is not always available. Molecular testing may assist clinical practice in the management of controversial FNAs since 67% of thyroid cancers bear at least one genetic alteration. Next-generation sequencing (NGS) provides parallel high-throughput alternative to assess multiple targets of the genome and, in recent years, several mutational panels that include genetic alterations identified in thyroid cancer have been developed and tested for performance.
Aim
In view of the above, the aim of this study was to investigate the presence of not yet described genetic alterations occurring in FNA samples with indeterminate cytology, by using a custom multi-gene NGS panel, in order to better characterize indeterminate cytology nodules.
Materials and methods
The study includes 56 random FNA samples yielding Bethesda III or IV cytological analysis that underwent surgery, therefore histopathological diagnosis is available: 32 are benign nodules, 22 are papillary thyroid carcinomas (PTCs) and 11 are follicular thyroid carcinomas (FTCs). NGS was performed by using a custom library on Ion PGM™ sequencer. Reporter variant caller pipeline was used for data analysis and R and PLINK software were used to compute logistic regression and principal component (PCA) analyses.
Results
PCA analysis did not show any significant variation between PTC, FTC and benign nodules, indicating the heterogeneous nature of thyroid nodules. However, we did find genetic alterations in intronic regions of PI3KCA and HRAS genes that were significantly associated with our population of FTCs, showing an odds ratio >15 and $P>0.001$.

Conclusions
Our results indicate that FNA samples with Bethesda III or IV cytological analysis show genetic alterations in intronic regions of PI3KCA and HRAS genes in 16% of the samples and associate with a final histology consistent with FTCs. Several groups have developed Genetic Classifiers for thyroid cancer in order to increase sensitivity and specificity of molecular testing. However, unknown and/or intronic genetic alterations are usually discarded. We found an intronic HRAS point mutation that was strongly and positively associated with FTC phenotype that should be investigated for its' potential predictive value.

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GP88

An analysis of false-positive uptake on radioiodine whole-body scintigraphy

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Introduction
Radioiodine can be used for the ablation/treatment and imaging of thyroid cancer. However, radioiodine uptake is not specific for thyroid tissue. Iodine-131 can show physiologic accumulation in several organs as breast, thymus, liver and gastrointestinal tract, or in benign conditions, such as cysts and inflammation, or in a variety of benign and malignant non-thyroidal tumors, which could be mistaken for thyroid cancer or cancer metastasis. Here we aimed to evaluate extrathyroidal uptakes in radioiodine scan of our patients with differantiated thyroid cancer.
Patients and methods
We reviewed the data of 701 planar ^{131}I whole-body imaging findings of consecutive 585 patients with differantiated thyroid cancer. The patients were referred either for initial post-surgical ^{131}I ablation, for subsequent ^{131}I therapy of residual, recurrent or metastatic disease or for diagnostic ^{131}I whole-body imaging after initial treatment. We evaluated the false-positive uptake of radioiodine in the whole body and noted the confirmed diagnosis of the incidental finding with further imaging modalities.
Results
Of the 585 patients, 214 (36.6%) had diagnostic whole body scan during their follow up for thyroid cancer, 255 (43.6%) had scans after radioiodine remnant ablation or adjuvant therapy, 116 (%19.8) had both diagnostic and posttreatment scans. The extrathryoidal uptakes are listed in Table 1. Of the 701 planar ^{131}I whole-body imaging, 365 (62.4%) showed no incidental findings. The most commonly reported incidental finding was dental pathology ($n=82$; 14%).

Extrathyroidal uptake	N; %
None	365; 62.4%
Dental pathology	82; 14%
Sialoadenitis	50; 8.6%
Nasal inflammation	62; 10.6%
Bronchopulmonary infection-Bronchiectasis	17; 2.9%
Esophageal retention-Gastroeosophagial reflux disease	11; 1.9%
Arthritis	5; 0.9%
Liver	5; 0.9%
Non lactating breast (fibroadenoma; breast cancer)	4; 0.7%
Thymus	4; 0.7%
Trauma	3; 0.5%
Inguinal hernia	3; 0.5%
Thryoglossal duct	2; 0.3%
Ovarian cyst	1; 0.2%

Discussion
In our study we detailed the extrathyroidal uptake of diagnostic or posttherapy whole body scan of our patients with differentiated thyroid cancer which majority of them considered to be physiologic. Most commonly encountered uptake appeared in the oral cavity and was thought to be due to dental pathology. Further imaging was necessary in only a minority of patients. The awareness of these findings will lead us to be in contact with imaging physcians for characterizing the increased uptakes with additional imaging tehcniques and we can be more confident in establishing proper management for patients with differantiated thyroid cancer.

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GP89

Prospective sonographic assessment of 214 consecutive nodules as per the ATA 2015 guidelines. Real world data

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Introduction
Most studies which scrutinized the ATA 2015 thyroid nodule guidelines were performed retrospectively, in tertiary centers of excellence and in Western populations. We sought to prospectively apply these guidelines, under 'real world' conditions and in an eastern Mediterranean population.
Methods
Thyroid nodules were prospectively and independently assessed by two experienced sonographers and classified as per the guidelines. Only nodules that underwent USS-guided FNA were included for this study. Descriptive statistics are provided. Statistical analysis was performed using the chi-square test.
Results
214 nodules in 175 consecutively assessed patients were included (mean age 54.3 years; females 84.6%). They were sonographically classified as per the ATA guidelines as very low, low, intermediate and high risk in 7 (3.3%), 110 (51.4%), 65 (30.4%) and 32 (15%) nodules, respectively. Their cytological classification was Thy1, Thy2, Thy3a, Thy3f, Thy4 and Thy5 in 10 (4.7%), 169 (79%), 15 (7%), 9 (4.2%), 5 (2.3%) and 6 (2.8%). The correlation between the sonographic and cytological classification of nodules was excellent ($P<0.0001$); for example, Thy2 appearances were observed in 7/7 (100%), 100/110 (90.9%), 52/65 (80%) and 10/32 (31.2%) of nodules sonographically classified as very low, low, intermediate or high risk, respectively. Histology was available for 47 nodules; 16/47 (34%) were malignant. The risk of malignancy was 1/1 (100%), 2/17 (11.8%), 2/12 (16.7%) and 11/17 (64.7%) with very low, low, intermediate and high risk USS appearances, respectively ($P=0.002$). The two patients with low risk USS features who were diagnosed with malignancy included one patient with a nodule at 5 cm and another with incidental mPTC not in the nodule which was aspirated. The risk of malignancy was 0/1, 3/18 (16.7%), 1/10 (10%), 2/7 (28.6%), 4/5 (80%) and 6/6 (100%) with Thy1, Thy2, Thy3a, Thy3f, Thy4 and Thy5 cytological appearances, respectively ($P=0.001$). The three patients with Thy2 cytology with malignancy on histology included a 49-year-old lady with a positive family history and a large cystic nodule with very dark/viscous material aspirated, a 25 year-old with intermediate risk nodule but rapid growth associated with discomfort and a 66-year-old lady with a low risk nodule with a diameter up to 3.7 cm.
Discussion
Apart from the relatively higher rate of malignancy observed in Thy2 cytology results, our prospective data are similar to those provided at the guidelines, indicating the utility of the guidelines in routine secondary care practice and in different populations. Notwithstanding, clinical acumen remains of paramount importance when applying the guidelines.

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GP90

Treatment modalities in DTC patients with neck disease persistence. Second surgical intervention is more beneficial than only radioiodine (RAI) treatment

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Objectives
DTC has a favorable clinical course. A small percentage of patients undergoing surgery and RAI ablation may have local disease persistence and further therapeutic interventions may be needed such as further RAI administration following or not a second surgery. We investigated whether additional therapeutic interventions may be beneficial for the clinical course in DTC patients with disease persistence.
Methods
812 DTC patients (men 25.7%, age at diagnosis 42.4 ± 15.5 yrs) who received RAI ablation were followed-up in our department for 1–44 yrs (median 3 yrs). 206 of them received further RAI treatment with or without additional cervical surgery. They were classified in 3 groups according to the treatment modality that was followed: RAI-only ($n=47$, 22.8%), RAI+Surgery ($n=86$, 41.7%) multiple-interventions group ($n=73$, 35.4%). Clinical and histological characteristics were compared between groups.

Results
One year after diagnosis and before further intervention, stimulated thyroglobulin levels (sTG, median (IQR)) were in the groups RAI-only 4.9(23) vs RAI+ surgery 6.7(47) vs multiple-interventions 62(179) ng/mL ($P=0.01$). After the additional interventions sTG changed to 5.3(26), 2.4(21), 33(143) respectively in the 3 groups ($P<0.001$). Patients in the RAI-only group showed less frequently disease remission compared to RAI+Surgery group (24.4% vs 43.5%, $P<0.001$). The occurence of distant metastases during follow up was higher in RAI-only group (33.3% vs 16.0%, $P=0.002$). Age at diagnosis, histology type, tumour size, multifocality, presence of lymph node infiltration, capsular invasion, soft tissue invasion, did not differ significantly between groups. The 10-year probability of lack of progression of disease was: RAI-only 67.4% vs RAI+ Surgery 89.5% ($x^2=18.06$, $P<0.001$). Disease progression, RAI refractory DTC and distant metastases were more prevalent in the group of multiple interventions ($P<0.001$).
Conclusions
In DTC patients with disease persistence a second RAI administration without prior surgical intervention may not be beneficial in the majority of cases. Surgical removal of the metastatic disease prior to RAI administration could be a better therapeutic option for these patients.

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GP91

Detection of *EIF1AX*, *CHEK2* and *PPM1D* gene variants in thyroid carcinomas

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Objectives
The identification of novel causing genes in thyroid carcinoma is very important in diagnosis and prognosis of the disease. Recently, The Cancer Genome Atlas (TCGA) study found *EIF1AX, CHEK2* and *PPM1D* genes as new minor causing genes in the papillary thyroid cancer (PTC) development. The goal of this study was to detect variants in these genes in PTC, follicular thyroid carcinoma (FTC) and anaplastic thyroid carcinoma (ATC) cohorts.
Methods
DNAs were isolated from 324 fresh-frozen thyroid tissues of the patients – 316 with PTC, 2 with FTC and 6 with ATC. Exons 1, 2, 5 and 6 of the *EIF1AX* gene, exons 3, 4, 7, 11, 13 of the *CHEK2* gene and exons 1, 4, 5 and 6 of the *PPM1D* gene were analyzed by next generation sequencing (NGS) using Nextera XT kit for the preparation of library and sequenced on MisDefault (Illumina). These exons were selected based on the TCGA study results.
Results
In summary, 5 variants in the *EIF1AX* gene were detected - 2 in PTC (0.6%), 1 in FTC (50%) and 2 in ATC (33.3%). A113_splice variant in the exon 6 with *TERT* C250T and *TP53* P153Afs*28 mutations in the first ATC tissue and G9V variant in the exon 2 with *TERT* C228T and *TP53* S215G mutations in the second ATC were detected. c.429+1 G>A splice variant affecting donor site with *HRAS* Q61K mutation in FTC was found. K3N variant in the exon 1 with *BRAF* V600E and *TERT* C250T mutations in one PTC and P2L variant in the exon 1 with *KRAS* Q61R mutation in the other PTC were detected. Only germline variants in *CHEK2* and *PPM1D* genes in 21 PTC (6.6%) and 10 PTC (3.2%) were revealed, respectively. Eight different variants with main I157T variant in the *CHEK2* gene and seven different variants with the most frequent A152A variant in the *PPM1D* gene were recognized.
Conclusions
Totally, five different somatic variants in the *EIF1AX* gene in 5 cases (in ATC, FTC and PTC) were identified. All these variants co-occurred with other known mutations and contribute to cancer behaviour. Only germline variants in the other two genes were detected. Thus, *EIF1AX* gene is verified as a minor causing gene, but *CHEK2* and *PPM1D* genes have predisposition function. However, it is necessary to enlarge the studied cohorts, because the detection rates of variations are low. This work was supported by AZV 16-32665A and MZ ČR-RVO (EÚ, 00023761) grants.

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GP92

Diagnostic performance evaluation of a computer-assisted imaging analysis system for ultrasound risk stratification of thyroid nodules

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Aim
To evaluate the diagnostic effectiveness of the first commercially available computer-aided diagnostic (CAD) imaging analysis system.
Methods
Ultrasound images of 300 thyroid nodules (135 malignant) acquired prior to surgical treatment were retrospectively reviewed by a thyroid expert, and then the classification of each image was compared to the classification rendered by an image analysis program (AmCAD-UT®). The American Thyroid Association (ATA), the European Thyroid Imaging Reporting and Data System (EU-TIRADS), and the American Association of Clinical Endocrinologists (AACE/ACE/AME) classification systems were used for risk stratification.
Results
Diagnostic performance of the thyroid expert using the ATA system was: 87.0% sensitivity, 91.2% specificity, 90.5% positive predictive value (PPV) and 90.9% negative predictive value (NPV). Compared to the clinical expert, sensitivity of the CAD program based on the three reporting systems was similar, whereas specificity and PPV were lower. Regarding NPV, results for the clinician did not differ from the CAD program when it applied the ATA classification system (90.9% vs. 86.3%, $P=0.07$), but when it applied the EU-TIRADS and AACE/ACE/AME classifications it performed less well (82.6% and 80.8%, respectively; $P=0.01$ in both cases). The area under the receiver operating characteristic curve (AUC) was 0.88 for the expert clinician and 0.72 for the CAD based on ATA reporting system.
Conclusions
The CAD ultrasound image analysis program evaluated in this study is a useful tool for risk stratification of thyroid nodules, but does not perform better than a clinical expert.

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GP93

Tirads classification and final diagnosis of thyroid nodules classified as bethesda-3 after fine-needle aspiration

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Introduction
Ultrasound is the main diagnostic tool for imaging pathology of the thyroid gland. The TI-RADS classification allows the evaluation of a risk of malignancy in the case of thyroid nodules, indicating the need to perform a puncture for a histological study. Bethesda system classifies them according to the cytological malignancy risk. Bethesda category 3 (B3) comprises 'follicular lesion of undetermined significance' or 'atypia of undetermined significance'.
Aim
Determine final diagnosis of B3 nodules and study associations between malignancy and other variables, as ACR TIRADS classification.
Methods
Retrospective study of thyroid nodules classified as B3 after FNA referred to our hospital between 2012 and 2018. Statistical analysis: SPSS v.22.0 (Student's t-test to compare means and Chi-square/Fisher's test for proportions).
Results
Two hundred two patients (80.7% female); mead (SD) age, 53.5 (13.7) years. Sonographic features of included nodules are shown in table 1. Of the nodules, 7.9% were TIRADS 2 (maximum mean diameter (DMM) 39.86 mm), 14.7% TIRADS 3 (DMM 34.32 mm), 56.5% TIRADS 4 (DMM 29.24 mm), 20.9% TIRADS 5 (DMM 25.66 mm). Eigteen (8.9%) lesions met the reference-standard criteria for malignancy: 13 papillary thyroid cancers, 4 follicular thyroid cancer, 1 thyroid metastases from other malignancies. Application of the ACR TIRADS

system's FNA criteria would have reduced the number of biopsies performed by 19.2%. Of the nodules without indication of FNA, only one was malignant; of those who had an indication for FNA, 16.5% were malignant. In our cohort, the sensitivity of this system was 94.4% and the specificity was 19.6%. The positive predictive value (PPV) of the test was 94% and the negative predictive value (NPV) 19.6%. A false negative rate of 5.6%. The area under the ROC curve was 0.735 (0.588–0.881, *P* 0.001).

Table 1 Sonographic features of included nodules.

Structure/composition		*Echogenicity*		*Shape*	
	%		%		%
Cystic or almost completely cystic	**1.7%**	Anechoic	**0%**	Wider tan tall	**87.6%**
Spongiform	**0.6%**	Hyperechoic o isoechoic	**27.2%**	Taller tan wide	**12.4%**
Mixed	**9%**	Hypoechoic	**56.4%**		
Solid	**88.7%**	Very hypoechoic	**4%**		

Table 1 Continued.

Margin		*Echogenic foci*	
	%		%
Smooth or defined	**64.9%**	None or large comet-tal artifacts	**77.4%**
Lobulated or irregular	**21.8%**	Macrocalcifications.	**12.4%**
Extra-thyroidal extension	**1%**	Periferical calcifications	**2.5%**
		Punctate echogenic foci	**6.4%**

Conclusions
Internationally-endorsed sonographic risk stratification systems vary widely in their ability to reduce the number of unnecessary thyroid nodule FNAs. The ACR TIRADS outperformed the others, classifying over half the biopsies as unnecessary with a FNR of 5.6%.

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Adrenal and Neuroendocrine - Basic

GP94

Somatic transmembrane domain mutations of a cell adhesion molecule, CADM1, cause primary aldosteronism by preventing gap junction communication between adrenocortical cells

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Background
PA is the commonest curable cause of hypertension. Whole exome sequencing (WES) in 2011 and 2013 identified common somatic mutations in genes regulating membrane polarisation in 60-80% of aldosterone-producing adenomas (APA). In search of the missing variants, we undertook further WES. One APA from a 46-year-old gentleman revealed a novel somatic mutation (Val380Asp); which introduced a charged amino-acid into the single transmembrane domain of Cell Adhesion Molecule 1 (CADM1). The search for similar mutations led to a Gly379Asp mutation from a PA patient in Munich.
Method
Wild-type (WT) and mutant *CADM1* genes were cloned into lentivirus vectors and transduced into adrenocortical (H295R) cells to assess its effect on aldosterone secretion. Previous studies suggest CADM1 contributes to gap junction (GJ) communication between cells. This was assessed using dye transfer assays. Single H295R cells transfected with WT or mutant *CADM1* were microinjected with a calcein dye permeable through GJs, and the effects observed using fluorescent microscopy. H295R cells were also treated with peptide gap27, a specific inhibitor of the adrenocortical GJ protein CX-43. Finally WT or mutant H295R cells were co-transfected with CX-43 tagged by mApple or Venus fluorophores and mixed, allowing confocal visualisation of GJ formation between adjacent cells.
Results
Cells transduced with mutant *CADM1* showed 3-6-fold increase in aldosterone secretion ($P<0.05$) and 10-20-fold increase in CYP11B2 expression ($P<0.05$) compared to WT. RNA sequencing showed *CYP11B2* to be the most upregulated gene (30×) in mutant cells. Dye transfer assays showed paucity of dye transfer between neighbouring mutant *CADM1* cells, while calcein passed easily through GJs in WT cells. Inhibition of CX-43 caused 2-fold increase in aldosterone secretion, and 3 to 8-fold (<0.05) increase in CYP11B2 expression in non- and angiotensin-II stimulated cells respectively. Protein modelling suggested that mutations increased the angle of ectodomains to cell membrane, from 49° in WT cells, to 62° and 90° in Gly379Asp and Val380Asp respectively; increasing inter-cell distance from 21.2 nm to 24.7 and 27.9 nm. A key role of CADM1 may be to bring opposing CX-43 hemichannels close enough to form GJ channels. Mixing of Venus and mApple-tagged CX-43 transfected cells showed fewer intact GJ channels in *CADM1*-mutant cells.
Conclusion
Discovery of the *CADM1* mutation has again demonstrated the importance of membrane proteins in aldosterone regulation, although *CADM1's* impact on cation traffic is indirect. The unsuspected role of cell-adhesion in regulating GJs suggests a role for these in the regulation of aldosterone by oscillating Ca^{2+} currents.

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GP95

The role of filamin A (FLNA) in the regulation of IGF2/IGF1R pathway in adrenocortical carcinomas

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Adrenocortical carcinomas (ACCs) are rare endocrine tumors with poor prognosis. The insulin-like growth factor 2 (IGF2) is overexpressed in the great majority of ACC, and IGF2/IGF1R pathway acts as a proliferative autocrine loop, but to date IGF1R-targeted therapies have demonstrated a limited efficacy and the molecular mechanisms regulating this pathway are still unknown. The cytoskeleton acting-binding protein filamin A (FLNA), determinant in cancer progression and metastasis in different tumors, affects the intracellular trafficking and signalling of many receptors, including growth factor receptors such as EGFR, but a possible role of FLNA in regulating IGF1R has never been investigated. The aims of this study are: 1) to test FLNA involvement in modulating IGF1R signaling in human ACC cell lines H295R and SW13; 2) to evaluate FLNA expression in ACCs and a possible correlation with IGF1R pathway activation. By immunoprecipitation we found that IGF1R interacted with FLNA in basal condition, with an increased recruitment of FLNA after IGF2 stimulation, in both cell lines. As expected, IGF2 promoted H295R and SW13 cell proliferation and migration and accordingly increased ERK and cofilin activation. Interestingly, all these tumorigenic actions of IGF2 were potentiated in the absence of FLNA. Indeed, in cell silenced for FLNA, IGF2 induced a further increase of proliferation ($+69\pm40\%$ in SW13 and $+11\pm1.3\%$ in H295R, $P<0.05$), migration ($+10\pm7\%$ in SW13 and $+17\pm8\%$ in H295R, $P<0.05$), p-ERK/tot-ERK ratio ($+1.14\pm0.2$ fold in SW13, $P<0.05$) and a decrease of p-cofilin/tot-cofilin ratio (-0.20 ± 0.02 fold in SW13, $P<0.05$) vs IGF2-stimulated control cells. Furthermore, FLNA silencing in SW13 cells was associated to an increase of IGF1R expression after IGF2 stimulation ($+1.60\pm0.7$ fold vs IGF2-stimulated control cells, $P<0.05$), suggesting that FLNA is involved in receptor downregulation. Finally, western blot analysis showed significantly lower FLNA expression in ACCs ($n=5$) than in adrenocortical adenomas ($n=19$) (FLNA/GAPDH ratio 0.98 ± 1.4 and 4.37 ± 2.5, respectively, $P<0.01$). Moreover, FLNA expression levels in ACC samples were negatively correlated with ERK phosphorylation status. In conclusion, we demonstrated that low levels of FLNA enhance IGF2/IGF1R pathway activation in adrenocortical tumor cells, suggesting FLNA as a new factor possibly influencing the response to the therapy with IGF1R-target drugs.

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GP96

An unusual association of P450 oxidoreductase Deficiency and Argininosuccinatelyase Deficiency

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Background
P450 Oxidoreductase (POR) Deficiency(PORD) represents the most complex form of congenital adrenal hyperplasia. It usuallycauses genital ambiguity in both sexes, and eventually peculiar skeletal malformations resembling Antley-Bixler syndrome. Co-occurrence of POR deficiency and Argininosuccinatelyase Deficiency (ALD)in the samepatient born to non-consanguineous parents has never been reported.
Case report
A male patient was born at term to non-consanguineous parents, with a weight of 3.35 kg. He was diagnosed with ALD (genotype: homozygous p.V178M mutation) at the age of 3 years, following diagnosis in his older brother. Despite good compliance to diet, during follow-up the child developed epilepsy (7 years of age), keratoconus (7.5 years of age), optic and auditory nerve atrophy (8 and 11 years, respectively), the latter being not typical of ALD.He came to our attention at the age of 17.4 years because of short stature (Height -2.02 SDS; target height 0.46 SDS), delayed puberty (pubic hair stage 2, testicular volume 10 ml bilaterally; normal penile length) and bone age of13 years. No skeletal malformations were detected.Laboratory work-up revealed: LH(14.3 mU/ml), FSH (16.1 mU/ml), testsosterone (100 ng/dl), DHEA-S 41 ug/dl (80–560), androstenedione $<$0.3 ng/ml (1.1–3.5), ACTH (222 pg/ml), 17-OHP (28.75 ng/ml), progesterone (21.1 ng/ml), normal electrolytes, renin 36.4 pg/ml (0.9–20). Synacthen test showed suboptimal cortisol response (peak Cortisol 69 ng/ml), so that the patient was started on hydrocortisone. Urinary steroid profile was suggestive ofcombined signs of 21-hydroxylase and 17-hydroxylase deficiency, typical of POR deficiency. Genetic analysis of the POR gene showed homozygous p.N82I mutation, identified in heterozygosis in both parents. Given the lack of progression into puberty, the boy has been started on testosterone.
Conclusions
This is the first description of POR deficiency in a patient with Argininosuccinatelyase Deficiency. Our patient presented with a mild phenotype mainly characterized by delayed puberty underlying the phenotypc heterogeneity of POR gene mutations.

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GP97

Structural changes in the zona glomerulosa of normal aging adrenals

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Background and study aims
Increased aldosterone production in the adrenal gland plays a role in many hypertensive patients. Structural changes of the zona glomerulosa with age in normotensive patients have been described in literature but the influence of aging on aldosterone secretion and physiology is unclear. The aim of this study is to investigate changes in the ZG in order to gain insight in the origin, development and definition of aldosterone producing cell clusters (APCCs) in the normal aging adrenal in patients aged 0 to 40 years old.
Material and methods
We studied one or both adrenal glands collected at autopsies of normotensive patients aged 0 to 40 years who died of non-adrenal disease. We divided patients in age groups 0–5 years, 6–10 years, 11–18 years, 19–30 years and 31–40 years. We related aldosterone synthase (CYP11B2) expression, assessed by immunohistochemistry, with age.
Results
Eighty seven adrenal glands from 58 normotensive patients were collected and classified according to age group. All adrenal glands of patients aged 0 to 10 years show a continuous pattern of aldosterone producing cells without clustering in the outer layer of the adrenal cortex (zona glomerulosa), see Figure 1. In adolescence

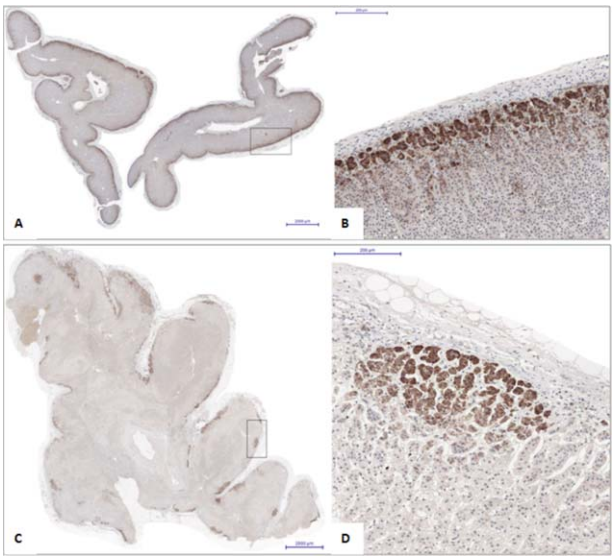

Figure 1 Relationship between CYP11B2 expression patterns and age in normal adrenals. Findings of CYP11B2 immunohistochemistry. CYP11B2-expression is brown. Scale bars in **A**+**C** are 2000 μm and scale bars in **B**+**D** are 200 μm. **A** adrenal gland of a 6-year-old boy showing continous CYP11B2 expression with no clustering. **B** magnification of the boxed area in **A**. **C**. adrenal gland of a 39-year-old women showing a discontinuous CYP11B2 expression with a lot of cell clusters. **D** magnification of the boxed area in **C**.

a discontinuous pattern arises and aldosterone-producing cells start to form clusters (APCCs). With increasing age the number of APCCs then increases. In cases where both adrenal glands of an individual were available ($n=29$) the CYP11B2 expression was symmetric.
Conclusion and discussion
The pattern of CYP11B2 expression in the adrenal cortex evolves over time, and this change can be described as an increase in APCC number with disruption of the continuity of the zona glomerulosa. However, we encountered the problem that a clear definition of APCCs is lacking, rendering quantification of volume and number of APCCs difficult. We nevertheless hypothesize that changes in aldosterone production patterns, exemplified by emergence of APCCs and rarefaction of the zona glomerulosa, may play a causative role in the development of both resistant hypertension and primary aldosteronism.

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GP98

Methylation status and gene expression of steroidogenic enzymes in benign adrenocortical tumors

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Background
DNA methylation has been recognized as a putative regulatory mechanism for *CYP11B2* in primary hyperaldosteronism. We aimed to investigate the DNA methylation and the expression of a panel of genes encoding several enzymes involved in steroidogenesis in adrenocortical benign tumors.
Methods
We collected a total of 60 adrenocortical tissues, including 9 non-functioning adrenal adenomas, 9 adenomas associated with autonomous cortisol secretion, 17 adenomas associated with Cushing's syndrome, 13 Conn's adenomas and 12 tissues derived from adrenal gland adjacent to the Conn's adenomas. Non-functioning tumors and autonomous cortisol secretion were defined according to

cortisol levels after 1 mg dexamethasone suppression test ≤ or > 50 nmol/L, respectively. The DNA methylation level of *CYP11A1*, *CYP11B1*, *CYP11B2*, *CYP17A1*, *CYP21A2*, *DHCR24*, *HSD3B1*, *HSD3B2*, *NR5A1*, *STAR*, and *TSPO* was evaluated by quantitative Bisulfite Next Generation Sequencing (bisulfite-NGS). Bioinformatic analysis was performed in a GalaxyProject environment and processed by BSPAT (Bisulfite Sequencing Pattern Analysis Tool). Spearman correlation coefficients were calculated using IBM SPSS 21 (IBM). *CYP11B1*, *CYP11B2*, *CYP17*, *CYP21*, *STAR* and β-actin gene expressions were examined by quantitative Real-Time PCR using a Sybr Green Assay kit (Thermo Fisher Scientific). The Default $2-\Delta\Delta Ct$ was used to calculate the fold changes in gene expression between the categories of samples.

Results

When compared to other adrenal tissues ($P<0.001$), *CYP11B2* was significantly hypomethylated in Conn's adenoma. No difference in methylation status was found among groups for the remaining genes. *CYP11B2* mRNA levels were significantly higher in Conn's adenoma than in the remaining adrenal tissues ($P=0.001$). *CYP21* mRNA was significantly higher in all but Conn's adenomas, when compared to normal adrenal tissues ($P<0.001$). Overall, we found a negative correlation between *CYP11B2* expression and DNA methylation (rho = −0.379; $P=0.003$).

Conclusion

DNA methylation seems to be a pivotal regulatory mechanism for *CYP11B2* expression. It is feasible that epigenetic mechanisms may be responsible for aldosterone hypersecretion in Conn's adenoma.

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GP99

Implementation of two preclinical ACC models for a comparative drug screen and initial mechanistic investigations

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Current systemic treatments are not satisfying for the treatment of adrenocortical carcinoma (ACC). However, translation of preclinically promising approaches were often disappointing indicating that existing tumor models might have inadequately predicted clinical applicability. Thus, our workgroup initiated a comparative drug screen of relevant chemotherapies and therapies targeting IGFR, EGFR, VEGFR/PDGFR and Wnt signalling pathway in the classical NCI-H295R and recently developed MUC-1 tumor model. BrdU-assay based investigation of cell-proliferation demonstrated significant anti-proliferative activity for almost all tested single agents and combinatory approaches (n = 20) with more pronounced effects for classical chemotherapies. Subsequent analysis by MTT-assays revealed e.g. for Etoposide (E) and Cisplatin (P) the inhibition of cell viability of NCI-H295R cells in a highly significant (E 180 uM: 2.5%; *P* 160 uM: 17%) and dose-dependent manner, while even at extraordinary high drug concentrations cell viability remained high for MUC-1 (E 180 uM: 67%; *P* 160 uM: 70%, both $P<0.001$ vs NCI-H295R). Moreover, for single treatments with Doxorubicin (D), 9-cis-Retinoic acid (RA), Erlotinib (Erl), XAV-939 (X) and Isoquercitrin (I) we detected comparably low or even a complete lack of toxicity in either MUC-1 alone (for D and Erl) or both tumor models (for I). Of-note, Mitotane (M), Paclitaxel (PTX), Linsitinib (L), Sunitinib (S) and Sorafenib (SF) displayed overall improved toxicities. Interestingly, among combinatory approaches tested so far (such as EDP-M, S + M, S + PTX, S + P, PTX + SF, P + RA, PTX + G, G + P and P + PTX), additive reduction of cellular viability and diminished clonogenicity was observed with treatment of G + P in both tumor models ($P<0.001$). Additionally, P + PTX displayed most promising anti-tumoral efficacy and reduced clonogenicity in both tumor models among all tested drug combinations ($P<0.001$). Mechanistically, G alone induced a dose-dependent increase in expression of, both RRM1 and RRM2, genes that are involved in the development of clinically relevant G-resistance. Interestingly, in combination with either P or PTX these effects were significantly reversed down to basal levels or even below (NCI-H295R RRM1, G: 791% $P<0.001$; G + P: 188%; RRM2, G: 336% $P<0.001$; G + P: 60% and in MUC-1 RRM1, G: 275% $P<0.01$; G + P: 97%; RRM2, G: 474% $P<0.01$; G + P: 175%; vs. 100% controls). Of note, also siRNA-mediated RRM2 silencing alone led to a significant decrease of cell count in both tumor models ($P<0.001$). In summary, our findings indicate that a combination of both tumor models might help to identify potentially new drug combinations for the treatment of ACC.

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GP100

Characterization of cell death induced by mitotane in adrenocortical carcinoma cells

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Background

Mitotane is the only drug approved for treatment of adrenocortical carcinoma (ACC). We have found that mitotane leads to endoplasmic reticulum stress and decreased viability in ACC cells. It is not known by which downstream mechanisms cell death is induced by mitotane.

Aim

To characterize the mechanisms underlying cell death resulting from mitotane treatment in ACC cells.

Methods

Lipid peroxidation in the ACC cell line NCI-H295R was measured with BODIPY 581/591 C11 and cell viability quantified by CellTiter Glo assay. Combination treatment with pan caspase inhibitor zvad-fmk, inhibitors of necroptosis (necrostatin-1) and ferroptosis (liproxstatin, deferoxamine) and ferroptosis activator RSL3 in three ACC cell lines was applied. Marker protein expression was assessed by immunoblotting.

Results

Mitotane induced caspase3 cleavage but caspase inhibition was unable to rescue ACC cells from mitotane-induced cell death. Necroptosis markers were unchanged after mitotane treatment, while lipid peroxides accumulated after mitotane treatment in a concentration dependent manner. Deferoxamine prevented mitotane induced cell death by up to 40%. In line with this finding, synergism of mitotane and RSL3 was observed. RSL3 showed cytotoxicity at nanomolar concentrations in ACC cells (EC_{50}: NCI-H295R: 240 nM, CU-ACC1: 814 nM, CU-ACC2: 14.5 nM) but not in cells of non-adrenal origin.

Conclusion

Mitotane-induced cell death involves caspase action. Iron-dependent accumulation of lipid peroxides are hallmarks of ferroptosis. In addition, synergism of mitotane and RSL3 suggests relevance of this novel pathway but detailed mechanisms require further Investigation.

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GP101

Infiltrating CD68 + /CD163 + macrophages regulate Gonadotroph-tumour invasion through collagen remodelling

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Introduction

Pituitary Neuroendocrine tumours (PitNETs) present heterogenic characteristics based on their hormonal expression and secretion. While most PitNETs have a slow progression rate, a subset of them exhibit an aggressive behaviour with recurrence properties despite current surgery, radio- and chemotherapy. To explore new clinical strategies based on immunotherapy we initiated a systemic cartography of the pituitary tumour immune microenvironment (PiTME).

Methods

Flow cytometry (FACS) and immunohistochemical (IHC) analysis were performed on a cohort of 43 freshly resected human PiNETs (18 Somatotroph and 25 Gonadotroph tumours). Patient derived xenografts (PDXs) were also performed using Rag2KO mice to further explore the interaction between pituitary tumour cells and mouse macrophages.

Results
Identification of various content of infiltrating T, B, NK and macrophage immune population was confirmed by FACS in all PitNETs. Interestingly, we found Gonadotroph and Somatotroph tumours to show a respective and specific immune signature. While Gonadotroph tumours were presenting a significant increase of $CD68^+$ macrophage infiltration, Somatotroph tumours were showing a larger number of infiltrating T cells. Those observations were subsequently validated by IHC on FFPE tumour-sections, confirming the increased number of CD68+/$CD163^+$ macrophages found within Gonadotroph lesions. Analysis of clinical data demonstrated that macrophage infiltration was correlated with local invasion of Gonadotroph-tumours. Interestingly, we also found those invasive lesions to have a significant histological reduction of collagen deposition, pointing a possible mechanism that could link invasion to a collagen-matrix remodelling by infiltrating macrophages in Gonadotroph tumours. Finally, through the use of a Rag2KO-PDX-model of PitNETs, we found mouse macrophages capable of an increase infiltration potential in grafted Gonadotroph tumours compared to Somatotroph grafted lesions, a result we further found associated with a reduced collagen deposition in Gonadotroph grafted tumours.
Conclusion
Our work underlines the specific immune landscape that respectively exist in Somatotroph and Gonadotroph tumours. It further pinpoints the potent role of CD68+/CD163+ macrophages in Gonadotroph tumour invasion through a collagen-matrix remodelling. Future experiments are needed to explore whether macrophages ablation or re-education could represent beneficial immune therapies for PitNET patients.

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GP102

Development of a simple experiment to distinguish ARMC5 missense mutants from rare ARMC5 polymorphisms in PBMAH patients using a quantitative western blot approach

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Introduction
Germline inactivating *ARMC5* (Armadillo repeat containing 5) mutations are responsible for Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH). *ARMC5* presents the characteristics of a tumor suppressor gene. Mutations are observed in more than 85% of patients with a clear familial presentation and 20 to 25% of apparently sporadic cases. Genetic alterations are spread all over *ARMC5* coding sequence and more than two-third of them are missense variants. In this case the pathogenicity prediction is mostly based on bioinformatics *in silico* analysis. We have previously developed an apoptosis assay using immunochemistry caspase staining on cells lines overexpressing transiently *ARMC5* wild type (wt) or its missense variants to demonstrate the deleterious effects of newly identified missense variants. However this approach is time consuming and therefore difficult to transfer for routine use in the oncogenetic laboratory of our hospital. We have previously observed that the stability of the ARMC5 mutant is altered.
Aim
To develop a simple functional test to confirm bioinformatic predictions of pathogenicity of newly identified *ARMC5* variants.
Method
HeLa cells are transiently transfected with vectors expressing Flag-tagged *ARMC5* wt or *ARMC5* missenses. Cell lysates are prepared after 14 and 24 hours of transfection and proteins are resolved by SDS-PAGE. Flag-ARMC5 protein levels are analyzed by Western blot experiment using an antibody against the Flag tag (Sigma®).
Results
Similar protein levels were observed for *ARMC5* wt and all its variants tested at 14 hours of overexpression, demonstrating similar expression of all the vectors. By contrast, at 24h of overexpression we observed a marked protein level decrease for ARMC5 wt and for two benign polymorphisms (p.F14Y and p.507L) compared to all other mutants tested (p.R898W, p.L548F, C657R, I664S p,.F700del, p.Y736P, p.L754P, p.L778P, p.C139R, p. R315W, p.L331P, p.R362L, p.R454W).
Conclusion and perspectives
Using a simple ARMC5 protein expression assay, we managed to distinguish pathogenic missense mutants from benign polymorphisms. ARMC5 non-pathogenic polymorphisms have the same protein expression profile than ARMC5 wt. This study shows the potency of this simple assay to confirm in routine practice the pathogenicity of new *ARMC5* variants identified in PBMAH patients. The mechanisms of this observation – stability or apoptosis- is an interesting research question that might help to progress in the understanding of PBMAH pathophysiology.

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GP103

Abstract Unavailable.

GP104

Identification of genes mediating dysregulated cell growth in aldosterone-producing adenomas

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Background
Aldosterone-producing adenomas (APA) are a major cause of primary aldosteronism. Somatic mutations explain the excess aldosterone production in the majority of patients with APA with mutations in the potassium channel *KCNJ5* the most prevalent. In contrast, mechanisms driving cell proliferation are largely unresolved.
Objective
To identify genes that modulate cell growth in APAs.
Methods
Quantitative transcriptome analysis using RNA-seq was used to identify differentially expressed genes between macro-APAs ($n=9$, diameter ≥ 30 mm) and micro-APAs ($n=12$, diameter <10 mm). Validation of RNA-seq by TaqMan real-time PCR was performed for 15 genes in a broader cohort of APAs (wild type, $n=28$; *KCNJ5*-mutated, $n=43$).
Findings
Hierarchical cluster analysis of the top 500 differentially expressed genes indicated sample clustering based on genotype (*KCNJ5* or wild type) and APA diameter. Differential expression of 155 and 348 genes was found between micro- and macro-APA with *KCNJ5* mutations and wild type, respectively. Several genes were identified with a known function related to cell growth. Expression of *BEX1* (a reported tumour suppressor) was 2.8-fold down regulated in macro-APAs relative to micro-APAs ($P=0.001$), and a linear negative correlation of *BEX1* expression with APA diameter was observed in wild type APA ($r=-0.501$, $P=0.007$). Genes involved in β-catenin signalling, *SFRP2*, *DKK1* and *TSPAN12* were 5.9-fold ($P=0.001$), 1.8-fold ($P=0.038$) and 8.3-fold ($P<0.0001$) down regulated in macro-APAs compared with micro-APAs, respectively.
Interpretation
APA display distinct transcriptome profiles according to adenoma diameter which may help identify genes involved in the dysregulated cell growth associated with these tumours.

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GP105

Reappraisal of the human adrenal cortex and fate

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The zonation of the human adrenal cortex has long been established morphologically and histologically as three distinct layers of cells. The outer zona glomerulosa (ZG) comprises densely packed cells arranged in clusters that produce aldosterone; the zona fasciculata (ZF) is composed of cells with large cytoplasm, containing lipid droplets arranged in radial columns that synthetize cortisol; and the zona reticularis is composed of compact and pigmented cells producing androgens. The main purpose of this work was to study the expression of aldosterone synthase (CYP11B2 which catalyzes the last steps of aldosterone synthesis) and 11β-hydroxylase (CYP11B1 which catalyzes the last step of cortisol synthesis) in normal adrenal glands to address issues regarding the zonation and the fate of the cells constitutive of each zone through the expression of Ki-67 and cleaved Caspase-3. Thirty eight normal human adrenals (16 females, 22 males, ranging in age from 22 to 81 years old with a median age of 52 years old) were obtained from brain-dead organ donors (kindly provided by the Organ Transplant Clinics, University Hospital of Rouen). As early as 22 years old, we found that the histological ZG (h-ZG) does not correspond to the functional ZG (f-ZG) expressing CYP11B2. Moreover, the h-ZG CYP11B2- cells were CYP11B1+ showing that these cells ascribed to the h-ZG are in fact cortisol producing cells. The progressive replacement of CYP11B2+ cells by CYP11B1+ cells in the h-ZG might demonstrate the role of the extracellular matrix in the morphological maintenance of the adrenal cortex. Our analysis also showed that steroidogenic cells were either CYP11B1 or CYP11B2 positive. By immunofluorescence, we observed in many cases isolated or clusters of CYP11B2+ cells located deeply in the h-ZF and sometimes in the vicinity of the central vein. We were able to show that those cells were probably issued from CYP11B2+ cell clusters located in h-ZG which migrated centripetally. Ki-67 immunoreactivity was highly variable and observed throughout the entire cortex. We also found a positive correlation between the steroidogenic and endothelial cells proliferation. It is interesting to note that some Ki-67+ cells located in the h-ZG were CYP11B1+. Cortical cells positive for cleaved Caspase-3 were extremely rare but detected in all zones when present. These findings challenge the classic view of lineage conversion of differentiated ZG cells and show a new pathway where the CYP11B2+ cells migrate without changing their phenotype.

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GP106

Gene expression changes in visceral adipose tissue of Cushing syndrome.

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Introduction
Visceral adipose tissue (VAT) is the key target tissue of glucocorticoids (GC) during active Cushing Syndrome (CS) and a metabolic tissue associated to insulin-resistance and an increased cardiometabolic risk. Till date there are no data regarding gene expression in VAT in CS and only few data about the mRNA in subcutaneous one. The aim of this study was to study the visceral VAT tissue transcriptional changes in ACTH-independent CS.
Methods
7 ACTH-independent CS patients due to adrenal cortical adenomas diagnosed in our hospital during the last 3 years and 14 sex (3m/4w), age (32–60y), BMI (29.1 ± 0.5 kg/m^2), cardiovascular and metabolic comorbidities matched controls (CTR) were included in the study. Clinical and analytical phenotype data were obtained prior to surgery. VAT (omentum) was collected after overnight fasting during the laparoscopic abdominal, programmed surgery. VAT plasticity (histology, immunochemistry) and function (RNAseq, rt-PCR) were analyzed. Differentially (up and down, $P^* < 0.05$) expressed genes in CS and CTR were compared and genes identified. RT-PCR was performed to validate the results and pathway analysis is ongoing.
Results
VAT of patients with active CS presented increased hypertrophic adipocytes and macrophage infiltration independent of the associated comorbidities. Heat map, PCA and t-SNE analysis and RT-PCR validation showed 10 up and 18 down regulated genes involved in macrophage activation, adipogenesis, insulin-signaling and lipid metabolism. Analysis of the overall gene changes network and relationship with the CS hormonal and phenotype characteristics are in process.
Conclusion
This is the first study providing insights to tissue transcriptomic changes in VAT of CS that may be have a causative effect on the comorbidities associated with the chronic hypercortisolism.

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GP107

Abstract Unavailable.

Calcium and Bone 2

GP108

Exploring the mechanism of TGF-β1 signaling in counteracting BMP activities during the osteogenesis of mesenchymal stem cells

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Bone is not only a skeletal scaffold but also an endocrine organ. Its formation and remodeling initiate from the recruitment and subsequent differentiation of m*esenchymal stem cells* (*MSCs*), in which the signals are known to be dominated by SMAD2/3 signaling driven by TGF-βs and SMAD1/5/8 signaling driven by BMPs, respectively. Of interest, distinct from the above concepts, we found that TGF-β1 induces not only SMAD2/3 phosphorylation but also SMAD1/5/8 phosphorylation in either primary MSCs or C3H10T1/2 MSC line. To further investigate the underlying mechanism, individual *Smad* knockdown, receptor profiling and signaling inhibitors were applied. Our results indicated that TGF-β1 mainly induces SMAD1 phosphorylation via ALK5-containing receptor complexes in MSCs. In terms of functional characterization, we demonstrated that TGF-β1-induced phosphorylated SMAD1 complexes can be translocated into the nucleus; this then increases the transcription of BMP-responsive genes, such as *Id1* and *Timp3*. However, in contrast to SMAD2/3 activation, we found that SMAD1/5/8 phosphorylation driven by TGF-β1 retained transiently and this may in turn dampen the BMP4-mediated activities in C3H10T1/2 MSC line. Indeed, TGF-β1 co-treatment significantly inhibited BMP4-activated reporter activity as well as expression of osteogenesis-related genes, such as *Runx2*. Using co-immunoprecipitation assay, we proposed that the aforementioned inhibitory effect may involve the formation of SMAD1/5-SMAD2/3 mix complex, which then recruits yet unknown co-repressors in MSCs. Taken together, our findings unveil a previously uncharacterized TGF-β-stimulated SMAD mechanism in MSCs and would further draw interests in exploring whether this signaling participates in balancing the BMP activity during MSC specification.

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GP109

Sex steroids as determinants of Wnt-Signalling markers in men

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Background
Canonical Wnt-signalling is important for bone by regulating osteoblastogenesis and osteoblast function. Bone metabolism is also partly determined by sex steroid exposure and sex differences in serum sclerostin levels have been reported. However, it is unclear whether serum sclerostin and other circulating Wnt-signalling components are sex steroid dependent within healthy men.
Objective
To determine whether serum sclerostin, osteoprotegerin (OPG) and Dickkopf-1 (DKK-1) levels associate with sex steroid exposure in men.
Methods
Cross-sectional data comprised 108 healthy males (34 ± 5 years) from the SIBLOS-cohort, and from the ENIGI-cohort 50 transgender women (TW) (35 ± 15 years) and 50 transgender men (TM) (23 ± 6 years) were evaluated before and 1 year after gender-affirming hormone treatment (cyproterone + estrogen and testosterone treatment, respectively). Sclerostin, OPG and DKK-1 were measured using a quantitative sandwich ELISA (Biomedica). Testosterone (T), estradiol (E2) were measured using LC-MS/MS, free fractions calculated.
Results
In SIBLOS, OPG was weakly inversely associated with E2 ($r = -2.8$; $P = 0.017$) and free T levels ($r = -2.4$, $P = 0.043$) and sclerostin with T ($r = -.237$; $P = 0.045$), whereas no significant associations were found in the transgender groups. Sclerostin levels were non-significantly lower in TM than TW (29.67 pmol/l, 35.56 pmol/l, respectively; $P = 0.135$), but otherwise there were no between-group differences in Wnt-signalling markers. After hormonal treatment, sclerostin, OPG and DKK-1 levels were unchanged in TM (30.97 pmol/l). In TW, however, sclerostin levels decreased (28.04pmol/l; $P < 0.001$), this difference being associated with changes in E2 levels ($r = -3.21$; $P = 0.025$).
Conclusion
Although circulating levels of Wnt-signalling components appear not strongly related to native sex steroid exposure in men, combined anti-androgen and estrogen treatment in TW reduced sclerostin levels. Contrastingly, no changes in sclerostin, OPG or DKK-1 were seen in TM receiving T treatment, suggesting that sclerostin production and secretion is regulated by estrogen but not androgen exposure.

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GP110

Denosumab in post-liver transplantation osteoporosis: preliminary data on the effects on bone mineral density and turnover markers

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Introduction
Several risk factors are involved in post-liver transplantation osteoporosis. Immunosuppressive agents, glucocorticoids, decreased renal function associated with secondary hyperparathyroidism and immobilization are the main determinants of fragility fractures in this population. Denosumab is highly effective in increasing bone mineral density (BMD) and preventing fragility fractures. However, the efficacy of denosumab in liver transplantation osteoporosis has never been described. The aim of this study was to evaluate bone turnover markers and BMD following denosumab administration in post-liver transplantation osteoporosis.
Subjects and methods
Twenty-nine patients seen at the Endocrinology Unit of Policlinico di Sant'Orsola, Bologna (7 post-menopausal females and 22 males, mean age 64 ± 8 years) who underwent liver transplantation between 1990 and 2018 were retrospectively evaluated. All patients had multiple fragility fractures, namely, vertebral fractures (with a mean of 3 fractures for each patient), diagnosed both clinically and with morphometry. All started denosumab 60 mg every 6 months between July 2014 up to May 2018 (96 ± 70 months after transplantation). Twenty-eight patients were on calcineurin inhibitors and 6 patients were on 5 mg to 10 mg/day prednisone regimen. All patients were receiving cholecalciferol (mean dose of 1860 IU/day). Four patients had recently terminated teriparatide and ten patients were switched to denosumab from oral bisphosphonates. BMD by dual-energy X-ray absorptiometry (DXA) was measured at baseline and every 18-24 months. Baseline and 6-month bone turnover markers were assessed. All patients had a minimum follow-up period of 6 months.
Results
Denosumab was effective in reducing total ($P = 0.010$) and bone-specific ($P = 0.007$) alkaline phosphatase as well as ß-CTX ($P = 0.002$) at six months after the first administration, regardless of prior bisphosphonate or teriparatide treatment. During follow-up, no significant change in BMD at femoral neck (+0.031 g/cm^2; %change 3.4 ± 11.2; $P = 0.290$) or spine (+0.017 g/cm^2; %change 5.6 ± 11.5; $P = 0.355$) was observed in a mean follow-up period of 27 ± 10 (range 13-44) months. We found a slight but significant increase of total hip BMD (+0.033 g/cm^2; %change 6.1 ± 7.0; $P = 0.045$). One atraumatic compound diaphyseal femoral fracture was observed in a diabetic male patient naïve to any osteoporotic treatments, 14 months after starting denosumab. No further clinical fractures were reported in our study population.
Conclusion
Denosumab is highly effective in reducing bone turnover markers in post-liver transplantation osteoporosis. Only mild total hip BMD gain was observed during the period of observation. A longer follow-up is needed to confirm this apparently blunted response.

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GP111

Hip structure analyses in acromegaly: Decrease of cortical bone thickness after treatment

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Background
Long standing growth hormone (GH) excess causes the skeletal clinical signs of acromegaly with typical changes in bone geometry including increased cortical bone thickness (CBT). However, a high prevalence and incidence of vertebral fractures has been reported. The aim of this study was to assess the course of cortical bone dimensions in the hip by comparing patients with acromegaly and clinically non-functioning pituitary adenomas (NFPA) at baseline and one year after pituitary surgery (1 year PO).
Patients and methods
Dual energy absorptiometry (DXA) was performed in patients with acromegaly ($n = 56$) and NFPA ($n = 47$). CBT in the femoral neck (CBTneck), calcar (CBTcalcar) and shaft (CBTshaft) were determined by Hip Structural Analysis (HSA). CBT at baseline and the change to 1 year PO were compared. Test results were adjusted for differences in gender distribution, age and gonadal status.
Results
Cortical thickness analyses showed higher values [mm] at baseline in patients with acromegaly compared to NFPA: CBTneck median [25th; 75th] 6.2 [4.7; 8.0] *vs.* 5.1 [4.1; 6.4] ($P = 0.006$), CBTcalcar 4.8 [4.2, 5.7] *vs.* 4.0 [3.2, 4.5] ($P < 0.001$), CBTshaft 6.2 [5.1, 7.2] *vs.* 5.2 [4.6; 6.0], ($P = 0.003$). In acromegaly, GH was correlated with CBTneck ($r = 0.31$, $P = 0.020$), whereas IGF-1 was correlated with CBTcalcar ($r = 0.39$, $P = 0.003$) at baseline. In acromegaly, CBTneck decreased with 11.2%, $P = 0.002$ during follow-up. Finally, the decrease in CBTneck and CBTcalcar in acromegaly was significant compared to NFPA ($P = 0.023$ and $P = 0.017$, respectively).
Conclusions
Previous observations of increased CBT in acromegaly were confirmed with DXA-derived HSA in a large, well defined cohort. The decline in CBT in acromegaly could contribute to the increased fracture risk in acromegaly despite increased bone dimensions and disease control.

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GP112

Body composition determines muscle strength in osteoporotic patients with vertebral fractures

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The aim of the study was to evaluate the degree of muscle dysfunction and relationship of trunk muscle strength and body composition in patients with

osteoporotic vertebral fractures (VFs). Methods. Study comprised 90 men and woman 40-80 years old with primary osteoporosis. Study group (n = 60) included patients with at least 1 VF (confirmed by X-rays), control group ($n = 30$) consisted of osteoporotic patients of the same age, BMI and BMD without any fracture. Trunk muscles strength was measured with tenzodynamometry at Back-Check Dr. Wolff diagnostic unit. Body composition was evaluated by DXA Total Body. Muscle function was evaluated with Up-and-go test, 10-meters-walk test, testa for static and dynamic of back and abdomen muscles. Results. Patients with VFs had a significant muscle strength deficiency in trunk flexors (TF) −40.9% and extensors (TE) −18.1% with an adequate function of the left (LLF) and right lateral flexors (RLF). Patients in study group had lower muscle strength vs controls in TF (15.6 ± 9.8 vs 27.7 ± 9.9 kg, $P < 0.001$), TE (14.6 ± 8.9 vs 21.3 ± 8.4 kg, $P < 0.001$), LLF (13.1 ± 7.2 vs 24.1 ± 8.9 kg, $P < 0.001$) and RLF (13.4 ± 7.4 vs 24.3 ± 7.7 kg, $P < 0.0001$). No significant difference in functional tests results were registered ($P > 0.05$). Body composition analyses showed differences between study and control groups in relative skeletal muscle index (RSMI, 6.5 ± 1.2 vs 7.5 ± 2.1 kg/m^2, $P = 0.02$) and fat mass (29717 ± 8367.4 vs 35464 ± 9127.4 g, $P = 0.01$). There was no significant difference in soft tissue mass and lean (muscle) mass between groups. Strength of all studied trunk muscles strongly negatively correlated with the number of VFs ($P < 0.001$) and positively correlated with femoral neck BMD (g/m^2), fat mass, soft tissue mass and lean mass ($P < 0.001$), but not with age and RSMI ($P > 0.05$). Conclusions. Patients with VFs have a decrease in trunk muscles strength and lower RSMI, mass and % of body fat in compared with patients without fractures. Number of VFs, low BMD, fat mass, soft tissue mass and lean mass are the main factors of trunk muscle dysfunction in osteoporotic patients. Functional tests showed less specificity for estimation of muscle function than tenzodynamometry.

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GP113

Vertebral fracture in outpatients with type 2 diabetes mellitus

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According to numerous studies, type 2 diabetes mellitus (T2DM) is associated with an increased risk of low traumatic non-vertebral fracture. There are a limited number of studies which evaluate lateral vertebral X-Rays in order to diagnose vertebral fractures in patients with T2DM. The goal of our study was to investigate the difference in vertebral fracture rate registered on lateral X-Ray between subjects with T2DM and a control group being under observation in the same outpatient clinic.

Materials and Methods

We enrolled 501 subjects from a single outpatient clinic in Moscow. All T2DM patients ($n = 251$) and non-DM controls ($n = 250$) had lateral spine X-Rays at the Th4-L5. All available vertebrae were graded by an experienced radiologist, vertebral fracture was confirmed if visual inspection perceived at least a 20% reduction in vertebral height (anterior, posterior or middle), as described by Genant et al.

Results

Among enrolled subjects 92 (18.4%) were male and 409 (81.6%) were female; the mean age was 64 (95% CI 47–91) years. Vertebral fractures were found in 78 subjects (15.5%) and 108 individuals (21.5%) reported low-traumatic non-vertebral fractures, in total low traumatic fracture was registered in 165 (32.9%) cases out of 501 enrolled. In total among subjects with T2DM ($n = 251$) vertebral fracture was present in 36 cases, in subjects without T2DM ($n = 250$) in 42 cases ($P = 0.408$). There was no statistically significant difference in the number of non-vertebral fractures (62 with T2DM and 42 in the control group) ($P = 0.062$). It seems that among women with T2DM non-vertebral fractures occurred slightly more commonly ($n = 52$) vs the group without T2DM ($n = 42$) $P = 0.031$. Subjects with T2DM (65 male and 186 female) had BMI – 30.5 (27.1–34.6) kg/m^2. The mean duration of T2DM was 8 (4–13) years. They suffered from macrovascular complications in 54.8% of cases; polyneuropathy −54.8%; retinopathy −25.6%; nephropathy −15.2%. Treatment with insulin was prescribed in 82 cases (32.8%). The glucose control was acceptable with HbA1c – 7.4% (6.6%–8.3%) in this group of outpatients with T2DM

Conclusion

Outpatients with T2DM with well-compensated diabetes do not demonstrate an increased risk of vertebral fracture as assessed by lateral X-Ray.

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GP114

Qualitative and quantitative parameters of diabetic osteopathy in type 1 diabetes mellitus

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Background and aims

Diabetic osteopathy in patients with type 1 diabetes (T1DM) is obvious. However, approaches to its diagnosis are still ambiguous. Thus, the aim was to study the features of serum osteo-specific parameters and dual energy X–ray absorptiometry (DXA) data in T1DM patients.

Materials and methods

157 patients with T1DM (105 women, 52 males) (mean age: 32.5 (25.5–41.6) yrs, duration of DM: 13 (7–20) yrs, age of manifestation: 19 (14–23) yrs, BMI: 23.43 (21.55–25,70) kg/m^2; HbA1c: 8.2 (7.6–8.9) %) and 98 (67 women, 31 men) controls, comparable in sex, age and anthropometric data. The research involved general clinic examination, serum bone-specific parameters, DXA (bone mineral density (BMD) and trabecular bone score (TBS) of lumbar spine). Z–score of –2.0 or less was regarded as «low bone mineral density».

Results

There were no significant differences in L1-L4 BMD and TBS in women compared with men: 1.16 (1.08–1.26 vs. 1.16 (1.08–1.28) g/sm^2; (U = 5506; $P = 0.694$) and 1.40 (1.35–1.46) vs. 1.44 (1.37–1.49) (U = 3230; $P = 0.097$). Similar results were obtained in subgroups of T1DM patients and controls. There was a definite link between BMD (L1–L4) and TBS (L1–L4) – $r^2 = 0.33$, $P < 0.001$. Low BMD was detected in 14.6% (23) of the surveyed patients with T1DM and 4.1% (4) of controls. T1DM patients compared to controls had lower BMD and TBS: BMD 1.14 (1.04–1.22) vs 1.23 (1.13–1.33) g/cm^2; U = 3606; $P < 0.001$; TBS 1.39 (1.33–1.46) vs 1.45 (1.39–1.48); U = 2775; $P < 0.001$), T-score TBS −0.30 (−1.90–0.30) vs 0.10 (−1.025–0.90); U = 248.5; $P = 0.018$; Z-score TBS −0.30 (0.00–0.50) vs. 0.15 (−0.50–1.00), U = 617; $P = 0.092$. In T1DM patients was established decreased alkaline phosphatase (77.98 (67.78–85.18) vs 93.4 (75.58–110.8) U/l; U = 698; $P < 0.001$) and osteocalcin (10.58 (8.08–15.70) vs 19.73 (15.16–26.30) ng/ml; U = 545; $P < 0.001$) compared with the control group. There were an increased osteoprotegerin levels (4.44 (3.38–5.77) vs 2.74 (2.15–3.54) pmol/l; U = 94; $P < 0.001$) and a decreased the RANKL/osteoprotegerin ratio (0.03 (0.02–0.06) vs 0.05 (0.04–0.07), U = 155; $P = 0.017$).

Conclusions

T1DM patients have decreased bone formation markers (alkaline phosphatase, osteocalcin) and elevated resorption markers (osteoprotegerin), which can lead to impaired mineralization (low BMD) and microstructure (low TBS).

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GP115

Different impact of marrow and visceral adipose tissue on bone phenotype

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Introduction

Central obesity and the consequent metabolic syndrome have global devastating effect on the health system due to their strong association with type 2 diabetes

mellitus and cardiovascular disorder. There are contradictory results about the influence of insulin resistance and visceral adipose tissue on bone phenotype. The study was designed to evaluate the association between bone quality and bone mineral density (BMD) with bone marrow adipose tissue (MAT) as well as with insulin resistance-related parameters (i.e. HOMA-IR, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and intrahepatic lipids (IHL).
Material and Methods
The study comprised 56 subjects (36F/20M), which were submitted to biochemical exams of (glucose, HbA1C, calcium, phosphorus, alkaline phosphatase, insulin, PTH, 25-OHD, osteocalcin, telopeptide carboxiterminal of collagen type 1), dual X-ray absorptiometry for the assessment of BMD [lumbar spine, femoral neck, and total hip BMD, as well as lumbar spine trabecular bone score (TBS)]. In addition, all subjects underwent to Magnetic resonance exams for the evaluation of MAT (^{1}H spectroscopy), SAT, VAT and IHL.
Results
No subject had diabetes mellitus based on fasting glucose and HbA1c determinations. The group showed: age $=47\pm14$ years, weight $=67.8\pm10.9$ Kg, height $=1.65\pm0.10$ m; and BMI $=24.8\pm3.9$ Kg/m^2 (17.5–33.6 Kg/m^2). The mean of L3 TBS was 1.4 ± 0.1 (1.17–1.77) and MAT was $32\pm11\%$ (10.6–69.1). There was a negative association between VAT, SAT, IHL with TBS ($R^2=0.29$; $P<0.0001$ and $R^2=0.23$; $P<0.005$; $R^2=0.14$; $P<0.05$, respectively). In addition, there was a negative association between TBS with MAT and HOMA-IR, respectively, $R^2=0.16$; $P=0.001$ and $R^2=0.23$, $P=0.0002$, which was maintained after adjustment age and BMI. There was no association between BMD with SAT, VAT, IHL and HOMA-IR.
Conclusion
The present study shows for the first time that MAT affects bone quantity and quality, while insulin resistance parameters (VAT, IHL and HOMA-IR) are only associated with bone quality (TBS). The present results encourage further studies to verify if TBS may serve as tool for BMD-independent fracture risk assessment in metabolic syndrome.

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GP116

FGF-23 beyond the kidney: a new bone mass regulator in the general population

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Aim
Fibroblast growth factor-23 (FGF-23) has been proposed as a predictor of bone abnormalities in chronic kidney disease patients (CKD), with recent data showing that it may also predict bone mass in the general population. We aimed at investigating the relationship between FGF-23 and bone mass parameters in apparently healthy individuals, according to sex, menopausal and nutritional status.
Materials and methods
Bone mass (bone mineral density-BMD, bone mineral content-BMC; assessed by Dual X-Ray Absorptiometry-DXA), body composition (DXA evaluation), and also the serum levels of FGF-23, parathormone (PTH), 25(OH)D_3, bone resorption marker C-terminal telopeptide of type I collagen (CTx) and leptin were determined from 123 apparently healthy volunteers (38 premenopausal women, 55 postmenopausal women and 30 young and middle-aged men). Primary osteoporosis under treatment and secondary osteoporosis (including CKD) were excluded.
Results
FGF-23 was negatively and independently associated with BMD and/or BMC in all groups, explaining up to 10% ($P<0.05$) of femoral neck BMD variance in postmenopausal women, and up to 20% ($P<0.01$) and 32% ($P=0.001$) of 1/3 radius BMC variance in premenopausal women and men, respectively. FGF-23 was increased in postmenopausal women with osteopenia/osteoporosis, but was not an accurate discriminator of normal versus low bone mass (AUC $=0.622\pm0.076$) according to ROC analysis. FGF-23 did not correlate with vitamin D, CTx, body weight, body composition parameters or leptin. FGF-23 was independently associated with PTH in premenopausal women and men only.
Conclusions
FGF-23 was negatively associated with bone mass parameters in both sexes, but was not a discriminator of high accuracy between normal bone mass and osteopenia/osteoporosis in postmenopausal women. The mechanism through which FGF-23 acts upon bone seems not to be mediated by leptin and, thus, requires further investigation. FGF-23 may find its place as a new marker for fine tuning the evaluation of primary osteoporosis and its associated fracture risk.

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GP117

Bone health and final height in craniopharyngioma patients.

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Introduction
Craniopharyngioma (CP) is a benign tumor of the sellar/hypothalamic region. It is associated with excess mortality, obesity and endocrinopathies. These endocrinopathies may influence bone health, and increase the risk of fractures.
Methods
In this retrospective study, Dutch/Swedish patients with CP were included if data was available on final height (at age >18 years) or DXA-scan results. Information from the first and last DXA-scans were gathered (i.e. bone mineral density (BMD), T- and Z-scores). Data is presented as mean $\pm$ standard deviation. Z-scores of final height were calculated (based on sex + country of origin).
Results
The cohort included 177 patients, of which 84 (47%) were females. Data was available on final height in 173 patients (98%) and of DXA-scan results in 117 patients (66%). At last follow-up (FU) (mean age 47 ± 18 years), 149 patients had growth hormone deficiency (85%), 155 hypogonadotropic hypogonadism (88%), 146 ACTH insufficiency (83%), 162 TSH insufficiency (92%), and 113 diabetes insipidus (64%). TSH deficiency was significantly more common in male than in female patients (39% vs. 25%, $P=0.042$). At last FU, 69% used growth hormone replacement therapy and the mean daily hydrocortisone dose was 21 ± 6 mg. BMD improving treatment was given to 33 patients (19%), which was higher in females (26% vs. 13%, $P=0.03$). Fractures in the total group occurred in 32 patients (19%). Fractures occurred more frequent in males than in females (29% vs. 10%, $P=0.002$) and more frequent in non-irradiated patients (13% vs. 26%, $P=0.028$). Mean time between DXA-scans was 10 ± 7 years and mean difference in height was 3.0 ± 10 cm. At first DXA-scan, mean T-score and Z-score for the BMD of total body, femur neck and L2–L4 were -0.1 ± 1.5 and -0.5 ± 1.4, -0.6 ± 1.5 and -0.6 ± 1.3, -0.7 ± 1.6 and $\pm-0.7\pm1.6$, respectively (no differences between sexes). Improvement in BMD occurred, expressed by mean change in T and Z-score of the total body (0.7 ± 1.1, 0.7 ± 1.0, $P<0.001$), Z-score of femur neck (0.6 ± 1.9, $P=0.03$) and T- and Z-score of L2–L4 (0.9 ± 1.6, 0.7 ± 1.8, $P<0.01$). Mean final height for male and female subjects was 178.1 ± 7.9 and 165.6 ± 8.0 cm (Z-score Swedish subjects -1.0 ± 4.3 and -0.1 ± 1.2 ($n=69$)).
Conclusion
Fracture rate is high in patients with CP. BMD improves during the FU period. Males had more fractures than females without difference in BMD; they might be undertreated with bone health improving medication.

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GP118

Gene variants of osteoprotegerin, estrogen-, calcitonin- and vitamin D-receptor genes and serum markers of bone metabolism in patients with Gaucher disease type 1

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Purpose
Osteopathy/osteoporosis in Gaucher disease type 1 (GD1) shows variable responses to enzyme replacement therapy (ERT); the pathogenesis is incompletely understood. We aimed to investigate the effect of several gene variants on bone mineral density (BMD) and serum markers of bone metabolism in GD1.
Patients/methods
50 adult Caucasian patients with GD1/117 controls were genotyped for gene variants in the osteoprotegerin (TNFRSF11B; OPG), estrogen receptor alpha (ESR1), calcitonin receptor (CALCR), vitamin D receptor (VDR) genes. In patients and 50 matched healthy controls, we assessed: clinical data, serum markers of bone metabolism, subclinical inflammation. BMD was measured for the first time before/during ERT (median 6.7 years).
Results
42% of patients were splenectomized. ERT led to variable improvements in BMD. Distribution of gene variants was comparable between patients/controls. The AA genotype (c.1024 + 283G > A gene variant; VDR gene) was associated with lower Z scores before ERT vs. GA ($P = 0.033$), was encountered in 82.3% of patients with osteoporosis and was more frequent in patients with pathological fractures. Z score increases during ERT were higher in patients with the CC genotype (c.9C > G variant, TNFRSF11B; OPG gene) compared to GC ($P = 0.003$). The CC genotype (c.1340T > C variant, CALCR gene) was associated with higher Z scores before ERT than the TT genotype ($P = 0.041$) and was absent in osteoporosis. Osteocalcin and osteoprotegerin were lower in patients vs. controls; beta crosslaps, interleukin-6, ferritin were higher.
Conclusions
We suggest for the first time a protective role against osteoporosis in GD1 patients for the CC genotype of the c.9C > G gene variant in the TNFRSFB11 (OPG) gene and for the CC genotype of the c. 1340T > C gene variant (CALCR gene), while the AA genotype of the c.1024 + 283G > A gene variant in the VDR gene appears as a risk factor for lower BMDs. Serum markers suggest decreased osteosynthesis, reduced inhibition of osteoclast activation, increased bone resorption and subclinical inflammation during ERT.

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Diabetes: Late Complications

GP119

Glycemic variability and mortality in patients hospitalized to general surgery wards

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Background
Glucose variability (GV) is common among hospitalized patients but the prognostic implications among patients hospitalized to surgical wards are unknown.
Objective
Investigate the association between GV, length of stay (LOS) and mortality.
Methods
Historical prospectively collected data of patients ≥18 years, hospitalized to general surgery wards between January 2011–December 2017. GV was assessed by coefficient of variance (CV) and standard deviation (SD) of glucose values during hospitalization. The main outcomes were LOS, 30-day and end-of-follow-up mortality.
Results
Cohort included 8,894 patients (mean age 63 ± 19 years, 48% male, mean follow-up 3.0 ± 1.8 years); 2,012 (23%) patients with diabetes mellitus (DM). Mean LOS was longer with higher CV or SD in patients without and with DM. 30-day mortality was 6%, associated with higher vs. lower CV (9% vs. 3%) and SD (9% vs. 3%) in patients without DM and with DM (9% vs. 5%; 8% vs. 5%, respectively). Mortality at the end-of-follow-up was increased in patients without DM with higher CV (27% vs. 18%) and SD (29% vs. 17%) and in patients with DM (33% vs. 24% and 32% vs. 21%, respectively). Multivariate analysis indicated increased risk for 30-day and end-of-follow-up mortality, in both groups. Adjustment for glucocorticoid treatment or hypoglycemia did not affect the results. In patients with high or low CV, mortality was higher with median glucose levels during hospitalization ≥180 mg/dl, compared with <180 mg/dl.
Conclusions
In patients with and without DM hospitalized to general surgery wards, increased GV is associated with longer hospitalization and increased short- and long-term mortality.

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GP120

High prolactin levels within the normal range are associated with improved metabolic profile and lower carotid intima media thickness in premenopausal women

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Introduction
A growing body of evidence is supporting a beneficial impact of breastfeeding on maternal metabolism and overall cardiovascular risk. The aim of this study was to evaluate the association between prolactin levels and metabolic parameters as well as indices of subclinical atherosclerosis, in a sample of premenopausal women with normal levels of prolactin.
Patients and Methods
This cross-sectional study included a total of 64 non-lactating premenopausal women. We evaluated anthropometric parameters and obtained blood samples for hormonal and biochemical assessments. Sonographical evaluation included indices of structural vascular disease (carotid intima media thickness, IMT) as well as pulse wave velocity (PWV).
Results
Lower levels of IMT were observed in cases with higher levels of prolactin (carotid IMT 5.87 ± 0.78 mm vs 6.47 ± 1.24 mm, P-value = 0.023), an association that remained significant even after adjusting for age and BMI. Measures of PWV did not exhibit a significant difference between high vs low levels of prolactin; instead, we confirmed a direct linear independent association (PWV, b-coefficient = 0.370, P-value = 0.013) in a model adjusted for age, BMI, pulse pressure, HOMA-IR and lipids. Higher levels of prolactin were associated with lower levels of glucose (78.9 ± 6.2 mg/dl vs 85.2 ± 9.5 mg/dl, P-value = 0.025), almost significantly lower values of HOMA-IR (1.17 ± 0.29 vs 1.56 ± 0.70, P-value = 0.058). Women with prolactin levels in the 4th quartile vs 1st quartile presented with higher levels of HDL-cholesterol (69.0 ± 11.8 mg/dl vs 60.13 ± 9.80 mg/dL, P-value = 0.027) and almost significantly lower levels of LDL-cholesterol (93.2 ± 25.3 mg/dL vs 113.8 ± 32.8 mg/dL, P-value = 0.056).
Conclusions
High levels of prolactin within the normal range in non-lactating pre-menopausal women are associated with a beneficial impact on carotid IMT and an adverse effect on arterial stiffness. Moreover, higher levels of prolactin are also associated with improved levels of insulin resistance and blood lipids.

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GP121

The A allele of the rs4636297 (G/A) polymorphism in the microRNA-126 is associated with protection for diabetic retinopathy

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Background and aims
Diabetic retinopathy (DR) is an important chronic complication of diabetes mellitus (DM), and is the leading cause of new cases of blindness in adults. Although several single nucleotide polymorphisms (SNPs) have been associated with DR, more information is needed to unravel the genetics of this complex disease. MicroRNAs (miRNAs) are a class of small noncoding RNAs that regulate expression of at least 60% of all protein-coding genes. A number of miRNAs have been described as having abnormal expressions in patients with DR, including miRNA-126, which regulates endothelial cell response to VEGF, an important pro-angiogenic growth factor involved in DR pathogenesis. Polymorphisms in genes codifying miRNAs (miRSNPs) may alter the expression of the corresponding miRNA and, thus, confer susceptibility for DR. Therefore, miRSNPs in miR-126 gene could be associated with DR susceptibility. Therefore, the aim of this study was to investigate the association between the rs4636297 (G/A) miRSNP in miRNA-126 gene and DR.
Methods
This case-control study comprised 196 type 1 DM (T1DM) patients with DR (cases) and 219 T1DM patients without this complication and with ≥ 10 years of DM (controls). The rs4636297 miRSNP was genotyped by allele discrimination – real-time PCR technique, using TaqMan MGB probes (Thermo Fisher Scientific).
Results
Genotype distributions of the rs4636297 miRSNP were in Hardy-Weinberg equilibrium in controls. The A allele frequency was 40.0% in cases and 46.0% in controls, and this allele was associated with protection for DR under recessive (OR $=0.294$, $P=0.032$), additive (OR $=0.087$, $P=0.001$), and dominant (OR $=0.348$, $P<0.001$) inheritance models, adjusting for age, presence of hypertension, diabetic renal disease, and cholesterol levels.
Conclusion
Our results suggest for the first time in a Brazilian population, an association between the A of rs4636297 miRSNP in the miR-126 gene and protection for DR.

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GP122

Vitamin D supplementation and dynamics of LDF skin microcirculation in patients with diabetes mellitus and diabetic polyneuropathy

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Hypothesis
High doses of vitamin D (VitD) improves dermal microcirculation (MC) in diabetic patients with type 2 diabetes mellitus (T2DM) and diabetic neuropathy (DN).
Purpose
To study the effect of different VD doses on skin MC values in T2DM patients and DN.
Materials and methods
Sixty-two non-smoking T2DM patients with DN were randomized into two groups: Group 1 received 5000 IU (G1) and Group 2 received 40000 IU (G2) of cholecalciferol per week. Inclusion criteria included HbA1c up to 9.0%, neuropathy disability score (NDS) of 4 and higher. MC parameters (value of perfusion – M, standard deviation of blood flow – σ and Kv - coefficient of microcirculation, %) were assessed by Laser Doppler Fluorometry (LDF) (LAKK-M, Russia); two functional tests: postural (blood flow reduction rate was calculated - BFR) and occlusion (capillary blood reserve index was calculated - CBR), 25(OH)D were studied at baseline and after 24 weeks. The MC values of control healthy subjects (Group 3; G3) were used for comparison.
Results
The clinical characteristics of patients werecomparable (G1: $n=31$; age 52.4 ± 5.7, BMI 30.2 ± 4.3; serum 25(OH)D $28.0\pm16,9$ (units); HbA1c $7.6\pm0.8\%$ and G2: $n=31$; age 51.4 ± 6.1; BMI 31.1 ± 4.5; serum 25(OH)D 23.9 ± 7.9; HbA1c $7.7\pm0.9\%$; ($P>0.05$). G3 ($n=16$; age 51.8 ± 3.7; BMI 30.1 ± 2.7, 25(OH)D 29.11 ± 13.6) only difference was HbA1c level ($4.8\pm0.5\%$; $P=0.001$). The MC parameters in T2DM pts were significantly lower than in G3 ($M_{G1+2}=7.2\pm0.8$, & $M_{G3}=10.4\pm5$ ($P=0.007$); $\sigma_{G1+2}=3.1\pm0.4$ & $\sigma_{G3}=4.2\pm0.6$ ($P=0.013$); Kv_{G1+2} 35.2 ± 15.1 & $Kv_{G3}=40.3\pm14.5$ ($P=0.003$) respectively. No changes of MC were seen in G1 after treatment ($M=6.9\pm0.5$ & $M=7.3\pm0.4$; $\sigma=3.5\pm0.6$ & $\sigma=4.4\pm0.8$; Kv 34.7 ± 13.2 & $Kv=35.2\pm14.1$ ($P>0.05$). In G2 HbA1c decreased, 25(OH)D increased, all parameters of MC improved ($M=7.3\pm0.6$, & $M=8.7\pm0.9$ ($P=0.003$); $\sigma=3.4\pm0.3$ & $\sigma=5.3\pm0.7$ ($P=0.005$), $Kv=36.8\pm11.7$ and $Kv=38.1\pm12.1$ ($P=0.008$). The postural test was more informative due to good portability and ease of implementation and revealed lower baseline BFR in pts compared to G3 ($P=0.027$). Positive correlation between BFR, CBR and 25(OH)D after treatment was find only in G2 ($r=0.72$, $P=0.03$ & $r=0.85$, $P=0.02$, respectively).
Conclusions
High dose of VitD supplementation (40,000 IU/week) for 6 months in T2DM patients with DN was associated with HbA1c decrease and improvement in microcirculation parameters.

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GP123

Four out of five patients with type 2 diabetes mellitus have hearing loss

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Objectives
This study was undertaken to ascertain the prevalence of hearing loss (HL) in patients with Type 2 Diabetes (T2DM) and to understand its relationship with diabetic neuropathy.
Materials and Methods
Patients between the ages of 30 to 60 years (both ages inclusive) with T2DM were recruited and divided in two groups. Group 1 with moderate to severe distal sensory-motor neuropathy (Michigan Diabetic Neuropathy Score >12) or Group 2 were those with no neuropathy (MDNS score <6). Patients with mild neuropathy (MDNS score 6–12), history of intake of ototoxic drugs, ear surgery or infections, neurological disorders, Meniere's disease, head injuries, renal failure and with occupational exposure to loud noises were excluded. After informed consent HL was assessed with pure tone audiometry (PTA) for various frequencies (250Hz to 8000Hz).
Results
Of the 200 patients recruited (151 with neuropathy and 49 without) the prevalence of any hearing loss (AHL) was overall 81% with 85.5% prevalence among those with neuropathy and 66.6% among those without neuropathy ($P-0.004$). The prevalence of clinical significant hearing loss (CSHL) (moderate and above) was 28.5% (overall), 30.5% (with neuropathy) and 22.8% (without neuropathy ($P-0.28$). On univariate logistic regression with AHL in any ear as outcome, age, gender, taking regular ACE inhibitors, MDNS score, MDNS grade and presence of neuropathy was found to have significant correlation.On multivariate binary logistic regression with AHL in any one ear as outcome, age, gender, taking regular ACE inhibitors and MDNS score was found to have significant correlation.
Conclusions
Four out of five adult patients (30–60 years) with T2DM had some degree of HL on PTA. Of these one in three had CSHL. In addition to age and gender there was some association of HL with the degree of diabetic neuropathy.

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GP124

Unrecognized high risk for diabetic foot ulcer among hospitalized patients

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Aim
Loss of protective sensation (LOPS) commonly precede Diabetic foot ulcer (DFU) which is one of the most fearsome/serious diabetic complications and the

leading cause of foot amputation in T2D patients. However, the prevalence of this high risk state is unknown.
Methods
To estimate the presence of LOPS among hospitalized diabetes patients in internal wards, vibration perception and 10-g monofilament tests were done. Patients with foot ulcer or status post amputation were excluded.
Results
A total of 305 patients were tested. 165(54.1%) males and 140(45.9%) females. mean age was 70.3 ± 12.2 years old. The mean duration of diabetes was 12 years (IQR 6–20). Mean HBA1C was 6.8 (IQR 6.15–7.98). 79(25.9%) patients had known retinopathy and 68(22.3%) had known nephropathy. 150(49.1%) had LOPS (either abnormal monofilament test or vibration test or both). Patients with LOPS tend to be older 72.1 ± 11.8 vs 68.6 ± 12.6 years old, $P = 0.005$ (95% CI 0.53–0.657), had higher creatinine, 1.45 ± 1.1 vs. 1.38 ± 1.4, $P = 0.02$ (95% CI 0.513–0.641), lower albumin, 35.3 ± 5.1 vs. 36.9 ± 4.7, $P = 0.014$ (95% CI 0.518–0.647), lower hemoglobin, 11.5 ± 2.3 vs 12.3 ± 2.3, $P = 0.006$ (95% CI 0.527–0.655) and compelling significant higher RDW, 16.2 ± 2.1 vs 15.3 ± 2.2, $0 < 0.001$ (95% CI 0.583–0.708). Moreover, patients with LOPS tend to have abnormal feet pulses, $P = 0.001$ (95% CI 0.552–0.706). No significant correlation was found between LOPS and disease duration, insulin-treatment, background-diseases or hospitalization cause.
Conclusions
Half of the diabetic patients in internal wards have unrecognized LOPS, the leading cause for DFU. Some simple clinical measures are correlated with LOPS. This window of opportunity should be used to recognize these patients and take measures for DFU prevention.

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GP125

Vitamin D3 deficiency is associated with more severe insulin resistance and metabolic profile in patients with type 2 diabetes

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Introduction
Recently, vitamin D3 (cholecalciferol) deficiency has been considered as one of the factors for the development of type 2 diabetes mellitus (T2D) and metabolic syndrome (MS), which contributes to increased insulin resistance (IR) and reduced insulin secretion. The most pronounced vitamin D deficiency is observed in persons suffering from morbid obesity. The aim of this study was to assess IR, b-cell functional activity and metabolic profile parameters according to the 25 (OH) vitamin D3 (vitD3) status in patients with T2D.
Materials and methods
The study included 109 patients with T2D. All patients were divided according to the Endocrine Society clinical practice guideline for vitD3 status on 3 groups as follows: group 1 ($n = 11$) – no deficiency, with optimal level vitD3 (> 40 ng/ml); group 2 ($n = 38$) – vitD3 insufficiency (21–29 ng/ml); and group 3 ($n = 60$) – vitD3 which was determined as less than 20 ng/ml. The IR, b-cell functional activity were assessed as change C-peptide and HOMA-β (homeostasis model assessment-estimated β-cell function) which calculated using HOMA2 calculator (Diabetes Trials Unit, University of Oxford). Continuous variables were analyzed using one-way ANOVA with Tuckey Post Hoc test. Data with non-parametric distribution was analyzed using Kruskall-Wallis test. The significance level was considered significant at $P < 0.05$. Association between vitD3 amount and metabolic changes was assessed with univariate Pearson's correlation analysis.
Results
In patients with vitD3 deficiency we observed significantly higher C-peptide as compared to both other groups. The HOMA2 (3.29 ± 1.89 vs. 2.12 ± 0.71; $P = 0.049$) and HbA1c (9.11 ± 1.63 vs. 7.75 ± 1.06; $P = 0.016$) levels changes significantly only in vitD3 deficiency group as compared to patient with optimal vitD3 (group 1). Furthermore, in univariate Pearson's correlation analysis, only in vitD3 deficiency group we observed significant association between vitD3 amount and C-peptide ($r = -0.461$, $P < 0.001$), insulin sensitivity ($r = 0.370$, $P = 0.004$), HOMA2 ($r = -0.292$, $P = 0.023$), triglyceride-glucose index ($r = -0.318$, $P = 0.013$), HbA1c ($r = -0.317$, $P = 0.014$) and BMI ($r = -0.285$, $P = 0.027$) respectively. B-cell functional activity changes insignificantly and we did not found significant associations between vitD3 amount and metabolic parameters across all groups.
Conclusions
Our study demonstrated that vitD3 deficiency in patients with T2D associated with more severe IR, obesity and poor glycemic control as compared to optimal value or vitD3 insufficiency. From the other hand, we did not found significant relationships between vitD3 status and β-cell functional activity.

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GP126

Depression and associated risk factors in older adults with diabetes: the 2010–2011 Korean national health and nutrition examination survey

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Aims
Diabetes is an important health condition in the aging population. The risk of depression is increased in older adults and should therefore be screened and managed. Especially, it is important to early detect and improvement of depression in older adults with diabetes because it is associated with glucose control and development of diabetic complication. We evaluated the prevalence of depression in diabetic older adults and identified associated independent risk factors using data of the Korea National Health and Nutrition Examination Survey (KNHANES) 2010–2011.
Methods
This study was based on data from the Korea National Health and Nutrition Examination Survey, which was conducted by the Korean Ministry of Health and Welfare in 2010–2011. The research selected 2,843 older adults whose data of health condition and mental health exist and ages are older than 65, from the KNHANES 2010–2011. The variables included general characteristics, disease-related characteristics, anthropometric measurements and blood tests, and mental health results. Multiple logistic regression analyses was performed to examinate independent risk factors associated with depression in subjects.
Results
The prevalence of diabetes were 18.2% (518/2,843) in older adults. The prevalence of depression in older adults with diabetes was significantly higher (21.0%) than older adults without diabetes (14.7%), respectively ($P = 0.045$). There was no significant differences in sucidal idea, neuropsychiatry visiting experience during one year, and stress status. Independent risk factors associated with depression in older adults with diabetes were older age group (75–79 years; odds ratio (95% CI), 2.10 (2.01–3.24), ≥ 80 years; 2.14 (1.02–3.24)), diabetes duration ≥10 years (1.34 (1.31–3.62)), and increasing number of comorbid diseases (1; 1.13 (1.01–2.34), ≥2; (2.213 (1.03–3.01)).
Conclusions
The prevalence of depression in diabetic older adults was significantly higher compared to the older adults who do not have diabetes in Korea. Older age, longer diabetic duration, and increasing comorbid diseases were independent risk factors associated with depression. In the management of older adults with diabetes, an individualized approach is required that focus on early diagnose and improving of the depression.

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GP127

Genetic polymorphisms in patients with type 2 diabetes mellitus and coronary heart disease

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It is known that presence of certain genetic polymorphism plays important role in development of chronic complications in patients with type 2 diabetes (T2D).
Aim
To analyze distribution of VEGF G/C polymorphisms and PAI-1 4G/5G polymorphisms in patients with T2D and IHD.
Materials and methods
The following groups of studies were formed: 1 – 24 almost healthy people; 2 – 28 patients with prediabetes; 3 – 37 patients with T2D; 4 – 35 patients with T2D and IHD. Genetic study included qualitative *in vitro* detection of two alleles of VEGF (G/C) and PAI-1 (4G/5G) genes by polymerase chain reaction.
Results
Genotype G/C of the VEGF gene was associated with IHD in patients with T2D and was revealed in 26 out of 35 patients in group 4, which was 74.3%, compared to group of patients with T2D without accompanying IHD, where the heterozygous variant was registered in 4 out of 37 patients (10.8%) ($F = 0.1$, $P = 0.001$). C/C genotype was not registered in patients with IHD (0%), and was found in 15 patients without IHD (16.9%). When studying the genotype

distribution of the PAI-1 gene, taking into account the presence or absence of IHD, it was found that the presence of the 5G/5G genotype of the PAI-1 gene is the most typical for patients with type 2 diabetes in combination with IHD. This genotype was registered in 16 out of 35 patients with IHD, which was 46.7%, and in 5 out of 37 patients with DM2 without IHD (11.1%) ($\chi^2=9.1$, $P=0.003$). Based on the genotyping results, it was determined that the allele 4 is associated with the absence of IHD ($\chi^2=11.0$, $P=0.001$). This allele was registered in 48 cases in the absence of IHD and in 26 cases in the presence of IHD, allele 5 was registered in 26 cases in the absence of IHD and in 44 cases in the presence of disease.

Conclusion

Genotype G/G of VEGF gene is associated with reduced risk of IHD development ($P=0.024$) and absence of progression of renal dysfunction in case of type 2 diabetes ($P=0.002$). The 5G/5G genotype of the PAI-1 gene is associated with the development of IHD in patients with type 2 diabetes ($P=0.003$). The 4G allele is associated with the absence of IHD ($P=0.001$).

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GP128

Clinical and metabolic characteristics of a population of diabetic patients previously educated having fasted all month of Ramadan

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Introduction

The purpose of this study was to describe the clinical and metabolic characteristics of a population of diabetic patients previously educated and having fasted all month of Ramadan.

Methods

This is a prospective study that involved 140 patients who wish to fast the month of Ramadan (2016).They presented themselves at consultations dedicated to preparing diabetic patients wishing to fast, organized at the National Institute of Nutrition of Tunis (departement C). These patients were given an interview, a thorough clinical examination and a biological assessment and were well informed about the risks they face. They had the appropriate therapeutic adaptation (ADA recommandations of 2010), as well as an adequate hygiene and dietary education. We have totally banned fasting for unbalanced patients.

Results

Of the 140 patients, 102, all diabetics type 2,fasted all month of Ramadan. The average age was 56.83 ± 10.77 years. The sex ratio was 0.8.The average weight was 79.21 ± 14.08 kg. Diabetes was evolving since $8,4\pm6.8$ years on average. 20.4% of cases were insulin-dependent. 69% were unbalanced and fasted against medical advice. 26.5% were hypertensive and 27.46% were dyslipidemic. Mean systolic and diastolic arterial blood pressure was 12.71 ± 1.48 and 7.35 ± 0.78 mmHg, respectively. Fasting glucose averages and HbA1C were respectively 9.37 ± 3.68 mmol/l and 8.1 ± 1.58%. According to the glycemic equilibrium before fasting.Fasting blood glucose was respectively 7.82 ± 3.52 mmol/l in well-balanced patients and 10.09 ± 3.55 mmol/l in unbalanced ones. HbA1C was respectively 6.37 ± 0.45 mmol/l in well-balanced patients and 8.89 ± 1.26 mmol/l in unbalanced ones. The mean clearance of creatinine was 98.17 ± 21.37 ml/min. 4 cases of moderate hypoglycemia and 11 cases of hyperglycemia greater than 3 g/l were reported, but patients continued to fast. No other metabolic complication had occurred. After fasting, the average weight was 79.01 ± 14.19 kg. The systolic and diastolic arterial blood pressure averages were 12.74 ± 1.18 and 7.5 ± 0.7 mmHg, respectively. Fasting blood glucose and HbA1C were 8.99 ± 3.15 mmol/l and 8.1 ± 1.57%, respectively. Fasting glucose was 7.8 ± 2.22 mmol/l in balanced patients and 9.54 ± 3.36 mmol/l in unbalanced one. HbA1C values were 6.47 ± 1.01 mmol/l for balanced patients and 8.47 ± 1.37 mmol/l in unbalanced one. Mean creatinine clearance was 98.04 ± 21.88 ml/min.

Conclusion

In our population, the fasting of the whole month of Ramadan had been well tolerated with an improvement in the poorly balanced glycemic patients.Studies with larger numbers are needed to better characterize the effect of fasting on clinical and metabolic parameters.

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GP129

Efficiency of application of silicate sorbents in surgical treatment of patients with neuro-ischemic form of diabetic foot ulcer

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Aim

To investigate the clinical efficacy of the treatment of patients with neuro-ishemic diabetic foot ulcers (DF) by using sorption-antimicrobial nanocomposition based on silica sorbents.

Methods

Hydrophobic-hydrophilic sorption-antibacterial nanocomposition, offered for the treatment of ulcers and wounds, contains sorbents (nano-disperse silicon dioxide, polymethylsiloxane) and antibacterial components (decamethoxin, metronidazole). In this study 78 patients with a neuroishemic form of DF and purulent complications on the foot were treated. The control group consisted (CG) of 34 patients, and study group (SG)-44 patients. Groups were comparable. Patients in both groups received standard treatment. The criteria for treatment effectiveness were the presence of epithelization and the dynamics of microbial contamination of the wound.

Results

At the 3rd day of treatment no signs of epithelization were detected in any patient of both groups. At the 7th day of treatment, signs of epithelization appeared in both groups, with the frequency of detecting signs of wound healing in SG with 57.83% higher than in CG ($P<0.001$). The number of patients with signs of marginal epithelization in CG significantly (by 58.90%) increased by the 10th day of treatment. But in EG at the 10th day of treatment, the relative number of patients with signs of marginal epithelization exaggerated such in CG at 31.32% Although healing of wounds depends not only on the degree of regional epithelization, but also on microbial contamination, compensation of diabetes and the course of its complications, the use of sorbent stimulates the development of wound epithelization, which eventually improves ultimate healing ($P=0.0021$) wounds compared with this process in patients with CG.

Conclusions

The analysis of the dependence of the rate of development of boundary epithelization on the level of microbial contamination has been carried out. The negative correlation between the rate of edge epithelization of the wound against the level of microbial contamination, in other words, the direct linear dependence of the development of boundary epithelization on the "purity" of the wound. The use of sorbents leads to a rapid wound cleansing, which is determined by the likely reduction in the number of microbial contamination. Such cleaning contributes to a significant acceleration of the appearance of epithelization, which is a guarantee of healing of ulcers against the background of diabetes.

Keywords: diabetes mellitus, wound, antimicrobial sorbents, diabetic foot syndrome.

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Obesity

GP130

Glucagon activity in human adipose precursors

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Obesity is associated with increased and dysfunctional white adipose mass. In the past, pharmacological approaches have not yielded significant results in terms of stable weight loss. Glucagon-like peptide 1 receptor (GLP-1R) agonists (GLP-1RA) used for the treatment of type 2 diabetes have more recently been proposed as anti-obesity drugs due to their relevant effects on weight loss. Furthermore, dual agonists engaging both GLP-1R and glucagon receptor (GCGR) are under investigation for their marked effects on weight loss. However, the mechanisms underlying such effects still need to be clarified. Our group has recently demonstrated that liraglutide and GLP-1 interfere with the proliferative and differentiation ability of human adipose precursors, supporting a peripheral action of GLP-1RA on weight loss. In the present study, we investigated glucagon activity in an *in vitro* model of primary human adipose-derived stem cells (ASCs). Glucagon significantly inhibited ASC proliferation, in a dose and time-dependent manner, with a maximal effect at 3 days of culture (14.0%, 25.2% and 37.1% for 1-10-100 nM glucagon, respectively, $P<0.005$ ANOVA, $n=5$). When added during *in vitro*-induced adipogenesis, glucagon (1-10-100 nM) significantly

reduced intracellular lipid accumulation evaluated by specific intracellular lipid staining (−20%, −31%, −27%, $P<0.001$, ANOVA, $n=5$) and expression of mature adipocyte markers FABP4 (−49%, 73%, 62%, $P<0.001$ ANOVA, $n=5$) and HSL (46%, 54%, 37%, $P<0.001$ ANOVA, $n=5$), respectively. Notably, the inhibitory effect of glucagon on both cell proliferation and adipogenesis was reverted by specific GLP-1R (exendin-9) and GCGR (des-His1-Glu9-glucagon (1–29)) antagonists. In conclusion, we demonstrated a direct inhibitory action of glucagon on the proliferation and differentiation ability of human adipose precursors, which seems to involve both GLP-1R and GCGR present on ASCs. In addition to the previously demonstrated lypolitic activity of glucagon on the mature adipocyte, our data suggest that the adipose stem compartment also is a target of glucagon, possibly contributing to the weight loss obtained with the dual activity molecules.

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GP131

A Study of the Effect of Laparoscopic Mini Gastric Bypass Versus Sleeve Gastrectomy On Obese Type 2 Diabetic Patients

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Recent guidelines on diabetes treatment provide that bariatric surgery should be the most logical & cost-effective means of controlling Type 2 diabetes.

Objectives

To compare laparoscopic mini-gastric bypass vs laparoscopic sleeve gastrectomy regarding the efficacy of control of D.M in obese patients.

Summary

A randomized controlled study conducted on 60 obese patients with type 2 D.M divided into, group (1): 30 patients treated by laparoscopic Sleeve gastrectomy (SG), group 2: 30 patients treated by laparoscopic Mini-Gastric Bypass (MGB). They were Type 2 Diabetic patients, above 18 years, (BMI) ≥ 30 kg/m^2, willing to sign an informed consent & comply with the follow up schedule. All patients were subjected to History taking, physical examination, laboratory & imaging investigation. The study was approved by the ethical committee of the faculty of medicine.

Key messages

The MGB group had greater FBG reduction (37.80 ± 6.41 mg/dl) vs (29.93 ± 12.84 mg/dl) in SG group and this was statistically significant (P value <0.004). The mean HBA1c drop after one year in MGB ($2.33 \pm 0.48\%$) vs ($2.01 \pm 0.59\%$) in SG group which was statistically significant ($P<0.024$). In the MGB group, diabetes resolution at 6 months was 46.7% vs 20% in the SG.

Conclusion

MGB has better& earlier effect than SG in diabetes remission. OHG, C peptide >3 ng/ml and diabetes duration <5 years are considered independent significant predictors for diabetes resolution.

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GP132

Variants in genes of the leptin / melanocortin pathway are involved in 3% of cases of early-onset severe obesity

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The leptin/melanocortin pathway plays a critical role in hypothalamic control of food intake. Variants in the genes involved in this pathway, such as leptin (LEP), its receptor (LEPR), proopiomelanocortin (POMC) or proconvertase 1 (PCSK1) are associated with early-onset severe obesity and endocrine abnormalities especially in case of homozygosity. Heterozygous variants in the melanocortin-4 receptor (MC4R) gene are associated with an increased risk of severe obesity. The aim is to describe the frequency of variants in the genes of the leptin/melanocortin pathway in obese children and adults consulting in a reference center. The coding eons of the LEP, LEPR, POMC, PCSK1 et MC4R genes were sequenced by Sanger. The 6100 patients included had severe obesity (BMI >35 kg/m^2 for adults and BMI Zscore $>+2.5$ s.d. for children). MC4R was sequenced in 5815 subjects, LEPR in 1180 patients, LEP in 800 patients, POMC in 556 patients and PCSK1 in 288 patients. The frequency of homozygous variants was $\leq 1\%$ with 13 (1.02%) variants in *LEPR* (p.C604G, p.L786P, p.H800_N831del, p.Y422H p.T711N, p.535-1G>A, p.P166CfsX7, p.Met1X), 3 (0.4%) variants in *LEP* (p.Q55X, p.R105W, p.V94M), 1 variant in *PCSK1* (0.4%) (c.286-2A>G), 3 variants in *POMC* (0.6%) (p.R75Profs*44; p.E214G; p.D53G) et 7 variants in *MC4R* (0.12%) (p.R165Q, p.S127L, p.C277X, p.V166I, p.C271R, p.I170V). Homozygous patients developed severe early-onset obesity (before the age of 3y) with major hyperplasia and associated endocrine phenotypes. The frequency of heterozygous variants was 2–3% for POMC, *MC4R* and *LEPR* whereas it was less than 2% for *PCSK1* (1.4%) and *LEP* (0.5%). The presence of one heterozygous variant with functional consequence in these genes was always associated with early-onset obesity (before the age of 10y) without endocrine abnormalities. Four patients had heterozygous combined variants on two genes in the pathway suggesting a cumulative effect. Our work confirms the implication of variants in genes of the leptin/melanocortin pathway in early-onset severe obesity (2-3% of patients with severe obesity) and is currently expanded to other genes modulating this pathway. This screening is critical because now effective therapeutic options by MC4R agonist (setmelanotide) exist and can restore the melanocortin signal despite its interruption in case of variants. Development of clinical tools helping for diagnosis and NGS molecular tests extended to other genes involved in the pathway will help to diagnose patients candidates for this novel therapeutic.

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GP133

Effect of IL1-receptor antagonist on renin-angiotensin-aldosterone system and hemodynamics in obese individuals

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Background

Interleukin (IL)-1 antagonism decreases systolic blood pressure in obese individuals. However, the underlying mechanism is unknown. Based on experimental data in animals we hypothesised a blood-pressure lowering effect of IL-1-antagonism via modulation of the renin-angiotensin-aldosterone system (RAAS).

Methods

In this post-hoc explorative study, we examined short- (2 days) and long-term effects (4 weeks) of IL-1 antagonism (anakinra/Kineret®) on RAAS-peptide-profiles and on hemodynamic parameters assessed by a non-invasive measurement using HOTMAN® system. In total, 128 obese (BMI $>$ 30kg/m^2) individuals with at least one feature of the metabolic syndrome from two previous interventional trials (CortIL trial a prospective interventional trial ($n=61$) and TestIL trial, a placebo controlled-double blinded interventional trial ($n=67$)) were evaluated.

Results

Upon IL-1 antagonism circulating levels of angiotensin II, angiotensin I, aldosterone and renin remained unchanged after short- and long-term treatment, respectively. In contrast, the vasodilatory angiotensin (1–7) peptide significantly increased after 4 weeks compared to placebo (in between group difference 16.35 pmol/L [1.22 to 30.17], $P=0.03$), without short-term effect on day 2. Concurrently, angiotensin (1–7) /angiotensin II-ratio significantly increased after 4 weeks in the anakinra-group compared to placebo (in between group difference 0.42 pmol/L [0.17 to 0.67], $P=0.02$). Non-invasive hemodynamic measurement revealed a decrease in the stroke systemic vascular resistance index (SSVRI) with an in between group difference of -62.65 dyn.sec.cm-5.m^2 [95% CI -116.94 to -18.36], $P=0.008$ (consistent with a 25%-decrease) after 4 weeks of treatment compared to baseline.

Conclusion

IL-1 antagonism increased the vasodilatory angiotensin (1–7) peptide after 4 weeks of treatment in obese individuals with features of the metabolic syndrome. This was consistent with a decrease in peripheral vascular resistance, reflected by the SSVRI. Thus, these findings point to a possible IL-1 mediated blood pressure lowering mechanism via modulation of the RAAS-System.

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GP134

Higher habitual intakes of dietary carbohydrates are associated with leptin gene expression in visceral and subcutaneous adipose tissues among non-diabetic people

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Introduction
Leptin is a well-known adipokine which has a critical role in the regulation of body weight, body fat mass, appetite, and food intakes. Energy-supplying nutrients such as carbohydrates is a dietary-related factor which has potential effects on plasma leptin levels. The effect of habitual carbohydrates intake on leptin gene expression was limited only in animal studies. The current study aimed to investigate the association of habitual carbohydrate intake with leptin gene expression in visceral and subcutaneous adipose tissue of non-diabetic adults.
Methods
In this cross-sectional study, visceral and subcutaneous adipose tissues were gathered from 102 participants aged ≥ 20, who had undergone elective abdominal surgery with minimal impact on dietary intake. All of the subjects were free of diabetes and cancers and without using anti-lipid medication. Habitual dietary intake of participants was collected before surgery using a reliable validated semi-quantitative food frequency questionnaire, and daily intake of carbohydrates including total carbohydrates, fiber, glucose, fructose, and total sugar were calculated. To adjust energy intake for dietary exposures, the residual method was used. The mRNA expressions of leptin gene in visceral and subcutaneous adipose tissues were measured by real-time quantitative PCR. Linear regression models were used to estimate dietary carbohydrate intake and leptin gene expression after adjustment for potential confounding variables.
Results
The mean age and body mass index (BMI) of participants was 41.7 years and 25.6 kg/m^2, respectively. Leptin mRNA expression in visceral was higher than subcutaneous adipose tissue (0.375 vs. -1.210, $P=0.891$). After adjusting for age, BMI, and insulin level, total carbohydrate intake was positively associated with leptin gene expression in visceral and subcutaneous adipose tissue ($\beta=0.484$ and 0.522, respectively). Usual intake of sugar ($\beta=0.425$, $P<0.001$), glucose ($\beta=0.323$, $P=0.004$), and fructose ($\beta=0.336$, $P=0.003$) was directly associated with leptin gene expression in subcutaneous fat depots, additionally, we found significant positive association between leptin expression in visceral adipose tissue and sugar ($\beta=0.377$, $P=0.001$), fructose ($\beta=0.263$, $P=0.018$), and glucose ($\beta=0.242$, $P=0.034$). However, dietary intake fiber was negatively associated with leptin mRNA expression in both subcutaneous ($\beta=-0.391$, $P=0.001$) and visceral ($\beta=$-0.330, $P=0.007$) adipose tissues.
Conclusions
There was the significant positive association of total carbohydrate, sugar, fructose, and glucose and inverse association of fiber on leptin gene expression in subcutaneous and visceral fat mass, independent of BMI, age and insulin level. This might provide an initial step towards understanding nutrient effects on energy homeostatic pathways to consider future clinical approaches to dietary weight loss interventions.

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GP135

Obesity is associated with a downregulation of UCP2 and miR-133a-3p but not NLRP3 in subcutaneous adipose tissue

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Background and aims
Obesity is a chronic multifactorial disease characterized by an excessive accumulation of body fat resulting from an imbalance between energy intake and caloric expenditure. Uncoupling protein 2 (UCP2) is located in the inner mitochondrial membrane and plays an important role in the regulation of energy expenditure. NLR family, pyrin domain-containing 3 (NLRP3) inflammasome seems to have a key role in obesity-induced inflammation through production of the pro-inflammatory cytokines IL-1β and IL-18. Accordingly, a number of studies have suggested that *UCP2* and *NLRP3* have important roles in obesity. In addition, the microRNA (miR)-133a-3p regulates *UCP2* expression and appears to be involved in the activation of NLRP3 inflammasome through *UCP2* blockade. However, to date, no study has evaluated the combined association of *UCP2*, *NLRP3* and miR-133a-3p expressions with obesity. Thus, we compared *UCP2*, *NLRP3* and miR-133a-3p expressions in subcutaneous adipose tissue (SAT) of patients with obesity and eutrophic individuals. We also evaluated if these genes correlate with body composition parameters, insulin resistance, and glycemic and lipid profiles.
Methods
SAT biopsies were obtained from 61 individuals who underwent bariatric surgery or elective abdominal surgery. Patients were divided into three groups according to body mass index (BMI): Group 1 (BMI $\leq$ 25 kg/m^2, $n=8$); Group 2 (BMI: 30.0 – 39.9 kg/m^2, $n=24$); and Group 3 (BMI $\geq$ 40 kg/m^2; $n=29$). All subjects underwent physical and laboratory evaluations. *UCP2*, *NLRP3* and miR-133a expressions were quantified using real-time qPCR.
Results
UCP2 expression was decreased in SAT from patients with obesity (Groups 2 + 3) compared to Group 1 [Group 3: median 1.1 (0.9 – 1.6, 25th – 75th percentiles) and Group 2: 1.2 (0.9 – 1.5) *vs*. Group 1: 2.2 (1.6 – 2.5) n-fold changes; $P=0.031$]. MiR-133a-3p expression was also downregulated in patients with obesity [Group 3: 1.6 (0.9 – 2.5) and Group 2: 0.9 (0.5 – 8.5) *vs*. Group 1: 13.5 (3.5 – 33.2); $P=0.029$]. *NLRP3* expression did not differ between groups ($P=0.238$); however, it was positively correlated with waist circumference and weight excess. *NLRP3* expression was also positively correlated with miR-133a-3p expression and negatively correlated with *UCP2* expression.
Conclusion
UCP2 and miR-133a-3p expressions are downregulated in patients with obesity. Although *NRLP3* expression did not differ between groups, it was positively correlated with waist circumference and weigh excess values.

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GP136

Administration of a growth hormone bolus down-regulates gene-expression of the g0/g1 switch gene 2 (g0s2) in subcutaneous adipose tissue in healthy, obese men: a randomized, placebo-controlled, cross-over study

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Background
Growth hormone (GH) potently stimulates lipolysis, and after GH exposure, levels of serum free fatty acids (FFAs) increase in a distinct temporal pattern characterized by a 1-hour lag phase and a peak after 3 hours followed by a gradual return to baseline. This effect predominantly operates during fasting and promotes utilization of lipids from adipose tissue (AT) at the expense of glucose and protein. Prolonged fasting also downregulates the expression of the G0/G1 switch gene 2 (G0S2), which is a suppressor of the adipose triglyceride lipase (ATGL). The molecular mechanisms underlying the lipolytic effect of GH, including putative effects on G0S2, remain elusive.
Aim
To study expression of the lipolytic regulators in consecutive human AT biopsies after a GH bolus.
Methods
In a randomized, placebo-controlled, cross-over study nine healthy, obese men were examined on two occasions: 1) after an IV GH bolus [GH], and 2) after injection of a GH receptor antagonist [control]. Serum FFAs were measured. Biopsies from subcutaneous AT were obtained at $t=0$, $t=60$, $t=180$, and $t=300$ min, and gene and protein expression of putative lipolytic regulators were studied by RT-qPCR and western blotting.
Results
Serum FFAs increased 1 hour after GH exposure and peaked after 3 hours. In AT, we recorded phosphorylation of signal transducer and activator of transcription 5 (STAT5) after 1 hour and increased genexpression of cytokine-inducible SH2-containing protein (CISH) and insulin-like growth factor-1 (IGF-1) after 3 hours, indicative of GH signaling. Furthermore, GH exposure suppressed gene expression of the ATGL inhibitory protein G0S2 in addition to upregulation of PTEN, a known suppressor of insulin-stimulated anti-lipolysis.

Conclusions
1) An intravenous GH bolus acutely induces GH receptor signaling in human AT in vivo. 2) This was associated with a significant increase in serum FFA levels after 1-3 hours and the underlying mechanisms involves suppression of anti-lipolytic signaling in AT. 3) Characterization of the targets for GH-induced lipolysis may have physiological and therapeutic implications.

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GP137

Empagliflozin as well as Anakinra reduce symptomatic hypoglycemia in patients after Roux-Y-gastric bypass by lowered insulin secretion

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Background
Postprandial hypoglycemia is an increasingly recognized complication after bariatric surgery. Its hallmark is a pronounced glycemic rise after carbohydrate ingestion followed by an exaggerated hyperinsulinemic response. Recent studies have shown that IL-1β contributes to postprandial stimulation of insulin. Furthermore, inhibition of SGLT2 reduces excessive plasma glucose increase. Therefore, we investigated whether inhibition of IL-1β with the IL-1 receptor antagonist anakinra or inhibition of SGLT2 with empagliflozin may reduce postprandial hypoglycemia.
Methods
We performed a placebo controlled, double-blind, randomized, cross-over proof-of-concept study with 12 subjects with confirmed postprandial hypoglycemia after gastric bypass. Subjects received on each of the 3 study days either empagliflozin p. o. or anakinra s. c. along with the respective placebos followed by a standardized liquid mixed-meal-test over three hours with regular clinical assessments and measurement for glucose, insulin, c-peptide, GLP1, glucagon and inflammatory parameters.
Results
Compared to placebo, empagliflozin reduced peak glycaemia at 30 (11.2 vs. 10.1 mmol/l), 60 (9.1 vs. 6.9 mmol/l) and 90 (4.5 vs. 3.5 mmol/l) minutes after ingestion of the mixed meal and was followed by a significant reduction of glucose-requiring hypoglycemic events ($n=2$, 16.6% vs. $n=8$, 61.5%, p-value 0.041). Similarly, treatment with anakinra also reduced the rate of glucose-requiring hypoglycemic events ($n=2$, 16.6%) compared to placebo ($n=8$, 61.5%). Anakinra (AUC 63,458) and empagliflozin (AUC 55,116,) significantly lowered insulin secretion compared to placebo (AUC 80,029). Glucagon and GLP1 levels remained unchanged.
Conclusion
Empagliflozin and anakinra prevented glucose-requiring hypoglycemic episodes in patients after Roux-Y-gastric bypass by decreased insulin secretion via two different mechanisms. Empagliflozin by preventing an excessive postprandial rise in glycemic rise and anakinra may exert direct inhibitory effects on insulin secretion.

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GP138

Androgen metabolism during weight loss in men with obesity

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Background
Men with obesity often have low total and, with increasing adiposity, also free testosterone (T) levels, which can partially restore when they lose weight. Although this is in part explained by lower sex-hormone binding globulin (SHBG) production and hypothalamic-pituitary downregulation, it is still not fully unraveled whether changes in androgen metabolization contribute to this phenomenon.
Aim
Investigating metabolisation of sex steroids during weight loss in men with obesity.
SUBJECTS AND METHODS
Eleven obese men (age 49 ± 10 years, BMI 44.9 ± 5.0 kg/m^2) were recruited prior to adhering dedicated lifestyle changes ($n=1$) or undergoing gastric bypass surgery ($n=10$). Before start of weight loss and 3 weeks, 6 weeks, 6 months and 1 year thereafter, 24h urine collections and fasting serum samples were collected. Serum T and estradiol (E_2) levels were analyzed using LC-MS/MS and serum SHBG concentrations using immunoassays. Urinary T, 3α-androstanediol, androsterone, 3α-etiocholanediol, etiocholanolone, estrone, E_2 and estriol levels were analyzed using gas chromatography coupled to mass spectroscopy. Statistical analyses were performed using linear mixed modelling.
Results
Obese men significantly reduced their BMI through this one-year follow-up study with a mean BMI of 30.3 kg/m^2 after one year ($F(4, 9.173)=139.105$, $P<0.001$). Serum T and SHBG concentrations increased by 102% and 87%, respectively (both $P<0.001$), while serum E_2 levels decreased non-significantly ($P=0.129$). A significant increase of total urinary T concentration was observed during follow-up ($F(4, 29.112)=4.529$, $P=0.006$), with a total increase of 101% one year after start of weight loss ($P=0.001$), while the ratios E_2/T and estriol/T decreased ($P=0.001$ and $P=0.010$; respectively) suggesting lower relative aromatization. In addition, T metabolisation by 5α-reductase and 3α-hydroxysteroid dehydrogenase (HSD) reflected by 3α-androstanediol/T- and androsterone/T-ratio, decreased during follow-up ($P=0.006$ and $P=0.002$; respectively) whereas 3α-etiocholanediol/T-ratio and etiocholanolone/T-ratio, reflecting T metabolisation from the 5β-reductase and 3α-HSD pathway, showed a non-significant decrease ($P=0.065$ and $P=0.070$; respectively).
Conclusion
Restoration of T levels into the eugonadal range during weight loss in men with obesity is not only brought about by normalization of circulating SHBG levels but also by increased T production *per se* as reflected by increased urinary secretion of T. In addition, changes in these men's urinary steroid profile, suggest that alterations in T metabolization also contribute to this. More specifically, besides relatively higher aromatization, higher 5α-reductase and 3α-HSD activity might also play a role in the phenomenon of low T levels in men with obesity.

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GP139

Prediction of clinically significant weight loss with Gelesis100 in the GLOW study as early as 8 weeks post-treatment

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Introduction
Identification of early responders is widely used in pharmacotherapy for weight loss to minimize unnecessary exposure to risks and unnecessary expenses. Gelesis Loss Of Weight (GLOW; NCT02307279), a multicenter, double-blind, placebo-controlled pivotal study, demonstrated that Gelesis100 offers a compelling new potential approach in the management of overweight and obesity.
Objective
A post-hoc area under the curve (AUC) for the receiver operating characteristic (ROC) analysis was conducted on data from the GLOW study to identify the optimal timepoint for predicting body weight responders ($\geq 5\%$ body weight loss at Week 24).
Material and methods
An AUC of the ROC was completed as a post-hoc analysis to model the predictive power of early weight loss for responder status in 322 subjects who were

treatment completers. The AUC ROC analysis optimized the balance between the positive predictive value (PPV) or percent of subjects with early weight loss response who were body weight responders and the negative predictive value (NPV) or percent of subjects with early weight loss response who were not body weight responders. The cutoff for PPV and NPV was set at 80%.
Results
AUC ROC analysis showed that an early response to Gelesis100 treatment ($\geq$ 3% weight loss from baseline at Week 8) successfully predicted clinically meaningful weight loss ($\geq$ 5%) at Week 24. More than 85% of subjects who achieved $\geq$ 5% weight loss at Week 24 had lost $\geq$ 3% of body weight at Week 8. Notably, early responders ($n=93$) achieved a mean weight loss of 9.9% vs. 2.1% in non-early responders ($n=77$) at Week 24. The placebo arm did not reach the required threshold for sensitivity and specificity until near the end of treatment. Safety and tolerability of Gelesis100 in the early responders were similar to the non-early responders, except for the incidence of abdominal pain that was higher in the early responders ($P=0.0415$) but of mild intensity in the majority of cases, and demonstrated no increased risk compared to placebo. No serious adverse events were observed.
Conclusion
The results of AUC ROC analysis suggest that a weight loss of $\geq$ 3% as early as 8 weeks after treatment with Gelesis100 is predictive of clinically meaningful weight loss ($\geq$ 5%) after 24 weeks. Although there are no overall increased safety risks with Gelesis100 treatment, predicting successful treatment early allows efficient use of resources and provides a key milestone to motivate subjects with overweight or obesity for personalized care.

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GP140

The efficacy of complex kinesiotherapy in weight loss and muscle function improving in obesity patients

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Aim of the study was to estimate the effect of complex 3-week treatment with 4 kinesiotherapy methods on body weight loss and muscle function in patients with obesity.
Material and methods
80 men and women aged 21-69 years old with alimentary obesity were enrolled in the study (mean age 52.4$\pm$11 years, weight 111.3$\pm$24.5 kg, BMI 40.3$\pm$8.1 kg/m^2, waist circumstance WC 113.4$\pm$16 cm, hip circumstance HC 124.2$\pm$16 cm). The complex kinesiotherapy administered daily for 3 week and included interactive sensorimotor trainings on double unstable platform, kinesiohydrotherapy in a pool, special complex of physical exercises in a gym and ergocycle trainings. Weight, WC, HC, fall number for last 3 weeks were measured at baseline and after the treatment was completed. Muscle strength and walking speed functional tests results assessment (10-meters-walk test, Up-and-go test, 4 special tests for back and abdomen muscle endurance to static and dynamic loading) were performed at baseline and in 3 weeks.
Results
There was a significant reduction in body weight (111.3$\pm$24.4 kg at baseline vs 107.9$\pm$23.1 kg in 3 weeks; $P=0.000$), in BMI (40.3$\pm$8.1 vs 39.1$\pm$7.7 kg/m^2; $P=0.000$), in WC (113.4$\pm$15.9 vs 109.2$\pm$15.1 cm; $P=0.000$) and in HC (124.1$\pm$15.5 vs 119.7$\pm$14.1 cm; $P=0.000$) in treated obese patients. 10-meters-walk speed increased from 0.84$\pm$0.15 m/sec at baseline to 0.88$\pm$0.17 m/sec in 3 weeks ($P=0.000$). Up-and-go test results improved from 8.4$\pm$2.1 to 7.9$\pm$2.09 sec ($P=0.000$). We registered statistically significant elevation of the endurance to static loading in abdomen muscles from 13.1$\pm$9.7 to 16.49$\pm$12.8 sec ($P=0.000$) and in back muscles from 14.8$\pm$11.9 sec to 18.6$\pm$14.9 sec ($P=0.000$). The endurance to dynamic loading increased in abdomen muscles from 29.9$\pm$11.2 to 34.84$\pm$11.93 times ($P=0.000$) and also in back muscles from 9.1$\pm$7.4 to 12.2$\pm$9.2 times ($P=0.000$). Fall number markably decreased from 0.14$\pm$0.34 at baseline to 0.0 (95%CI: 0.02; 0.25) aftercompletionof treatment.
Conclusions
Investigated complex treatment with 4 kinesiotherapy methods promotesbody weight loss, WC and HC reduction in obesity. 3-week special training of obese patients is associated with increasing in gate speed and lower extremities muscle strength, and it also causes improvement in static and dynamic loading endurance of back and abdomen muscles. Those changes may probably improve balance function and decrease risk of falling in obese patients.
Keywords: obesity, fall number, static and dynamic endurance

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GP141

Dietary inflammatory index is differently associated with ectopic fat depots in overweight and obese adults

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Introduction
In overweight and obesity energy unbalance is responsible for the accumulation of ectopic fat. Excess energy and metabolic alterations, namely insulin resistance, may favor ectopic fat depositions. However, the role played by dietary factors, especially the pro-inflammatory properties of dietary patterns, in ectopic fat storage is not thoroughly understood. The aim of our study was to investigate the association between the Dietary Inflammatory Index (DII) and different ectopic fat depots.
Methods
Participants were recruited among subjects admitted to the High Specialization Centre for the Care of Obesity (CASCO), at the Sapienza University, Rome, Italy. Inclusion criteria were: age 18-75 years, body mass index (BMI) $\geq$ 25 kg/m^2. The intrahepatic lipid content (IHL) and the intramyocellular lipid content (IMCL) were assessed through magnetic resonance spectroscopy, whereas intermuscular adipose tissue (IMAT, as adipose tissue between skeletal muscle bundles and beneath the muscle fascia), visceral and subcutaneous adipose tissue (VAT and SAT) were evaluated by magnetic resonance imaging. 3-day dietary records were administered and analyzed by a registered dietician. The DII score (adjusted for energy density) and the HOMA-IR were calculated. High-sensitivity C-reactive protein (hs-CRP) was measured.
Results
77 subjects (males: 18%) were included (age: 47.7$\pm$13.5 years, BMI: 37.1$\pm$5.7 kg/m^2). The DII score was positively associated to IHL (beta: 0.221, SE: 0.101, $P=0.03$) and IMAT (beta: 0.140, SE: 0.066, $P=0.04$) after adjustment for age, sex, hs-CRP levels, HOMA-IR, and VAT. No associations emerged between DII score and IMCL or VAT, or SAT.
Conclusion
A more pro-inflammatory dietary pattern is associated with fatty liver, and intermuscular adipose tissue, but it does not seem to affect intramyocellular lipid storage.

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Interdisciplinary Endocrinology 1

GP142

Impact of age and metabolic profile on the definition of 12 circulating steroid reference intervals measured by LC-MS/MS in an Italian healthy adult male cohort

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Background
Steroid profiling by LC-MS/MS is increasingly used in endocrine research, and is being introduced in the clinical practice. Due to the large disagreement with previous immunoassays, and to the enlarged panel of measurable steroids, novel and robust reference intervals (RIs) need to be established. Steroid circulating levels are known to be influenced by several physio-pathological factors, such as age, gender, stress and metabolic status. Therefore, generating unbiased reference cohorts is a non-trivial task.
Objective. Aiming at estimating robust and age-specific RIs for a broad steroid panel, our study evaluated the impact of aging and of the metabolic status on steroid levels in a cohort of disease-free adult men.
Methods. After excluding previous or current diseases, 318 drug-free men aged 18-90y were selected from the Italian general population. Blood was withdrawn in fasting conditions at 8-10am after 10min saline infusion. Cortisol (F) 11-deoxycortisol (11S), 17-hydroxyprogesterone (17OHP4), 17-hydroxypregnenolone (17OHP5), testosterone (T), androstenedione (A4), dheidroepiandrosterone (DHEA), dihydrotestosterone (DHT), progesterone (P4), corticosterone (B), estrone (E1) and estradiol (E2),were measured by two validated in-house LC-MS/MS assays. Anthropometric and metabolic parameters were analyzed by multiple stepwise-regression to estimate their independent impact of on each steroid. For steroids varying with ageing, decade-specific 2.5-97.5 centile RIs were calculated by fractional polynomial regression. For steroids influenced by

metabolic parameters, we excluded subjects displaying BMI $\geq$ 25.0kg/m^2, waist circumference $>$ 88 cm, systolic/diastolic blood pressure $\geq$ 90/140mmHg, HOMA-IR $>$ 2.5 or total-cholesterol/HDL-cholesterol $>$ 5.
Results. Aging negatively impacted 17OHP4, 17OHP5, A4, DHEA, P4 and B (all $P<0.001$), F ($P=0.015$) and 11S ($P=0.006$), while not influencing T, DHT, E1 and E2 levels. BMI positively influenced E2 ($P=0.031$), while negatively associating with 17OHP4 ($P=0.002$), T ($P=0.045$), DHT ($P=0.003$) and P4 ($P=0.023$). Waist circumference directly associated with E1 ($P=0.012$), while inversely associated with F ($P=0.004$). HOMA-IR negatively associated with T ($P=0.002$). Blood pressure positively associated with E1 ($P=0.034$). Finally, total-cholesterol/HDL-cholesterol ratio negatively associated with B ($P=0.001$) and 17OHP5 ($P=0.024$). According to regression results, age-specific RIs were generated on the whole cohort for 11S, A4 and DHEA, and after excluding subjects displaying metabolic abnormalities for F, B, 17OHP4, 17OHP5 and P4. At variance, age-independent RIs were estimated for T, DHT, E1 and E2 in the sub-cohort with no metabolic abnormalities. This study provided LC-MS/MS-based, age and metabolism-adjusted male RIs for a panel of circulating steroids, allowing the effective application of this technique in clinical investigations and in the diagnostic workup of diseases related to steroidogenesis imbalances.

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GP143

Impact of age, menstrual phase, menopausal status and metabolic profile on the definition of 12 circulating steroid reference intervals measured by LC-MS/MS in an Italian healthy adult female cohort

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Endocrine clinical practice strongly relies on normative data for the assessment of hormonal imbalance. However, the generation of robust steroids reference intervals (RIs) remains a challenge. As the steroids circulating levels are influenced by many procedural aspects related to blood collection (time, fasting state) and physio-pathological factors, such as age, sex, stress and metabolic status, the need for partitioning RIs is mandatory. Furthermore, unbiased healthy, drug-free cohorts for RI generation are scarce. After clinical examination we selected 333 drug and disease-free female volunteers aged 18-90y, with no signs of hyperandrogenism. Pre-menopausal women displayed regular menses. Blood withdrawal was standardized early in the morning, in fasting conditions and by 10min saline infusion. The steroid profile including cortisol (F) 11-deoxycortisol (11S), 17-hydroxyprogesterone (17OHP4), 17-hydroxypregnenolone (17OHP5), testosterone (T), androstenedione (A4), dheidroepiandrosterone (DHEA), dihydrotestosterone (DHT), progesterone (P4), corticosterone (B), estrone (E1) and estradiol (E2), was determined by two in-house LC-MS/MS methods previously validated by Certified Reference Materials and ring trials. We evaluated the impact of anthropometric and metabolic parameters over each steroid level by multiple stepwise regression. Then, we computed age-specific RIs for steroids impacted by age by fractional polynomial regression. To further refine RIs for steroid affected by metabolic parameters, we excluded subjects displaying abnormalities among BMI $\geq$ 25.0kg/m^2 and waist circumference $>$ 88 cm, systolic blood pressure $\geq$ 140mmHg and/or diastolic blood pressure $\geq$ 90mmHg, HOMA-IR $>$ 2.5, total-cholesterol/HDL-cholesterol $>$ 5 and triglycerides $>$ 150mg/dL. With the exception of F, 11S and B, aging was found in negative relationship with 17OHP4, 17HOP5, T, A4, DHEA, DHT, P4, E1 and E2 (all $P<0.0001$). BMI positively associated with E1 ($P=0.002$) while negatively associated with DHT ($P=0.048$). Waist circumference negatively associated with F, 11S and B (all $P<0.0001$). Triglycerides positively associated with F ($P=0.001$), 11S ($P=0.007$) and B ($P=0.004$), while negatively associated with E1 ($P=0.019$) and E2 ($P=0.036$). Finally, hypertension positively associated with 11S ($P=0.032$). According to regression results, we generated age-specific RIs on the entire cohort for A4, DHEA, T and 17OHP5. Age-independent RIs for F, 11S and B were computed by excluding subjects displaying metabolic abnormalities. Moreover, we applied additional partitioning considering the menstrual phase and menopausal status for 17OHP4, E1, E2, T and DHT. We provided LC-MS/MS-based, age, menstrual phase and metabolism-adjusted RIs fit for each steroid in a broad panel. The generated RIs represent a valuable tool in diagnostic work-up of steroidogenesis imbalances for women throughout the adult life, also providing insights into neglected steroid precursors and intermediates.

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GP144

Bilateral femoral head necrosis with low dose oral corticosteroid therapy for pan-hypopituitarism

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Introduction
Femoral head avascular necrosis is a dangerous complication that can occur during glucocorticoid therapy, its frequency having been counted up to 40% of patients using corticoids. Even though the complete mechanism involved in this steroid-induced injury is not completely elucidated, studies have shown there's some relation to bone remodelling, bone vasculature disfunction and apoptosis. We report here a case of femoral osteonecrosis associated to a very low dose corticosteroid therapy, which could not be withdrawn. A 48-year-old man presented four years ago with non functioning pituitary adenoma of 4.3 cm removed surgically. In the follow up with endocrinologist he began hormonal reposition with levothyroxine 25 mcg and prednisone 5 mg. Three years after the surgery he started feeling pain in the hips which worsened and lead to difficulties walking. The MRI showed acute/subacute osteonecrosis of right femoral head and osteonecrosis residue on the left femoral head. He, then, proceeded to surgery with no complications, during and after which he took a reposition dose of corticosteroid. When trying to suspend the corticoid he presented with malaise and episodes of hypotension as well as hyporexia, all of which improved after reintroducing 5 mg of prednisone.
Commentaries
Great part of the researches and case reports point out to a dose related occurrence, being a high dose use of corticoid the most frequent cause of non traumatic femoral damage. To be more specific, the studies show that the dose tends to be higher than 20 mg/day of prednisone in a prolonged period to cause such injuries. The occurrence of osteonecrosis with such a low dose of corticosteroid in a short period was surprising. Other reports show the occurrence of necrosis after a period of 10 years and use of intra-articular and intravenous injections over a shorter period of time. Similar to our case only 2 other reports have shown the appearance of femoral head necrosis after 2 years and 7 months of corticoid therapy. As our patient these cases couldn't stop steroid completely because of adrenal failure due to hypopituitarism. In such circumstance is critical to continue therapy in the lowest dose possible and preferably in a more physiological preparation such as hydrocortisone. It's important to bear in mind while consulting any patient with hip pain and in corticoid therapy to look for AVN since early recognition and treatment is crucial to prevent further deterioration of hip articulation and other dangerous complications.

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GP145

Final (FH) and target height (TH) in male and female patients with congenital hypogonadotropic hypogonadism (CHH)/Kallmann syndrome (KS): a monocentric study of 216 patients

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Context
CHH/KS is a major cause of pubertal and bone maturation delay due to sex steroids deficiency. FH and TH have not been evaluated in large series of CHH/KS patients. Analysis of auxometric measures in patients' siblings has never been performed.
Patients and methods
We selected 216 (164/52 men/women; 112/104 KS/normosmic CHH) with available auxometric measures. Sibling stature was available in a subgroup of 162 patients. Difference between the FH and the TH (Delta Height) was calculated. Relation between FH and age at diagnosis was evaluated. In a subgroup of 121 patients, therapeutically-induced growth gain was calculated.
Results
FHs in CHH/KS men and women were higher than in the sex-matched general population. FH was higher than TH (calculated from parents' heights): respectively 179 $\pm$ 8 vs 175 $\pm$ 6 cm in men and 166 $\pm$ 7 vs 162 $\pm$ 5 cm in

women ($P<0.001$ for both). Delta Height was positively correlated with age at diagnosis and age at beginning of hormonal treatment ($P=0.01$). FH and Delta Height were higher in patients than in their siblings ($P<0.01$), excluding a merely 'generational' effect. No difference in Delta Height was found between normosmic CHH and KS. The therapeutically-induced growth gain was inversely correlated with the age at initiation of hormonal treatment.
Conclusions
FH in CHH/KS is higher to either the general population, TH and even to their sex-matched siblings. Our findings show that CHH/KS does not negatively impact adulthood height, and there is no risk of short stature under therapy. Furthermore, the growth gain in CH/KS is disease-related and independent on a generational effect.

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GP146

Turner syndrome: mental health and social skills from childhood to emerging adulthood

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Background
The psychopathology of children and young people with Turner Syndrome (45,X; TS) has been well-documented. But these studies have never assessed neurodevelopmental disorders (NDD; autistic/attention-hyperactivity) alongside emotional and conduct disorders. The last extensive study of mental health assessed a narrow range of psychopathologies and excluded under 16s. This study aims to comprehensively examine mental health, NDD and social skills in TS from childhood to emerging adulthood.
Methods
Participants aged 4 to 25 were recruited through the UK Turner Syndrome Support Society and NHS clinics. Standardised assessments were administered to caregivers. (1) The Development and Wellbeing Assessment (DAWBA; $n=100$) is rated by clinicians to generate DSM-V diagnoses. It assesses anxiety, depression, conduct, autism spectrum disorders (ASD), attention deficit hyperactivity disorders (ADHD) and tic disorders, as well as eating, sleeping and feeding difficulties. It has been used in the English national surveys of child and adolescents mental health conducted in 1999, 2004 and 2017. (2) The Strengths and Difficulties Questionnaire (SDQ; $n=124$) measures emotional dysregulation, hyperactivity/inattention, conduct, peer relationship problems and prosocial ability. (3) The Social Responsiveness Scale-2 (SRS-2; $n=117$) measures autistic symptomatology. All assessments are widely used and well-validated.
Results
DAWBA analysis showed elevated rates of mental health disorder compared to female norms. Notably, 33% met criteria for at least one mental health diagnosis. 23% met criteria for ASD, 11% for anxiety disorders and 12% for ADHD. Mean SDQ total scores were raised compared to female norms ($t_{(123)}=12.89$, $P<0.0001$). Emotional dysregulation was positively correlated with age ($r=0.23$, $P=0.01$), whereas hyperactivity problems ($r=-0.47$, $P<0.0001$) and conduct problems ($r=-0.2$, $P=0.025$) were negatively correlated with age. Peer interaction problems were high compared to population norms ($t_{(123)}=12.22$, $P<0.0001$) and prosocial ability was slightly lower than females population norms ($t_{(123)}=-6.56$, $P<0.0001$). Mean total SRS-2 scores were in the moderately impaired range ($M=65.5$, $SD=14.9$). Autistic symptomatology was rated as severe in 27.4% of cases. Participants have 45.67 times the risk of having severe autistic symptomatology compared to female norms.
Conclusion
Girls with TS have higher rates of mental health disorders, NDD and social difficulties than general population females. 18% met criteria for a diagnosis of ASD and 27.4% had severe autistic symptomatology. Difficulties with hyperactivity/inattention and conduct resolve developmentally, however emotional problems increase. Implementing social skills training in adolescence and providing additional support at school to help with concentration/over-activity is recommended.

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GP147

Risk of nephrolithiasis and nephrocalcinosis in patients with chronic hypoparathyroidism (HypoPT): a retrospective cohort study

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Background
Little is known about the risk of developing nephrolithiasis and nephrocalcinosis in patients with chronic HypoPT treated with conventional therapy (ie, oral calcium and active vitamin D). This study evaluated whether HypoPT is associated with increased risk of these conditions.
Methods
This retrospective cohort study, based on a large US commercial claims database (Q1 2007–Q2 2017), was conducted to compare the risk of nephrolithiasis and nephrocalcinosis between chronic HypoPT patients (excluding those receiving parathyroid hormone) and randomly selected non-HypoPT patients over 5 years of follow-up. For HypoPT patients, the first date of follow-up (ie, index date) was the earliest HypoPT diagnosis date ≥ 6 months after the initial HypoPT diagnosis; for non-HypoPT patients, it was the date of a randomly selected medical claim. Patient characteristics at baseline (the 6 months before index date) and risk of nephrolithiasis (identified by diagnosis and procedure codes) were compared between cohorts, the latter using Kaplan-Meier analysis and Cox proportional hazards models adjusting for baseline demographic (age, sex, race, region, and index year) and clinical (nephrolithiasis, gout, hypercalciuria, hypertension, diabetes, and thiazide diuretic use) characteristics. Similar analyses, adjusting for demographics and hypercalciuria, were conducted on the risk of nephrocalcinosis (based on diagnosis codes) among those without the condition at baseline. A sensitivity analysis for nephrocalcinosis was conducted among those with study period kidney imaging.
Results
The study included 8097 chronic HypoPT patients and 40,485 non-HypoPT patients. At baseline, HypoPT patients were older than non-HypoPT patients (58.6 years vs 47.3 years), a higher proportion were female (76.2% vs 54.4%), and higher proportions had nephrolithiasis (3.3% vs 1.3%), nephrocalcinosis (0.6% vs $<0.1\%$), gout (3.0% vs 1.2%), hypercalciuria (23.8% vs 0.5%), type 2 diabetes (20.6% vs 10.8%), and hypertension (43.7% vs 25.2%) (all $P<0.001$). Over 5 years of follow-up, HypoPT patients had an increased risk of nephrolithiasis and nephrocalcinosis compared with non-HypoPT patients ($P<0.001$ based on Kaplan-Meier analyses). The adjusted hazard ratios (95% CIs) associated with HypoPT vs non-HypoPT were 1.81 (1.60–2.04) for nephrolithiasis and 6.94 (4.41–10.92) for nephrocalcinosis (both $P<0.001$). In the sensitivity analysis, 2.6% of HypoPT and 0.5% of non-HypoPT patients ($P<0.001$) had nephrocalcinosis during the study.
Conclusions
Chronic HypoPT was associated with increased risks of nephrolithiasis and nephrocalcinosis. Further research is warranted to understand the potential mechanisms for the relationship of chronic HypoPT and its management with the observed risk of these conditions.

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GP148

Risk of myocardial infarction (MI), stroke, and other cardiovascular (CV) conditions in patients with chronic hypoparathyroidism (HypoPT): a retrospective cohort study

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Background
Prior small studies have suggested increased risk of cardiovascular (CV) conditions in patients with hypoparathyroidism (HypoPT). We evaluated whether chronic HypoPT is associated with increased risk of select CV hard endpoints (i.e., myocardial infarction (MI), stroke, and a composite CV endpoint) in a large contemporary cohort.
Methods
A retrospective cohort study, based on a US commercial claims database (Q1 2007 - Q2 2017), was conducted to investigate the risk of select CV conditions associated with chronic HypoPT. The study cohort included chronic HypoPT patients (identified using diagnosis codes; excluding those receiving parathyroid hormone) and randomly selected non-HypoPT patients during 5 years of follow-up. CV outcomes (identified using diagnosis and procedure codes) included MI, stroke, and a composite CV endpoint consisting of cerebrovascular disease, coronary artery disease, heart failure, and peripheral vascular disease. For HypoPT patients, the first date of follow-up (i.e., index date) was the earliest HypoPT diagnosis date $\geq$6 months after the initial HypoPT diagnosis (to establish chronic HypoPT); for non-HypoPT patients, it was the date of a randomly selected medical claim. Patient characteristics at baseline (the 6 months prior to index date) were compared. The risk of each CV endpoint was compared between cohorts among patients free of the corresponding condition at baseline using Kaplan-Meier analysis and Cox proportional hazards models adjusting for demographic (age, sex, race, region, and index year) and clinical (chronic kidney disease, hypertension, and diabetes for all endpoints, and select CV comorbidities for MI and stroke) characteristics at baseline.
Results
The study included 8,097 chronic HypoPT and 40,485 non-HypoPT patients. At baseline, HypoPT patients were older than non-HypoPT patients (58.6 years vs. 47.3 years), a higher proportion were female (76.2% vs. 54.4%), and higher proportions had baseline MI (1.9% vs. 1.3%), stroke (4.6% vs. 2.4%), and any composite CV endpoint condition (19.4% vs. 9.5%) (all $P<0.001$). HypoPT patients had increased risk of MI, stroke, and the composite CV endpoint compared with non-HypoPT patients (all $P<0.001$). The adjusted hazard ratios (95% confidence interval; *P*-value) associated with HypoPT versus non-HypoPT were 1.19 (1.02, 1.39; $P=0.029$) for MI, 1.44 (1.30, 1.61; $P<0.001$) for stroke, and 1.64 (1.53, 1.76; $P<0.001$) for the composite CV endpoint.
Conclusions
Chronic HypoPT was associated with increased risk of incident MI, stroke, and the composite CV endpoint. Further research is warranted to understand the potential mechanisms for the relationship of chronic HypoPT and its management with the observed risk of CV conditions.

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GP149

Risk of chronic kidney disease (CKD) and CKD progression in patients with chronic hypoparathyroidism (HypoPT): a retrospective cohort study

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Background
Previous studies of smaller size signaled heightened risk of CKD in patients with chronic HypoPT treated with conventional therapy (ie, oral calcium and active vitamin D). However, little is known about CKD progression, including progression to end-stage kidney disease (ESKD), in HypoPT patients.
Methods
A retrospective cohort study, using a large US commercial claims database (Q1 2007–Q2 2017), was conducted to compare the risk of CKD between chronic HypoPT patients (excluding those receiving parathyroid hormone) and randomly selected non-HypoPT patients over 5 years of follow-up. For HypoPT patients, the first date of follow-up (ie, index date) was the earliest HypoPT diagnosis date $\geq$6 months after initial HypoPT diagnosis; for non-HypoPT patients, it was the date of a randomly selected medical claim. Diagnosis codes, estimated glomerular filtration rate (based on CKD-EPI formula), and dialysis procedure codes were used to identify CKD stages. Patient characteristics at baseline (the 6 months before index date) and risk of incident CKD stage $\geq$3 were compared between cohorts, the latter using Kaplan-Meier analysis and Cox proportional hazards models adjusting for baseline demographic (age, sex, race, region, and index year) and clinical (heart failure, hypertension, diabetes, and medication use) characteristics. CKD progression to a higher CKD stage and to ESKD was similarly analysed among patients with baseline CKD stages 3 or 4.
Results
The study included 8097 chronic HypoPT patients and 40,485 non-HypoPT patients. At baseline, HypoPT patients were older than non-HypoPT patients (58.6 vs 47.3 years), a higher proportion were female (76.2% vs 54.4%), and higher proportions had CKD stages 3-5 (16.4% vs 3.0%) and stages 3-4 (13.6% vs 2.6%). Among those with baseline CKD stages 3-4, HypoPT patients were younger than non-HypoPT patients (70.6 vs 72.1 years), and a higher proportion were female (67.1% vs 54.8%). HypoPT patients had increased risk of CKD stage $\geq$3, CKD progression, and progression to ESKD compared with non-HypoPT patients (all $P<0.001$ based on Kaplan-Meier analyses). Adjusted hazard ratios (95% CI) associated with HypoPT vs non-HypoPT were 2.57 (2.35, 2.82) for CKD stage $\geq$3, 1.62 (1.29, 2.03) for CKD progression, and 1.95 (1.41, 2.70) for progression to ESKD (all $P<0.001$).
Conclusions
Chronic HypoPT was associated with significantly increased risk of CKD stage $\geq$3, CKD progression, and progression to ESKD. Further research is warranted to understand the potential mechanisms for the relationship of chronic HypoPT and its management with these observed risks.

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GP150

Increased prevalence of overweight and obesity and its clinical predictors in children affected by x-linked hypophosphatemia

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Background/aim
X-linked hypophosphatemia (XLH) is a rare disease characterized by low phosphate level. Scientific evidence points to link between hypophosphatemia and obesity in general population. The aim of our longitudinal observational study was to investigate the prevalence of obesity and associated factors in a large cohort of children with XLH.
Patients/methods
We selected 172 XLH-children of 5-20 years (113 girls/59 boys). Anthropometric parameters (weight, height, BMI) were collected at birth and during follow-up at mean age of 5.3-8.2-11.3-15.9 years (group 1-2-3-4, respectively). In each group, subjects were classified based on International Obesity Taskforce (IOTF) cut off values of BMI for age and sex as overweight or obese (IOTF 25-30 or $\geq$30 kg/m^2, respectively).
Results
In each age-group, almost 1/3 of XLH-patients were classified as overweight/-obese (29.4% vs 28.7% vs 27.5% vs 36.7% for group 1-2-3-4, respectively). Children without XLH-family history had significantly higher BMI-IOTF at every point of follow-up ($P=0.015$), compared to those with positive XLH-family history. Similarly, higher BMI-IOTF is significantly associated with treatment duration (23.3 ± 4.4 vs 23.8 ± 3.8 vs 25.2 ± 4.5 kg/m^2, for subjects with treatment duration of <5, 5–10 and >10 years, respectively, p for trend $=0.025$). Multiple regression analysis confirmed that treatment length and lack of XLH-family history are positively associated with higher BMI-IOTF.
Conclusion
1/3 of XLH-children have phenotypically unfavourable metabolic profile expressed as increased prevalence of overweight/obesity in comparison to general population. Lack of XLH family history and length of treatment increase

the risk of higher BMI-IOTF. BMI should be carefully followed in children, and later adults, with XLH.

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GP151

MEN4: is there a link with autoimmunity?

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MEN4 is a rare disease characterized by the development of multiple endocrine tumors caused by mutations in the *CDKN1b* gene encoding the cyclin dependent kinase inhibitor $P27^{Kip1}$. Here we report two new cases and address the potential link of MEN4 with autoimmunity. The 1st patient, a 66-year old woman, presented at 35 years high prolactin levels without evidence of pituitary adenoma, treated medically. At 51 years, she was diagnosed with mild primary hyperparathyroidism associated to osteoporosis without any parathyroid lesion initially identified. Thirteen years later a retro-esophageal parathyroid adenoma was revealed and removed with normalization of blood calcium level. The patient also had breast cancer at 37, papillary ovarian serous cystadenoma at 50 and multifocal micropapillary thyroid carcinoma at 55 years. Heterozygous mutation of *CDKN1b* gene was found: c.281C>T, p.Pro941Leu in exon 1, not previously reported. Surprisingly the patient also had a remarkable history of autoimmune diseases, with myasthenia gravis at 12 justifying thymectomy for hyperplasia, Sjögren syndrome, type III cryoglobulinemia and asthma. Her father suffered from diabetes and Grave's disease, her paternal grand-mother from thyroiditis and breast cancer. The 2nd patient, a 70-year old lady was fortuitously diagnosed with a 27×30 mm non-functioning pituitary adenoma at 66 years during a stroke work-up. The volume progression and campimetric involvement led to surgery. Primary hyperparathyroidism was simultaneously discovered, attributed to a unique parathyroid lesion, not removed because of the absence of any complication (Calcium levels ∼2.6 mmol/l, PTH 118 ng/ml (N:15–68)). A mild autonomous cortisol secretion linked to a centimetric adrenal nodule was also confirmed. She also had a history of Crohn's disease treated with azathioprine then steroids and autoimmune thyroiditis. The familial history was difficult to assess because of cognitive impairment. A new heterozygous mutation in exon 1 of *CDKN1b* gene (c.206C>T, p.Pro69Leu) was identified. These two cases with proved germinal *CDKN1b* mutations are consistent with literature regarding MEN4, namely MEN1-like phenotype with late occurrence mostly focused on pituitary and parathyroid tumors. Interestingly, both cases were associated with multiple autoimmune disorders, including systemic and organ-related diseases. A previous meta-analysis has shown that *CDKN1B* was potentially involved in the pathophysiology of systemic lupus erythematosus, with a role in the induction of T-cell tolerance and B-cell lymphopoiesis. Future research about this rare condition will have to investigate this potential association, which confirms the link between neoplasia and immunity.

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GP152

UMD-MEN1 database: analysis of clinical and genetic data from 1,676 patients by the TENGEN network

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Context
Multiple Endocrine Neoplasia type 1 (MEN1) is an autosomal dominant disease caused by mutations in the *MEN1* gene. MEN1 is characterized by a broad spectrum of clinical manifestations, of which the most frequent are primary hyperparathyroidism, pituitary adenomas, and neuroendocrine tumors. *MEN1* presents a broad spectrum of variants, including large deletions, and truncating, missense, or splicing point mutations. The genotype-phenotype relationship remains under debate. The age-dependent penetrance and the variability of intra- and inter-familial expression of the disease increase the difficulty of interpretation of non-truncating variants in the *MEN1* gene, particularly regarding sporadic patients with incomplete diagnosis criteria.
Patients and Methods
The TENGEN network (French oncogenetics network of neuroendocrine tumors) has interpreted and collected all allelic variants and clinical characteristics of the *MEN1*-positive patients, identified through genetic testing performed in France from 1997 to 2015. We analyzed the clinical and genetic characteristics of patients from the UMD-MEN1 database cohort.
Results
370 distinct variants reported in 1,676 patients have currently been registered. This database analysis pointed out the low frequency of benign or likely benign missense variants in *MEN1* (only 6.6%). Eight families (1.9%) presented a familial isolated hyperparathyroidism and harbored the same mutation found in authentic MEN1-families. An association exists between large rearrangements and an earlier onset of the disease, whereas no difference was observed between truncating and non-truncating variants.
Conclusion
All variants were registered in a locus-specific database called the UMD-MEN1 database (www.umd.be/MEN1/), which provides an exhaustive overview of the *MEN1* variants present in the French population. For each variant, a classification based on the clinical data collection from patients and a standardized analysis is publicly available. Clinical data collections allow the determination of genotype-phenotype correlation and age-related penetrance of lesions in the cohort.

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Cushing's

GP153

Evaluation of the corticotrophin-releasing-hormone test and the high dose dexamethasone suppression test in ACTH dependent Cushing's syndrome: a 25-year prospective cohort study

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Introduction
In patients with ACTH-dependent hypercortisolism, the corticotropin-releasing-hormone (CRH) test and the high dose dexamethasone suppression test (HDDST) can be used to differentiate between pituitary ACTH production (Cushing's disease) and ectopic ACTH production. The rationale is that a pituitary adenoma will show some response to CRH and ACTH whereas an ectopic source is less responsive to ACTH and CRH. However, there is discussion about the clinical utility of the CRH-test and the HDDST. Many endocrinologists consider bilateral inferior petrosal sinus sampling a superior test. However, inferior petrosal sinus sampling is not ubiquitously available, has a risk of cerebrovascular complications, and can give false positive results. In this study, we aimed to determine sensitivity and specificity of the CRH-test and HDDST.
Methods
We analyzed all CRH-tests and HDDSTs performed in the period 1993–2018 at the Amsterdam UMC (location AMC) in patients with biochemically confirmed endogenous hypercortisolism. For the CRH-test (100 ug intravenously), we used a 20% plasma cortisol increase and/or a 50% plasma ACTH increase from baseline as a cutoff. For the HDDST we used a 190 nmol/l decrease of plasma cortisol from baseline to the average of 6:45–7:15 h after infusion of 8.75 mg dexamethasone as a cutoff. In 2018 we reviewed all patient records, and we determined the final diagnosis by clinical follow-up.
Results
For 52 patients with hypercortisolism (out of 68 patients) who underwent the CRH-test and/or HDDST, a final diagnosis could be determined: Cushing's disease ($n=35$), ectopic ACTH production ($n=3$) and adrenal cortisol production ($n=14$). To diagnose Cushing's disease (versus ectopic ACTH production) using our pre-determined cutoff values, CRH-test derived cortisol values yield a sensitivity of 71% and a specificity of 100%, CRH-test derived ACTH values yield a sensitivity of 74% and a specificity of 100%, and the HDDST has a sensitivity of 97% and a specificity of 100%.
Conclusion
In patients with ACTH-dependent hypercortisolism, the HDDST excellently differentiates between Cushing's disease and ectopic ACTH production, and may reduce the need for inferior petrosal sinus sampling.

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GP154

Pathway enrichment analysis in functioning and silent corticotroph pituitary adenomas reveals mechanisms to explain their distinct clinical behaviour

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Background
Functioning (FCA) and silent corticotroph (SCA) pituitary adenomas act differently from a clinical perspective, despite both subtypes showing positive ACTH staining by immunohistochemistry. They are challenging to treat, the former due to functional ACTH production and consequently hypercortisolemia leading to Cushing disease, whereas the latter due to invasive and recurrent behaviour. Moreover, the molecular mechanisms behind their distinct behaviour are not clear.
Aim
To investigate global transcriptome changes and identify signalling pathways that can explain FCA and SCA differences (*e.g.* hormone production *vs.* aggressive growth).
Material and methods
RNA sequencing was performed using Illumina HiSeq in 6 FCA (three women, five microadenomas) and 6 SCA (two women, all macroadenomas). Data was analysed using the tophat2- cufflinks-CummeRbund pipeline and the pathway enrichment analysis was performed using Pathview (https://pathview.uncc.edu). The candidate genes were evaluated by RT-qPCR in a larger cohort of adenomas (26 FCA and 10 SCA).
Results
By assessing the 631 differentially expressed genes (fold change (FC) >1.9, $q<0.05$), we identified eight signalling pathways to be enriched. Firstly, protein processing in endoplasmic reticulum (ER) (hsa04141) pathway was differentially regulated. Accordingly, FCA showed up-regulation of genes involved in ribosome anchor (RRBP1), glycosylation and folding process (RPN1, CALR, PDIA3, and UGGT2), protein recognition by luminal chaperones (HSPA5), and ER-associated degradation (HSPH1 and CRYAB), whereas the only gene to be up-regulated in SCA was EIF2AK2, a protein known to attenuate protein synthesis if activated. Secondly, five signalling pathways involved in cell adhesion (hsa04514, hsa04080, hsa04512, hsa04060, and hsa04510) were also differentially regulated. Of notice, the adenoma subtypes showed a distinct extracellular matrix profile with genes that were up-regulated in FCA (COL1A1, COL4A3, COL4A4, LAMA4 and NRCAM) and in SCA (COL2A1, CADM1, CNTN1, LAMC2, FN1, ITGB2, NECTIN3, NLGN1, PTPRC, SDC2, SPP1, SV2C and VTN). Lastly, two classical proliferation, growth, and survival pathways (MAPK – hsa04010, and PI3K-Akt – hsa04151) were differentially regulated, SCA showing, among other genes, higher levels of MAPK1 and SGK1 and lower DUSP4 gene expression.
Conclusion
Distinct clinical aspects of FCA and SCA may be explained by their different repertoires of activated signalling pathways, namely promoting growth in SCA and protein processing in FCA and their specific patterns of cell adhesion molecules. Further *in vitro* functional studies will be performed, in order to identify possible medical targets and to properly understand the involved mechanisms.

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GP155

Endocrine immune-related adverse events following immune check-point inhibitors in patients with advanced melanoma: single-center retrospective analysis

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Introduction
Immune-check point inhibitors (ICPis) has been shown to significantly improve survival in patients with advanced melanoma. Immune-related endocrinopathies (irEs) and in particular hypophysitis and thyroid dysfunction have been well described with an incidence varying from 9–17% and 3.8–13.2% respectively.
Methods
This is a retrospective analysis of irEs in 325 (190 men) patients with melanoma receiving ICPis (PD-1/PDL-1 or CTLA-4 as monotherapy, combined or sequential therapy) in a single center, between 2014 and 2018. Clinical data were reviewed in order to characterize cases of hypophysitis, thyroid dysfunction and other possible endocrinopathies. All patients had hormonal functional tests at screening (before the initiation of ICPis) and during the follow up, while in cases of relevant symptoms imaging with MRI was also performed.
Results
In our cohort, the total incidence of irEs was 12.3% and in particular, 9% for patients treated with anti-CTLA-4 ($n=120$) compared to 17.7% for patients treated with anti-PD-1/PDL-1 ($n=118$). Combination therapy increased the incidence of irEs to 34.7%. Hypophysitis was developed in 8.9% of ICPis-treated patients. A higher incidence (5%) of hypophysitis among patients treated with PD1/PDL-1, in contrast to 4.2% of those treated with ipilimumab was found. From patients who received sequential therapy, 18.7% developed hypophysitis during the second line treatment; the increased incidence was regardless of the class of ICPis given as first-line treatment. MRI abnormal findings were observed in 45% of patients with hypophysitis. Corticotroph axis was the most frequent pituitary failure which was not recovered during the follow up (mean: 19 ± 12.8months). Thyroid dysfunction was developed in 5.8% of total patients treated with ICPis. Thyroid disease was developed in 6.7% of those treated with anti-PD-1/PDL-1 with hypothyroidism being more frequent (79%), while only 4 patients developed transient hyperthyroidism. No patient treated with ipilimumab as monotherapy developed thyroid dysfunction, while combination and sequential therapy increased the incidence compared to PD-1/PDL-1 monotherapy. The most common symptom experienced by patients was fatigue. No severe (>Grade 3) endocrine toxicity was observed and no one patient discontinuated permanently the immunotherapy. Interestingly, one patient developed hypophysitis and three patients hypothyroidism, 26 months and 22–24 months post initiation treatment with ICPis, respectively.
Conclusions
Clinicians should be aware of the risk of irEs endocrine adverse events during treatment with ICPis and there is a necessity of long-term clinical and biochemical follow up. Sequential therapy with ICPis increased significantly the risk of developing endocrine adverse events and in particular hypophysitis.

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GP156

Correlation between responsiveness to CRH stimulation test in Cushing's disease patients and USP8 mutational status

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Corticotrophin-releasing hormone (CRH) stimulation test is used in the differential diagnosis of Cushing's syndrome. Cushing's disease tumours carry somatic driver activating mutations in the ubiquitin-specific-protease 8 (*USP8*) gene in almost half of the cases. The aim of the present study was to examine whether the *USP8* mutational status in Cushing's disease tumours influences the response to the CRH stimulation test. We did a monocentric, retrospective study on 46 (27 female) Cushing's disease patients with complete data after dynamic stimulation test with 100 μg i.v. CRH (basal serum cortisol and/or ACTH levels and their respective peak and percentage increase). The USP8 mutational status was determined by Sanger sequencing on DNA extracted from fresh frozen and formalin fixed paraffin embedded tumour tissues. *USP8* mutations were detected in 22 out of 46 tumours (15/27 female and 7/19 male, chi-square test $P=0.245$). Mean basal serum cortisol and ACTH levels were similar in patients with *USP8* mutant and wild type tumours (μg/dl 24.2 ± 9.5 vs 26.5 ± 11.2, *t*-test $P=0.47$ and pg/ml 70.49 ± 53.36 vs 89.46 ± 62.08, $P=0.97$). Similarly, no significant differences were observed in the cortisol and ACTH peaks after CRH injection between *USP8* mutant vs wild type (cortisol μg/dl 38.13 ± 14.02 vs 36.81 ± 16.08, *t*-test $P=0.78$ and ACTH pg/ml 164.90 ± 118 vs 179.41 ± 162.2, $P=0.73$). The percentage increase in cortisol and ACTH levels were higher in patients with *USP8* mutant tumours (% cortisol 65.82 ± 48.46 vs 41.57 ± 29.46 and ACTH 201.10 ± 259.74 vs 98.59 ± 86.97) even if they did not reach statistical

significance (*t*-test $P=0.053$ and $P=0.097$ respectively). Multivariant analysis showed that patient gender does not influence the response to the CRH stimulation test ($P=0.336$ and $P=0.546$ for cortisol and ACTH variation respectively). These data suggest that *USP8* mutant tumours may be more sensitive to the CRH stimulation test. This observation together with previously published reports of smaller tumour size and better response to high dose (8 mg) dexamethasone stimulation test (1) highlights the role of USP8 in corticotroph cell physiology.

Reference
1. Perez-Rivas *et al.*, *J Clin Endocrinol Metab*, 2015, 100(7):E997–E1004.

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GP157

DNA Methylation and fMRI responses in patients with Cushing's syndrome in remission – suggestions of a functional link between hypercortisolism and neurocognitive dysfunction

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Introduction
Compared with healthy controls, women with Cushing's syndrome (CS) in long-term remission have reduced functional brain responses during episodic and working memory testing and decreased overall levels of DNA methylation in blood cells. Here, we sought to test the hypothesis that functional brain responses in the prefrontal cortex and hippocampus are related to epigenetic changes in subjects with CS in long-term remission.
Methods
In this pilot study, 10 women with CS in remission were included. The mean (SD) age was 40 ± 11 yrs and the median (IQR) duration of remission was 9.6 (5–15) yrs. Six patients had Cushing's disease and 4 had a cortisol-producing adrenal adenoma. Functional brain responses were studied with functional magnetic resonance imaging (fMRI) during episodic- and working-memory tasks. DNA was isolated from whole blood and DNA methylation was analysed using the Illumina Infinium HumanMethylation450K BeadChip. In a previous analysis, 461 differentially methylated regions, containing 3,903 probes, were identified in patients with CS in remission compared to healthy controls. Correlations between individual probes and fMRI data were analysed in R, and a false discovery rate (FDR) adjusted *P* (q-value) < 0.2 was considered significant.
Results
Using the predetermined q-value cut off, significant correlations were found between probes and functional brain responses in both right and left hippocampi ($n=592$ and 967 unique probes, respectively). Correlations were also found for right posterior ($n=1145$ unique probes), left anterior ($n=900$ probes) and left posterior ($n=1.198$ probes) hippocampi. Gene ontology analyses revealed that probes correlating to fMRI responses mapped to genes associated with long-term memory function and regulation of synaptic plasticity, to mention some. Three probes in *COL11A2*, *DAGLB* and *TFDP1* genes, previously associated with psychopathology in CS, were also strongly correlated with functional brain responses. Furthermore, one gene with several significantly correlated probes was *RNF39*, a gene previously suggested to be a mediator of the effect of stress on central fear and stress circuitries in the brain.
Conclusions
In women with CS in long-term remission, DNA methylation is correlated with functional brain responses during memory encoding. Some differently methylated genes associated with functional brain response have previously been associated with psychopathology in CS and one, *RNF39*, is suggested to be a susceptibility locus for post-traumatic stress disorder.

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GP158

Cortisol and cortisone assays in hair by mass spectrometry for the diagnosis of Cushing's syndrome

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Background
According to the Endocrine Society's guidelines, the screening and diagnosis of Cushing's syndrome (CS) are based on the results of the overnight dexamethasone suppression test (DST), midnight salivary cortisol and 24-hour urinary free cortisol (UFC) measurements. These 3 tests reflect cortisol levels at the time of sampling without providing retrospective information. Hair cortisol concentration is a non-invasive way to measure cortisol exposure over longer periods of time (weeks and months) but only few studies report its usefulness for the diagnosis of CS. Most of studies were performed with cortisol immunoassays.
Aim
To assess the diagnostic power of the measurements of cortisol and cortisone in hair using liquid chromatography/mass spectrometry method. We provide reference and pathologic values in several populations: no-obese healthy subjects (H-group) and patients with Cs (Cs-Group).
Methods
After a 2-step extraction (incubation in a dithiothreitol solution followed by a dichloromethane extraction), concentrations of cortisol (HairF) and cortisone (HairE) were measured in the proximal 3 cm of scalp hair by using a home-developed multiplex mass spectrometry assay. Hairs were cut from the posterior vertex of 112 volunteers admitted in the Endocrinology Department of the University Hospital of Bordeaux: 76 (62F/14M, 38 [21–83] yrs, median [min-max]) in H-group (44 in a $H_{<50}$ subgroup were <50 year, 32 in a $H_{>50}$ subgroup were >50yr), 36 (29F/7M, 53 [19–78] year) in the Cs group. Based on clinical signs and biological markers (UFC, DST, serum or salivary cortisol at midnight), we included in the Cs-group patients either with mild and patent Cs.
Results
HairF and HairE reference values were similar in $H_{<50}$ and $H_{>50}$ subgroups. As a whole, the H-group reference values were 9.6 [45.0] (median [95th percentile]) and 14.5 [27.64] pg/mg hair, HairF and HairE respectively. In the Cs-group, both HairF and HairE were increased compared to the H-group: 24.9 [2.0 – 738.8] (median [min - max]) and 37.5 [7.0 – 192.4] pg/mg hair ($P<0.001$ for HairF and HairE). HairE ROC curve was significantly larger than HairF curve (areas 0.871 vs 0.733) to distinguish H-group from Cs-group ($P<0.001$).
Conclusion
HairF and HairE assays are useful for the diagnosis of Cs. Importantly, HairE seems to be a better reflect the excess of a long-term cortisol exposure than HairF. The determination of HairF and HairE using mass spectrometry assay may improve the diagnostic accuracy of this specific investigation.

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GP159

Skeletal muscle fatty infiltration in the thigh, as assessed by MRI T2-weighted and 3-point Dixon sequences, is associated with poor performance on muscle function testing in patients with Cushing's syndrome in remission

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Background
Muscle weakness may persist in patients with Cushing's syndrome (CS) long-term after resolution of hypercortisolism, but mechanisms determining this sustained impairment are not known. We hypothesized that alteration of muscle structure, due to fatty infiltration, is associated with muscle dysfunctions in these patients.
Patients & methods
Twenty-six CS women [mean(±s.d.) age 49 ± 12 years; mean(±s.d.) BMI 27 ± 4 Kg/m^2; mean(±s.d.) duration of remission, 132 ± 87 months], and 24 age- and BMI-matched controls were studied. The degree of fatty infiltration of the thigh

muscles was measured using magnetic resonance imaging (MRI), ultrashort multiecho T2-weighted and 3-point Dixon sequences in the anterior, posterior, and anterior + posterior compartments. T2 signal intensity was classified as 'high' (corresponding to fat), 'medium' (muscle), 'low' (macromolecules-muscle). The following muscle function tests were also performed: gait speed velocity (GS), timed up and go (TUG), 30-second chair stand and hand grip strength in both hands.

Results

Mean muscle fat fraction (%) in the posterior compartment, as determined by 3-point Dixon, was increased in patients as compared with control group (22.8 ± 6.4% vs 18.7 ± 3.4%; $P = 0.025$), indicating greater muscle fatty infiltration in the former. There was a tendency towards higher mean muscle fat fraction in anterior + posterior compartments of the tight in patients as compared with controls (21.8 ± 6.1% vs 18.2 ± 4.5%; $P = 0.052$). Greater mean muscle fat fraction in the posterior compartment was associated with slower GS ($r = -0.43$, $P = 0.025$), and poorer performance on both TUG ($r = 0.63$, $P < 0.001$) and 30-second chair stand ($r = -0.57$, $P = 0.002$) in patients only. An increase in the percent of high-T2 signal in overall tight muscles, suggesting increased intramuscular fat tissue, was associated with slower GS ($\rho = -0.049$, $P = 0.025$) and worse performance on TUG ($\rho = 0.58$, $P = 0.007$) in patients only. In a multiple linear regression model, mean muscle fat fraction in the posterior compartment predicted TUG in patients, after adjusting for age and BMI (ß 0.64, $P < 0.001$).

Conclusion

Rate of fatty infiltration in thigh muscles is increased in patients with CS in remission and is related to impaired muscle function. Muscle MRI could be a reliable biomarker to follow up treated CS patients who are at risk of developing muscle dysfunction. Future studies are needed to elucidate the mechanisms underlying the relationship between altered muscle structure and function after correction of hypercortisolism.

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GP160

Brain 18F-fluorodeoxyglucose PET/CT in localization of MRI-negative ACTH-producing pituitary adenomas

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Background

Detection of MRI-negative ACTH-producing pituitary adenomas is a challenge in the management of patients with Cushing's disease. There are some data on the possibility of pituitary adenomas to accumulate 18F-fluorodeoxyglucose (18F-FDG) during the 18F-FDG positron emission tomography and computer tomography (18F-FDG PET/CT).

Aim

To study the potential of brain 18F-fluorodeoxyglucose PET/CT for localization of MRI-negative ACTH-producing pituitary adenomas.

Materials and methods

Twenty one patients were enrolled. 16 patients had Cushing's disease (three men and thirteen women), among them seven had newly diagnosed disease and nine had persistence or recurrence of hypercortisolism after the previous transsphenoidal adenomectomy (TSS). MRI scans were negative in patients with newly diagnosed disease and uncertain (postoperative changes-8 patients; secondary 'empty sella'-1 patient) in patients after TSS. In all patients pituitary source of ACTH hyperproduction was confirmed by bilateral cavernous and inferior petrosal sinuses sampling. Five patients had neuroendocrine tumors (NETs) with ACTH-ectopic production (pheochromocytoma-1; thymus NET -1; lung NET – 3: among them two patients previously had underwent bilateral adrenalectomy due to severe hypercortisolism and failure to find the source of ACTH-ectopy). Brain 18F-fluorodeoxyglucose PET/CT was performed in all patients (in patients with suspected NET it was a part of total body 18F-FDG PET/CT).

Results

Among sixteen Cushing's disease patients fifteen had had focal increased 18F-FDG uptake on pituitary PET/CT scans. All this patients had undergone TSS. In eleven cases diagnosis of ACTH-producing pituitary adenoma was confirmed by pathology examination, among them in seven cases the remission of hypercortisolism was achieved. In four patients the result of pathology examination was negative, but all of them developed remission of hypercortisolism after the TSS. One patient had had negative18F-FDG uptake on PET/CT scans, he was re-examined and the remission of hypercortisolism was diagnosed. All patients with NETs, including those who had previously undergone bilateral adrenalectomy showed negative 18F-FDG uptake on pituitary PET/CT scans.

Conclusion

According to our study brain 18F-fluorodeoxyglucose PET/CT may be useful for localization of MRI-negative ACTH-producing pituitary adenomas, but further research is necessary for the confirmation of these data.

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GP161

Ubiquitin-specific protease 8 (USP8) potentiates glucocorticoid receptor activity in corticotroph tumour cells

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Cushing's disease tumours bear activating mutations in the ubiquitin-specific-protease 8 gene (*USP8*) gene in 40-60% of cases. We have previously observed that patients with USP8 mutant tumours have smaller tumour size and show a better response to high dose (8mg) dexamethasone stimulation test compared to those with wild type USP8 (1). The aim of this study was to define the role of USP8 on glucocorticoid receptor (GR) in corticotroph tumour cells. We did experiments in immortalized AtT-20 corticotroph tumour overexpressing USP8 wild type or mutants (Pro720Arg, Ser718Pro, Ser718del). Cells overexpressing the USP8 mutants showed better GR transcriptional response to dexamethasone treatment (determined by MMTV luciferase assay) compared to those transfected with wild type USP8. Furthermore, GR nuclear translocation determined as GR content in the nuclear fraction after dexamethasone treatment (10nM, 2 hours) was more prominent in cells overexpressing USP8 mutants than wild type. In addition, although GR protein levels were decreased after long-term exposure to dexamethasone (12 hours) in wild type cells, cells overexpressing USP8 mutants retained GR showing protection from treatment-induced degradation. USP8 knockdown increased GR ubiquitination and coimmunoprecipitation experiments showed that all USP8 forms physically interact with GR, indicating a direct effect of USP8 on GR. Introducing a mutation in the putative ubiquitination site lysine 419 halved the fraction of ubiquitinated GR and potentiated GR activity on POMC promoter and MMTV. These data show that USP8 deubiquitinates and rescues GR activity. USP8 is mainly a cytoplasmatic protein, but its mutants are also localized in the nucleus. Therefore, an intriguing hypothesis is that their closer topological association with GR may render USP8 mutant corticotroph cells more sensitive to the physiological negative glucocorticoid feedback. Resistance to the glucocorticoid negative feedback is a hallmark in Cushing's disease. Our data of a regulatory role of USP8 mutants on GR may explain the smaller size and increased glucocorticoid sensitivity of the USP8 mutant tumours and reveals a novel action of USP8 in corticotroph tumour pathophysiology.

Reference

1. Perez-Rivas *et al*., J Clin Endocrinol Metab, 2015, 100(7):E997–E1004.

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GP162

Pharmacokinetics of osilodrostat following single and multiple doses of osilodrostat in healthy subjects and patients with Cushing's disease

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Introduction

Osilodrostat is a potent oral 11β-hydroxylase inhibitor currently in Phase III clinical development for the treatment of Cushing's syndrome (CS). The key pharmacokinetic (PK) properties, drug–drug interactions (DDIs), and population PK findings for osilodrostat in humans are summarized.

Methods
Osilodrostat PK has been characterized in nine Phase I studies (healthy subjects and subjects with hepatic or renal impairment), two Phase II studies (patients with Cushing's [CD] disease or CS), and a Phase III study (patients with CD). Pooled population PK analyses were performed for healthy subjects and patients with CD.
Results
Osilodrostat was rapidly absorbed (tmax: ~1 h) and demonstrated a half-life of ~4 h across all examined doses (range: 0.5–200 mg after single and multiple doses). Median apparent volume of distribution (Vd) for osilodrostat was 101 L following a single oral dose (50 mg) in healthy volunteers. Osilodrostat is extensively metabolized by multiple enzymes, and no single enzyme contributed to >25% of total clearance of osilodrostat, thus it is unlikely to be a victim for DDIs. The total contributions of cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes to osilodrostat clearance were estimated at 26% and 19%, respectively; non-CYP-, non-UGT-mediated metabolism contributed to ~50% of total clearance. The main metabolite in plasma was LXB168, which is not pharmacologically active. Most osilodrostat-related material was eliminated in urine (~90.6% of administered dose), with only 5.2% as unchanged osilodrostat. Osilodrostat is a moderate inhibitor of CYP1A2, a weak-to-moderate inhibitor of CYP2C19, and a weak inhibitor of CYP2D6 and CYP3A4/5 (50 mg single dose). No clinically significant DDI was observed when osilodrostat was co-administered with oral contraceptives (OCs) in healthy females receiving hydrocortisone. A trend of increasing AUCinf (area under the concentration–time curve from zero to infinity) for osilodrostat was observed in subjects with moderate-to-severe hepatic impairment (geometric mean ratios: 1.44 and 2.66, respectively) compared with healthy subjects. Osilodrostat exposure was similar across three renal function cohorts (normal, severe, and end-stage renal disease), indicating that renal function has no impact on osilodrostat exposure.
Conclusion
The PK properties of osilodrostat in humans are favourable and allow twice-daily dosing. No dose adjustment is required for patients with renal impairment, although patients with moderate or severe hepatic impairment should undergo dose adjustment. Osilodrostat is unlikely to be a victim for DDIs but does produce modest inhibition of CYP enzymes (as perpetrator). OCs can be co-administered with osilodrostat without dose modification.

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GP163

Effects of a single dose of pasireotide on glucose metabolism in patients with Cushing's disease and predictors of diabetes mellitus developement during treatment

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Introduction
Pasireotide (PAS) is an effective treatment for Cushing's disease (CD) but its use is burdened by the high incidence of diabetes mellitus (DM). We aimed to evaluate the effect of a single subcutaneous injection of PAS on glucose metabolism in CD patients, to identify factors predicting rapid deterioration of glycaemic control.
Methods
14 patients [(f/m = 12/2, mean age 43 ± 11.3 years, follow-up 17 months (2-63)] with CD treated with PAS (600 µg b.i.d.) were studied; before treatment initiation, all patients were submitted to an acute PAS test (600 mcg s.c.) with measurements of ACTH, cortisol, glucose, insulin, c-peptide, insulin, GIP, glucagon, GLP-1, ACTH and cortisol at time 0' and then every 30' minutes for 2 hours to predict the development of DM.
Results
There was a significant reduction in urinary free cortisol (UFC, 582 ± 456 vs 254 ± 356 nmol/24h, $P = 0.001$) and late night salivary cortisol (LNSC, 12.2 ± 11.6 vs 3.8 ± 1.7 nmol/L, $P = 0.003$) in all cohort with concomitant improvement of weight ($P = 0.01$) and waist circumference ($P = 0.02$). Overall 10/14 patients reached UFC normalization whereas LNSC was within normal range only in 4 cases. A single PAS dose produced a significant decrease of all hormonal parameters assessed ($P < 0.0001$), except for glycaemia which reached the highest value 120' after the injection (baseline 4.65 ± 0.52 vs peak 8.91 ± 3.63 mmol/L, $P < 0.0001$). Overall 7/14 patients developed DM within the first 2 months of therapy. Among baseline characteristics, non-DM patients did not differ in age, weight, visceral adiposity, HOMA-index, fasting glucose and severity of CD from those who did not have glucose metabolism alterations; however, compared to non-DM patients, DM patients displayed higher baseline fasting c-peptide (respectively 694.4 ± 109.6 vs 947.4 ± 318.4 pmol/L, $P = 0.05$) and HbA1c levels (30 ± 3.0 vs 37.1 ± 1.8 mmol/mol, $P = 0.001$), with the latter being normal in all cases. Finally, glucose peak tent to be higher in DM-patients than in those who did not develop hyperglycaemia (7.2 ± 2.2 vs 10.6 ± 4.1mmol/L, $P = 0.06$).
Conclusions
PAS confirmed to be a valuable tool for the treatment of CD. It was able to rapidly suppress insulin secretion and the incretin system with a subsequent increase in glucose levels into the diabetic range producing also a concomitant decrease in glucagon values. Patients at higher risk of DM during PAS therapy were those with higher fasting c-peptide at elevated serum glucose peak during the acute test. Interestingly baseline HbA1c, seems to predict the risk of PAS-induced DM.

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GP164

Assessment of bone marrow fat by single-voxel vertebral magnetic resonance spectroscopy in cushing's syndrome with or without vertebral fractures

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Chronic hypercortisolism is associated with dramatic increase in fragility fractures. The evaluation of skeletal fragility in Cushing's syndrome (CS) is a clinical challenge, since fractures may occur even in presence of normal bone mineral density (BMD). Recently, measurement of bone marrow fat (BMF) by vertebral magnetic resonance spectroscopy (MRS) was proposed as alternative tool for evaluating skeletal fragility in primary and secondary osteoporosis. Noteworthy, recent evidence shows that cortisol excess may cause BMF increase but it is still unknown whether it may be a biomarker of fracture risk in CS patients. In this cross-sectional study, we evaluated association between BMF and vertebral fractures (VFs) in 20 patients (5 M, age 44 ± 13 years) with active CS (16 cases with ACTH-dependent and 4 with ACTH-independent CS). Fifteen healthy volunteers (4 M, age 43 ± 12 years) acted as control group (CG) for BMF evaluation. BMF was measured by a single-voxel MRS (1,5 Tesla) on lumbar vertebral bodies, whereas VFs were assessed by a radiological and morphometric approach on thoracic and lumbar spine X-ray images. CS patients were also evaluated for lumbar spine BMD by dual-energy X-ray absorptiometry (DXA). Fractured vertebrae were excluded from BMF and BMD evaluations. Baseline parameters of pituitary-adrenal function and bone metabolism were also measured in CS patients. Overall, vertebral BMF was higher in CS patients than in CG (51.1 + 22.6% *vs.* 28.4 + 17.0%, $P = 0.003$), and directly correlated with patients' age at CS diagnosis (rho: 0.48; $P = 0.03$), 24-hrs urine cortisol values (rho: 0.476; $P = 0.03$), midnight serum cortisol values (rho 0.50; $P = 0.02$), serum CTX (rho: 0.54; $P = 0.01$), serum alkaline phosphatase (rho: 0.57; $P = 0.009$) and urinary phosphate values (rho: 0.51; $P = 0.01$). VFs were found in 13 CS patients (65%; 3 with normal BMD, 4 with osteopenia and 6 with either osteoporosis or low BMD for age, according to WHO criteria). Patients with VFs showed higher BMF than patients without (59.4 *vs* 35.8%, $P = 0.03$). Fractured patients with either normal BMD or osteopenia showed comparable BMF to fractured patients with either osteoporosis or low BMD for age (60.8 + 18.0 *vs* 57.7 + 21.5%; $P = 0.71$). When the analysis was restricted to patients with normal BMD or osteopenia, VFs were still associated with higher BMF (60.8 ± 18.1 vs. 35.8 ± 21.8, $P = 0.05$). This preliminary study provides a first evidence that vertebral adiposity is a marker of hypercortisolism-induced skeletal fragility and measurement of lumbar spine BMF by MRS may be a reliable tool for predicting VFs in endogenous CS.

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Obesity

GP165

Role of invasive and non-invasive diagnostic tests in differential diagnosis of ACTH-dependent Cushing's syndrome

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Background
Differential diagnosis of ACTH-dependent hypercortisolism is crucial to indicate a proper treatment and is based on CRH-, high-dose dexamethasone suppression-test (HDDST) and pituitary MRI. However, up to 50% of cases of Cushing's disease (CD) present a negative MRI or a visible lesion < 6 mm. In these patients, guidelines suggest to perform bilateral inferior petrosal sinus sampling (BIPSS) in order to establish a correct diagnosis. Aim of this study was to analyze the need of BIPSS in particular in those patients with inconclusive neuroradiological examination.
Materials and methods
We performed a retrospective analysis on 122 patients (F/M 93/29, mean age 43.9 ± 14 yrs) affected by ACTH-dependent CS followed at two tertiary care centers in Italy. CRH test and HDDST were performed on the suspect of CD and all patients were submitted to pituitary MRI; the whole cohort underwent pituitary surgery (TSS). The pituitary origin of ACTH secretion was confirmed by biochemical remission after TSS, histology and/or hypoadrenalism (at least 6 months).
Results
A negative MRI or a lesion <6 mm were detected in 74 patients (60.7%, Group A); 26 patients had a pituitary adenoma between 6-10 mm (21.3%, Group B), 22 patients a macroadenoma (18%, Group C). Patients of Group C showed higher basal ACTH levels compared to patients with microadenomas (Group A + B) (116.8 ± 107.2 vs 50.6 ± 29.4 ng/L, $P<0.05$). No difference in basal cortisol, urinary free cortisol and late night salivary cortisol levels was found. A positive response to CRH test and HDSST was recorded in 92% and 93% of cases, respectively. The diagnosis of CD was confirmed by BIPSS in 24 patients. Overall, surgical remission was achieved in 90/122 (73.8%) patients, without differences between groups. Finally, considering patients of Group A with concordant positive HDDST and CRH test, no difference in surgical outcome was found between patients who performed BIPSS and those who did not (24/35 (68.6%) without BIPPS vs 13/19 (68.4%) with BIPSS, $P=1$).
Conclusion
Our study confirms that CRH test and HDDST have high accuracy in differential diagnosis of ACTH-dependent CS. In patients with negative MRI or with a microadenoma <6 mm, the presence of concordant positive noninvasive tests seems sufficient to establish the diagnosis of CD. BIPSS should be reserved to discordant cases.

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GP166

Results from the phase 3 multicenter SONICS study of levoketoconazole: subgroup analysis of Cushing's syndrome patients with diabetes mellitus

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Background
Cushing's syndrome (CS) has numerous comorbidities, including diabetes mellitus (DM). Levoketoconazole is a ketoconazole stereoisomer in clinical trials for treatment of CS.
Methods
SONICS is a prospective, open-label, phase 3 maintenance-of-benefit study in adults with confirmed CS and mean urinary free cortisol (mUFC) of ≥ 1.5x upper limit of normal (ULN). Repeated hospitalization due to hyperglycemia or any complication related to DM during the previous 12 months were exclusion criteria. There were 3 study phases: dose-titration (DT; to normalize mUFC; 2–21 weeks), maintenance (M; 6 months), and extension (6 months). The study met the primary end point of mUFC normalization at the end of M (EoM) without a preceding dose increase during M as recently described (Fleseriu M, et al. ICE 2018). Secondary end points included measures of glycemic control: fasting blood glucose (FBG) and hemoglobin A1c (HbA1c). This analysis compares patients with DM to overall study population.
Results
Intention-to-treat (ITT) population comprised 94 patients; 77 completed DT, 61 completed M. At baseline, overall median (range) age was 44 (18–75) years; 82% were female; 85% had Cushing's disease (CD); and 38% had DM at screening. In 36 patients with DM: median (range) age was 48 (22–75) years; 92% were female; 81% had CD. Median (range) baseline mUFC was similar for the DM subset (2.6x [1.2x–30x] ULN) and ITT population (3.0x [1.2x–30x] ULN). At EoM, 30% (95% CI, 21%–40%) of ITT population achieved the primary end point; DM was not a significant factor in the mUFC normalization model (odds ratio 1.25; $P=0.6058$). In the DM subset, 34% had mUFC normalization (95% CI, 19%–53%). Patients with versus without DM had mean baseline FBG of 123 mg/dL versus 92 mg/dL, and HbA1c of 6.9% versus 5.5%; at EoM, mean FBG was 105 mg/dL versus 84 mg/dL, and mean HbA1c was 6.2% versus 5.3%. Adverse events (AEs) were reported for 97% of DM and 98% of ITT patients; 11% with DM and 13% of ITT discontinued due to AEs. The most common AEs in DM patients were nausea (58%), vomiting (19%), and urinary tract infection (17%); and in ITT population were nausea (32%), headache (28%), and peripheral edema (19%).
Conclusions
In this prospective trial, levoketoconazole at a stable therapeutic dose maintained mUFC normalization for 6 months in 34% of patients with DM versus 30% in the ITT population. Improvements in HbA1c were more notable among patients with DM.

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GP167

Epigenetic regulation by miRNAs in corticotroph tumors

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Introduction
The silencing mechanisms of corticotroph tumors (CT) remain unclear. The most feasible hypothesis lies in a post-transcriptional deregulation of the *POMC* gene, precursor of ACTH. Micro RNAs (miRNAs) are small non-coding RNA molecules involved in the epigenetic regulation of gene expression through their inhibitory action on messenger RNA. miRNAs capable of inhibiting the expression of *POMC* have been described at the level of neurons of the hypothalamus, which gives us a basis to advance in the knowledge of CT.
Aim
The aim of the present study was to determine if epigenetic regulation by miRNAs is involved in the silencing mechanisms of CT.
Methods
We have quantified the relative gene expression of 8 factors (*PKA, MAP3K8, MEK, MAPK3, NGFIB, NURR1, PITX1, STAT3*) and 5 miRNAs (miR375, miR383, miR488, miR200a, miR103) related with the expression of *POMC* by qRT-PCR with TaqMan probes in 24 functioning CT (fCT) and 23 silent CT (sCT).
Results
sCT were significantly higher than fCT (maximum tumor diameter mean $\pm$ standard deviation: 22.44 mm ± 10.26 vs 13.76 mm ± 9.99, $P=0.003$). The expression of miR200a and miR103 was higher in sCT than in fCT ($P=0.007$ and $P=0.011$, respectively). No statistically significant data were found when we evaluated the correlations between gene expression of factors and miRNAs in

fCT. Conversely, we observed a strong negative correlation between miR488, miR200a and miR103 and the expression of *MAP3K8* (rho = −0.747, $P<0.001$, rho = −0.686, $P=0.001$ and rho = −0.782, $P<0.001$, respectively); between miR488 and miR103 and *MEK* expression (rho = −0.605, $P=0.006$ and rho = −0.665, $P=0.002$, respectively) and between miR383 and the expression of *STAT3* (rho = −0.544, $P=0.016$) in sCT. Finally, the maximum tumor diameter was positively correlated with the expression of miR488 (rho = 0.521, $P=0.027$) in sCT.

Conclusions

The inhibition of transcription factors (*STAT3*) and kinases related with proliferation, differentiation and transcription regulation (*MAP3K8* and *MEK*) could participate in the silencing of CT.

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GP168

Evaluation of utility of salivary cortisol levels after suppression with 1 mg Dexamethasone in screening of Cushing's syndrome

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Introduction

Salivary cortisol measurement is a non-invasive and easy test to carry out. It is painless and does not cause stress.

Aim

The aim of the present study was to evaluate the correlation between salivary cortisol (SaC) and serum cortisol (SeC) after 1 mg Dexamethasone (DXM) overnight and their diagnostic utility as screening test of Cushing's syndrome (CS).

Methods

We performed a prospective study in 92 patients with CS suspicion. Samples of saliva and peripheral blood were collected at 08:00h after oral administration of 1mg of DXM overnight (23:00h). CS diagnosis was confirmed in 10 patients. Salivary and serum cortisol measurements were performed by electrochemiluminscent immunoassay (ECLIA) method on an automated Cobas 8000 (Roche®). To analyze the correlation between SaC and SeC we used the Passing-Bablock nonparametric linear regression test with the statistical package Medcalc®. To calculate the sensitivity-specificity of SeC we used the stablished 1.8 mcg/dL cut-off value. To calculate the best cut-off point of SaC we used the Receiver Operating Characteristic (ROC) curves.

Results

There was a significant correlation between salivary and serum cortisol after 1 mg of DXM overnight, ($r=0.634$; $P<0.001$). The estimated cut-off point for SaC was 0.08 μg/dL. The sensitivity, specificity, PPV and NPV of this cut-off were: 60%, 82.93%, 18.18% and 93.22%, respectively. The sensitivity, specificity, PPV and NPV of 1.8 μg/dL cut-off point of SeC were 70%, 57.32%, 16.67% and 94% respectively.

Conclusion

If these results are reproduced in an independent and bigger sample, the measurement of salivary cortisol after 1 mg of DXM overnight could substitute the classical Nugent's test in the screening of Cushing's syndrome.

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GP169

The role of copeptin and cortisol in critically ill patients

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Introduction

Both cortisol and vasopressin are stress hormones. Earlier, our group demonstrated that serum concentrations of free cortisol at admissions to the Intensive Care Unit (ICU) were independent predictors of survival in critically ill patients. Other investigators have demonstrated that serum copeptin, a surrogate marker of vasopressin may also be a predictive factor in this patient population. The aim of our present study was to compare the prognostic roles of serum levels of cortisol and copeptin.

Methods

In the 69 critically ill patients (39 male, 30 female, mean age 69 ± 11 ys) in whom cortisol levels were determined earlier, serum concentrations of copeptin were measured in their stored samples which had been taken shortly after admission to ICU, using ELISA kits (Abbexa Ltd). The severity of the disease was calculated based on the SAPS II and APACHE II scoring systems. Statistical analyses were performed using SPSS 22.0 and MedCalc 13.3.3.0.

Results

Copeptin, total and free cortisol levels were typically highly elevated: baseline values (ranges) were as follows: 1409.7 pg/mL (98.1–6143.9), 1101.6 nmol/L (112.6–8797.8) and 106.2 nmol/L (0.4–759.9), respectively. Furthermore, these concentrations were significantly (i) higher in non-survivors than in surviving patients with medians (inter-quartiles) 1130.5 pg/mL (778.0–2663.1) vs 770.2 pg/mL (415.9–1672.3), 1141.3 nm/L (744.6–2154.2) vs 634.0 nm/L (394.9–987.4), and 178.7 nm/L (33.3–278.7) vs 15.1 nm/L (4.4–80.4), respectively and (ii) correlated with APACHE II ($R=0.331$; 0.455; and 0.559, respectively) and SAPS II ($R=0.382$; 0.542; and 0.584, respectively) scores. However, in respect to predicting mortality, compared to free cortisol, copeptin (i) showed lower area under the curve during receiver operating characteristic (0.679 vs 0.801), and (ii) was not an independent predictor in multiple binary logistic regression analyses.

Conclusion

In respect of critically ill patients' prognosis, the predictive power of free cortisol is higher than of copeptin.

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GP170

Microstructural white matter changes using diffusion tensor imaging in patients with Cushing's disease

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Cushing's disease (CD) results in chronic exposure to increased levels of cortisol leading to alterations in white matter microarchitecture and adverse effects on cognitive functioning. Diffusion tensor imaging (DTI) is a novel technique used to evaluate the integrity of white matter (WM) architecture. There is little information on DTI changes in CD. We studied WM changes in CD using diffusion tensor imaging and compared with healthy controls. 16 patients with active CD (abnormal low dose dexamethasone suppression test, elevated salivary cortisol, elevated ACTH, pituitary microadenoma on imaging) and 16 matched healthy controls were analysed through DTI (Voxel based analysis) for fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). We also studied cognitive function using a standardized testing protocol for Indian subjects. There were widespread alterations (reduced FA, increased MD, AD, and RD) in patients with CD as compared with controls. Areas of the brain which are involved in cognitive function were significantly affected, included the hippocampus, cingulum and corpus callosum. On cognitive assessment impaired cognitive functioning affecting memory and learning (specifically verbal learning and logical memory) were significantly impaired in patients with CD. In summary, verbal learning and logical memory were impaired in CD. White matter alterations are seen in multiple areas associated with cognitive functioning.

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GP171

A new generation somatostatin-dopamine chimeric analogue exerts potent antitumoral actions on primary pituitary neuroendocrine tumor cells

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Pituitary neuroendocrine tumors (PitNETs) constitute approximately 15% of all intracranial tumors and comprise a varied type of neoplasms that, despite being rarely metastatic, can cause severe comorbidities and increased mortality related to the mass effects and hormonal hypersecretion. The high expression levels of somatostatin and dopamine receptors in these tumors has led to the use of somatostatin analogues (SSAs) and dopamine agonists (DAs) as pharmacological treatments. Nevertheless, a high proportion of patients are or become resistant to these drugs, in that they are unable to respond clinically or biochemically to these treatments. In this context, somatostatin-dopamine chimeric compounds (dopastatins) were developed to increase the efficacy and improve the control of the disease compared with SSAs and/or DAs. The main objective of this study was to determine the direct therapeutic effects of a new generation dopastatin chimeric compound, BIM-065, on primary cell cultures from different PitNETs subtypes. To that end, a total of 31 PitNETs [9 corticotropinomas, 9 somatotropinomas, 2 prolactinomas and 11 non-functioning pituitary tumors (NFPTs)] were collected and dispersed cells were treated with BIM-065 to evaluate different functional endpoints such as cell viability, apoptosis, hormone release, expression levels of key genes and free cytosolic [Ca2+]i dynamics. Additionally, AtT-20 cell-line was used to evaluate signaling pathways in response to this chimeric compound. Our results demonstrate that BIM-065 decreased cell viability in all corticotropinomas and somatotropinomas, as well as, in AtT-20 cells. In contrast, in NFPTs (a tumor type commonly resistant to SSAs and DAs treatment), BIM-065 did not alter cell viability. Remarkably, we observed an increase on apoptosis, and a reduction on ACTH, GH and chromogranin-A secretion in corticotropinomas, somatotropinomas and NFPTs in response to the chimeric compound, respectively. These results were possibly mediated through the modulation of pivotal signaling cascades like [Ca2+]i kinetics and Akt- or ERK1/2-phosphorylation. Taken together, our results reveal a clear antitumoral effect of this new chimeric compound on different PitNETs subtypes, which suggests that this compound could be an efficacious therapeutic option to consider in the treatment of this pathology.

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GP172

Pituitary surgery as first-line therapy for microprolactinomas

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Introduction
Dopamine agonists (DA), reference treatment for microprolactinomas, rarely allow long term remission. The performance of endoscopic pituitary surgery should be examined as first-line treatment.
Objective
To evaluate the remission rate of microprolactinoma operated by endoscopic transphenoidal approach
Methods
We retrospectively studied the surgical results of the 35 microprolactinomas operated between 2010 to 2017 in our institution by a single surgeon (EJ). We analyzed the immediate (3months) and long term (last follow-up) remission rates, as well as the post-operative complications.
Results
The sex ratio was 7.8 (F=31) and the mean age at diagnosis was 27±8 years. Seven patients were immediately operated (patient choice), 28 received pre-operative DA (median 7.5 (0.2–188) months)) with cabergoline ($n=17$), quinagolide ($n=6$), bromocriptine ($n=3$), or indetermined ($n=2$). DA achieved prolactin normalization in 13/28 patients (46%). Surgical indication was DA intolerance ($n=13$), patient choice ($n=13$), resistance despite DA high dose ($n=2$). Most of adenomas were noninvasive for cavernous or sphenoid sinus (34/35) and non-proliferative (grade 1a $n=26/35$). No patient presented pituitary deficiency after surgery. Two presented hyponatremia due to SIADH with spontaneous resolutions in few days. Other complications included sinusitis ($n=3$) and one cerebral fluid leak without meningitis. At 3-months ($n=33$), remission rate was 97% (32/33): one patient, intolerant to high dose DA, with 9 mm invasive tumour before surgery, required post-operative Cabergoline treatment (0.5 mg/day). Long term remission rate ($n=33$) after a median follow-up of 1.3 year [0.25; 9.4] was 81.8% (27/33). Only two patients required DA to control clinical symptoms, 3 presented slight elevation of prolactin level without clinical symptoms or tumor recurrence. The median time before recurrence was 5.4 years [0.7; 9.4]. All women (29) recovered a normal gonadotropic function, allowing 6 pregnancies in 5 patients. Sex, age at diagnosis, pre-operative DA,prolactin level, tumor size, cavernous sinus invasion (radiological or operative) and grade tumor were not significantly associated with long-term remission using univariate analysis. However, all recurrent patients were DA pretreated.
Conclusion
This study showed a high long term remission rate compared to the rate of prolactin normalization under medical treatment, while post-operative complications were acceptable. Surgery could be considered as first line treatment in microplactinomas. Remission rate being higher without preoperative DA, surgery may be proposed before any medical treatment.

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GP173

Excellent tumor response to pasireotide therapy in an aggressive and dopamine-resistant prolactinoma

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Background
Prolactinomas are the most frequent secreting pituitary adenomas encountered in the clinical setting. Cabergoline is considered the mainstay medical treatment and transsphenoidal surgery (TSS) is recommended for patients that are medically resistant to dopamine agonist therapy. Resistance to dopamine agonists is commonly defined as failure to normalize prolactin and less than 50% decrease in tumor diameter at a maximal labeled dose of 2.0 mg/week. Pasireotide LAR (PAS-LAR) is a 2nd generation multi-somatostatin receptor (SST) ligand, with particularly high affinity for SST_5 receptor.
Case presentation
A 61-year-old woman was referred for evaluation of a dopamine agonist-resistant prolactinoma. In 1993, she presented in a local hospital with only secondary amenorrhea since the age of 25. Her laboratory results showed hyperprolactinemia and her MRI revealed an invasive macro-adenoma in the anterior lobe of the pituitary. In the local hospital the patient received twice TSS and radiosurgery due to regrowth of the tumour with visual field defects on dopamine agonists. She was treated with cabergoline (weekly 3.0 mg), but eventually therapy failed and both hyperprolactinemia and clinically relevant tumor growth occurred again (227.36 ng per milliliter, tumour size 2549 mm^3). We tried higher dosages of dopamine agonists (up to weekly 7 mg) as well as in combination with 1st generation SST analogues. This again appeared to be unsuccessful (679.25 ng per milliliter, tumour size 3900 mm^3). Before the use of temozolomide, we attempted PAS-LAR in combination with cabergoline to which our patient responded excellently (0.47 ng per milliliter, tumour size 1300 mm^3). An important argument supporting to initiate PAS-LAR was the absence of visual field defects, which provided a window of opportunity. Immunohistochemistry showed membranous expression score of IRS 9 for SST_2 and IRS 12 for SST_5 and strong reactivity for prolactin. PAS-LAR markedly reduced the tumour size from 3900 mm^3 before initiation to 1300 mm^3 24 months after treatment. Also, it lowered prolactin levels below upper limit of normal (43.9 ng per milliliter) within 2 months of administration to 0.47 ng per milliliter. Furthermore,

T2-hyperintense signal and inhomogeneity on T1-signal intensity of the adenoma was observed after PAS-LAR treatment, indicating cystic degeneration/or tumour cell necrosis, which suggests an antitumour effect.
Conclusion
PAS-LAR therapy holds potential in dopamine agonist- and 1st generation SST analogue resistant prolactinomas that express high affinity for SST_5. Furthermore, switching to PAS-LAR can be considered in patients with an aggressive tumour as an in between treatment step before starting with Temozolomide.

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GP174

Sleep disorders after craniopharyngioma surgery

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Introduction
Vicinity and adherence of hypothalamic nuclei to craniopharyngioma explain the high rate of complications and difficulties of removal of these tumors.
Subjects and methods
In this retrospective study 50 patients (10 adults and 40 children or adolescents) harboring craniopharyngioma were included. These patients were operated mainly by a frontal approach. We evaluated the frequency of sleep disorders secondary to hypothalamic damage and their predictive factors.
Results
Eight patients (16%) developed hypothalamic syndrome following craniopharyngioma surgery. Sleep disorders in the form of hypersomnia were reported in 3 patients (6%). Other reported abnormalities were: appetite disorders in 8 patients (16%) (one case of anorexia complicated by fatal cachexia and seven cases of polyphagia complicated by morbid obesity, metabolic syndrome and/or steatohepatitis) and thermoregulation disorders in 3 patients (6%). Circulatory and respiratory disorders were not reported in our patients. Extent of surgery and young age were the main predictive factors for the occurrence of hypothalamic damage.
Discussion and conclusion
Sleep disorders were reported in 6% after surgery of craniopharyngioma. Young age and extent of surgery were the main predictive factors. These factors are foreseeable as pediatric craniopharyngioma are of adamantine type. This type of craniopharyngioma is characterized by infiltration of surrounding tissues and a more pronounced peri-tumorous fibrosis making surgical removal more laborious and raising the risk of hypothalamic damage.

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GP175

Normal IGF-bioactivity and low free IGF-I in patients with Prader-Willi syndrome with high total serum IGF-I: immunoreactive IGF-I concentrations poorly reflect IGF bio-activity and bio-availability

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Introduction
Prader-Willi Syndrome (PWS) is a complex syndrome including hyperphagia, pituitary hormone deficiencies, low muscle mass and cognitive impairment. Treatment with recombinant Growth Hormone (GH) has beneficial effects on body composition, physical performance, cognition, psychomotor development, respiratory function, and quality of life of patients with PWS. GH treatment has a narrow therapeutic range. Clinicians measure serum immunoreactive Insulin-like Growth Factor 1 ('total IGF-I') levels to titrate the dose of GH. However, in patients with PWS, IGF-I levels are often much higher than expected based on GH dose. As a result, clinicians have to reduce the GH dose, with consequent loss of beneficial effects of GH. Preliminary data[1] showed that IGF-bioactivity was low and not related with total IGF-I in children with PWS, suggesting that IGF might be less active, or less available, in PWS. Proof of low IGF bioactivity or bio-availability in PWS would have great clinical consequences, as this would imply that high levels of total IGF-I might not have negative side effects and can therefore be accepted in patients with PWS.
Methods
We measured total IGF-I, bioactive IGF and free ('bio-available') IGF in 22 PWS (15 with and 7 without GH) patients and 112 healthy controls. In order to measure IGF-bioactivity, we have set up and optimized an in-house IGF-I receptor kinase activation assay (KIRA). KIRA is a cell based system where IGF bioactivity is reflected by phosphorylation of the IGF receptor. In order to measure IGF-I bioavailability ('free IGF-I), we used a new commercially available ELISA (Ansh Labs, Webster, TX). Both IGF-I bioavailability and IGF-bioactivity were compared with total (immunoreactive) IGF-I values.
Results
We found a striking difference in free IGF-I between PWS and control samples. Free IGF-I levels were extremely low in PWS. Both free IGF-I and IGF-bioactivity correlated poorly with total IGF-1 levels. IGF bioactivity in GH-treated PWS patients was comparable to (non-GH treated) healthy individuals. GH-treated patients with extremely high total IGF-I levels have normal IGF-bioactivity.
Conclusion
Total IGF-I is a poor marker of IGF-bioactivity and bio-availability in PWS patients. Our results suggest that a GH dose reduction may not be needed in PWS patients with a high total IGF-I. Further studies are needed to confirm our data and to investigate whether IGF-I bioactivity and IGF bio-availability are more reliable parameters for GH dose titration in PWS.
Reference
1. Bakker N, *et al*. *JCEM*.

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Benign Thyroid Disorders

GP176

Do different initial doses of L-T4 within the range of 10–15 mcg/kg/die influence neurodevelopment during the first two years of life in children with congenital hypothyroidism?

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Background
The initial L-T4 dose in the treatment of congenital hypothyroidism (CH) currently recommended is 10–15 mcg/kg/die.
Objective
We designed a multicenter randomized trial to evaluate the effects of different starting dose of L-T4 within the range 10–15 mcg/kg/die on neurocognitive development in children with CH.
Methods
Seventy-two children with CH diagnosed by neonatal screening were enrolled in the study. They were randomly assigned to receive an initial L-T4 dose of 10–12.5 mcg/kg/die (group A) or 12.6–15 mcg/kg/die (group B). All patients underwent clinical examination and FT4 and TSH measurement periodically during the first two years of life. At the age of 12 and 24 months they underwent Griffiths Mental Development Scales to evaluate cognitive development.
Results
Growth during the first two years of life was comparable in the two groups of patients. Neurodevelopmental evaluation showed no significant difference in Global and Subscales Quotients between the two groups – at 12 and at 24 months of age (Table 1).

Table 1

	Group A	Group B	P
Global Developmental Quotient 12 months	105.2±12.6	104.5±12.8	Ns
Locomotion DQ	99.1±14.7	96.7±18.4	Ns
Personal/social DQ	97.7±13.7	102.2±13.3	Ns
Language DQ	109.1±10.8	107.3±14.6	Ns
Eye-hand coordination DQ	107.6±17.5	104.4±17.8	Ns
Performance DQ	109.5±19.9	109.8±20.6	Ns
Global Developmental Quotient 24 months	96.9±16.6	100.6±16	Ns
Locomotion DQ	109.1±23.3	111.8±22.1	Ns
Personal/social DQ	93.3±25.3	99.9±21.4	Ns
Language DQ	87.7±21.7	91.2±20.1	Ns
Eye-hand coordination DQ	100.7±17.5	104.4±13.5	Ns
Performance DQ	102.4±15.4	105.4±15	Ns

Conclusion

Different initial doses of L-T4 within the range of 10–15 mcg/kg/die are not associated with differences in neurodevelopment during the first two years of life in CH patients.

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GP177

Abstract Unavailable.

GP178

Cystic fibrosis as a novel cause of thyroxine (l-t4) malabsorption and increased requirement

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Background

Cystic fibrosis (CF), a monogenic disease from mutations in the CFTR gene on chromosome 7, causes pancreatic insufficiency and impaired nutrients absorption. Unlike other malabsorption disorders, no data are available in literature on L-T4 absorption in CF. This study analyzed L-T4 absorption and requirement in hypothyroid CF patients.

Methods

Ten CF patients (7 F, 3 M; mean age 37 yr), with autoimmune ($n=6$) or post-thyroidectomy ($n=4$) hypothyroidism, were administered L-T4 tablets. None took medications known to alter L-T4 absorption or metabolism. Fifty age- and sex-matched subjects (43 F, 7 M; mean age 40 yr), with either autoimmune ($n=25$) or post-operative ($n=25$) hypothyroidism, served as internal reference group. All patients were advised to take oral L-T4 (starting dose 1.6 μg/kg/daily) at morning under fasting, at least 1 h before breakfast. Target serum TSH values were 0.5–3.0 μIU/ml, according to patients' age. In each patient, serum TSH and FT4 were measured at enrolment, 8 weeks after starting L-T4 and 4 weeks after every dose adjustment. Two CF patients (1F and 1 M) volunteered for an acute loading test of 600 μg L-T4.

Results

At enrolment, the 6 CF patients with HT had subclinical hypothyroidism (median TSH 6.1 uIU/ml; range 5.2–10) and the 4 patients who had undergone thyroidectomy were overt hypothyroid (median TSH 26.5 μIU/ml; range 11–61, on discharge). L-T4 was started as described. After 8 weeks, all CF patients had inappropriately high serum TSH (median 5.2 μIU/ml vs 2.0 μIU/ml in controls) despite an adequate L-T4 daily dosage, indicating T4 malabsorption. In such patients L-T4 dose has been increased by 25% to 50% or more (2.0 to 5 μg/kg/d) depending on the aetiology (autoimmune/post-operative) compared to controls (median dose 1.68 μg/kg/d; $P=0.001$). Also, target serum TSH (median 2.95 μIU/ml) was reached in 10±3 months compared to 4±2 months in controls ($P=0.001$). In the two patients participating to the acute loading test, T4 pharmacokinetic indices (total T4 at 0' = 4.38 μg/dl, normal values 5.1–14.1; Cmax = 5.62 μg/dl, AUC 0–4 h = 21.97 μg/dl) were compatible with malabsorption.

Conclusions

These preliminary observations provide the first evidence of increased need for T4 in CF patients. CF should be included among the digestive diseases causing intestinal malabsorption of L-T4, likely due to the combination of pancreatic insufficiency, chronic intestinal inflammation and reduced production of biliary salts.

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GP179

Long-term cardiometabolic effects of maternal sub-optimal gestational thyroid function and relative treatment in the Controlled Antenatal Thyroid Screening (CATS) study II

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Introduction

The effects of maternal suboptimal gestational thyroid function (SGTF) on age 3 offspring's cognitive function were investigated in the Controlled Antenatal Thyroid Screening (CATS) randomised trial, comparing SGTF mothers who received (SGTF-T), or didn't (SGTF-U), levothyroxine during pregnancy. The analysis was repeated at age 9 in the CATS-II follow-up study, also including children of mothers with normal gestational thyroid function (NGTF). Here we report the long-term effects on anthropometric and cardiometabolic outcomes in both children and mothers assessed at CATS-II.

Methods

Evaluation of 332 mothers aged 41.2±5.3 years (mean±SD) and 326 paired children 9.3±1.0 years after birth: 197 NGTF, 56 SGTF-U, 79 SGTF-T. The BMI was calculated in the whole cohort; in children it was expressed as BMI standard deviation score (BMI-SDS) against UK standards. Subsets also underwent: i) dual-energy x-ray absorptiometry scan of lean/fat mass; ii) Vicorder analysis of systolic/diastolic blood pressure, augmentation index and aortic pulse wave velocity; iii) serum measurement of thyroid function, lipids, insulin and adiponectin. Linear regression was used to analyse the difference between means of the 3 groups (NGTF, SGTF-U, SGTF-T).

Results

Children analysis showed no significant differences between groups in any of the parameters evaluated. Despite baseline (at CATS) maternal BMI was similar among the three groups, at CATS-II SGTF-U mothers had significantly higher BMI, fat mass. triglyceride and insulin levels compared with NGTF and SGTF-T. At CATS-II SGTF-U mothers also had higher TSH levels, since only 24.0% of SGTF-U were started on levothyroxine after CATS, versus 84.5% of SGTF-T ($P<0.001$) (Table 1).

Conclusions

No impact of levothyroxine supplementation during pregnancy in women with SGTF was observed on children's cardiometabolic parameters evaluated at age 9. However levothyroxine treatment commenced after screening for SGTF provided significant metabolic benefits among mothers: treated women avoided the

sustained long-term increase of BMI, fat mass, triglyceride and insulin levels observed in the untreated group.

Table 1

	NGTF	SGTF-U	SGTF-T	P
BMI Kg/m^2 median (IQR)	25.8 (22.9–30.0)	28.3 (24.6–32.6)	25.8 (23.1–29.8)	0.029
Subtotal FAT % mean ± SD	40.2±7.2	42.8±7.2	40.4±7.4	0.017
Triglyceride mmol/l median (IQR)	0.90 (0.70–1.10)	1.01 (0.78–1.40)	0.80 (0.64–1.29)	0.041
Insulin μIU/ml median (IQR)	5.90 (4.60–7.80)	6.30 (4.40–9.15)	5.50 (3.85–7.15)	0.046
TSH mU/l median (IQR)	1.54 (1.12–2.07)	2.45 (1.43–3.50)	1.68 (0.89–2.96)	0.015

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GP180

Urinary concentration of iodotyrosines correlates with the severity of iodine deficiency in dehal1 knockout mice

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Thyroid hormone (TH) synthesis requires iodine, a scarce element whose recycling is mediated by DEHAL1 through deiodination of iodotyrosines MIT and DIT. In humans, *DEHAL1* defects lead to severe congenital hypothyroidism (CH) non-detected by neonatal screening programs, which involves the risk of mental retardation in infants. The timing for establishment of this hypothyroidism remains unknown, but environmental iodine deficiency may represent a triggering factor. While urinary loss of iodotyrosines could represent early biomarkers for the disorder, its determination in fluids remains a technical challenge.
Objective
To measure urinary concentrations of iodotyrosines and test their correlation with urinary iodide in *Dehal1* knockout mice under experimentally controlled iodine deficiency.
Methods
Dehal$^{(-/-)}$ and wilttype (wt) mice were subjected to normal, low, and very low iodine diets (NID, LID, VLID) containing 5.6, 1 and 0.25 μgI/day, for 28 days. At d0, d15 and d28, urinary iodine concentration (UIC) was determined by Kolthoff method and MIT, DIT determined in urine using a novel LC/MS-MS protocol.
Results
At baseline andNID, MIT and DIT urinary levels were statistically higher in *Dehal1*$^{(-/-)}$ (5 and 8 ng/ml) than in wt (1 and 0.5 ng/ml), respectively ($P<0.02$). Accordingly, UIC was increased in *Dehal1*$^{(-/-)}$ (30 mg/dl) compared to wt (15 mg/dl) ($P<0.05$), suggesting that iodide content of iodotyrosines is freed during Kolthoff procedure and adds to the general iodide pool in the urine. This situation persists in time till d28. Under LID, MIT and DIT concentrations remain elevated in *Dehal1*$^{(-/-)}$ (5.5 and 8 ng/ml) compared to wt (0.5 and 0.5 ng/ml) ($P<0.05$) at d15, but start to decrease in both genotypes at d28. UIC was still higher in *Dehal1*$^{(-/-)}$ (4 mg/dl) versus wt (1 mg/dl) ($P<0.05$) at d15 and d28, but decreased with respect to NID. Under VLID, MIT and DIT levels were still remained significantly higher in *Dehal1*$^{(-/-)}$ (4 and 3 ng/ml) compared to wt (0.5 and 0.25 ng/ml ($P<0.05$) at d15. At d28, iodotyrosines lowered to barely detectable levels in wt mice. Finally, UIC levels in *Dehal1*$^{(-/-)}$ were intensely decreased (0.5 mg/dl) at d15 and d28, while wt mice showed undetectable levels, reflecting stringent iodine restriction.
Conclusion
Our data strongly suggest that the accurate measurement of increased urinary loss of MIT and DIT correlates with UIC increment in *Dehal1* deficient mice, which is triggered by iodine deficient intake. Therefore, urinary iodotyrosines may represent pre-clinical biomarkers for early detection and treatment of DEHAL1 deficiency and prevention of mental retardation risks related to late diagnosis of CH.

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GP181

Effect of anti-streptavidin interference when diagnosing thyroid disease using immunoassay analyses

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Background
The purpose of this study was to register the frequency and cause of method-dependent interference in the Roche thyroid immunoassays observed in our laboratory.
Methods
Serum samples to confirm discordant thyroid results were collected from June 2013 to September 2018, in samples sent to the Hormone Laboratory, Oslo University Hospital. The laboratory serves as a reference laboratory on thyroid diseases for about 2/3 of the inhabitants of Norway. We registered 106 samples with discordant pathological thyroid results when analyzed with the Roche methods, but with normal results when analyzed with alternative methods. 42 of the samples were sent to Roche Diagnostics for investigation of the interfering substance.
Results
In the 42 samples investigated we found interference by anti-streptavidin antibodies in 34 cases, antibodies against ruthenium or the idiotype of the ruthenium labelled antibody in three cases and human mouse antibodies (HAMA) in one case. We estimated the frequency of method-dependent interference to 0.2%. Euthyroid persons with streptavidin antibodies may have falsely elevated freeT4, freeT3, anti-thyroxin peroxidase and TSH receptor antibodies and decreased thyroid-stimulating hormone when analyzed with the Roche methods, mimicking a hyperthyroid disease.
Conclusion
Method-dependent interference in Roche thyroid immunoassays is caused mainly by streptavidin-antibodies, which occur more frequently than previously anticipated. This may lead to misdiagnosis and inappropriate medical treatment. Method-dependent errors should be reported to the supplier of the assay. If diagnostic tests showing method-dependent interference are not promptly improved, the laboratory should consider alternative methods.

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GP182

Can hepcidin be a useful marker in the diagnosis and monitoring of de Quervain thyroiditis?

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Introduction
Hepcidin is a reactive inflammatory protein, responsible for ferrum homeostasis. Its concentration was already measured in hyperthyroiditis in the course of Graves disease and after restoration of euthyroidism, but also in growth hormone deficiency, hyperprolactinemia, however no significant changes were noted. De Quervain thyroiditis is a rare type of subacute thyroid inflammation, caused by interplay of unknown infectious, genetic and autoimmune factors and resulting in thyroid hormones imbalance. Thyroid hormones disturbances are frequently accompanied by anemia and affect iron metabolism. The aim of the study is to prospectively assess hepcidin changes in patients with subacute thyroiditis at the time of diagnosis and after remission. To our knowledge it's the first study concerning the issue of hepcidin in patients with de Quervains thyroiditis.
Materials
Out of 40 patients due to restrictive inclusion criteria 21 patients (including 2 males) aged 45±10 years were enrolled to the study at the time of diagnosis and the same number of healthy controls. Hepcidin and thyroid parameters were measured in blood serum before and at 12th week of follow-up after 8 weeks of successful prednisolone treatment.
Methods
Hepcidin 25 was measured by the high sensitive ELISA kit (DRG Instruments GmbH, Germany). TSH, fT3, fT4, aTPO, aTG were measured by ECLIA (Roche, Diagnostics, Indianapolis, IN, USA). Additionally we assessed also complete blood count (RBC, HGB, HCT, MCH, MCHC, RDW-CV) and iron metabolism (Fe, ferritin).
Results
The median of Hepcidin 25 serum concentration was markedly elevated in the de Quervain's patients (48.8 vs. 18.2 ng/mL, $P=0.009$) in comparison to control subjects and decreased significantly after therapy (48.8 vs. 4.0 ng/mL, $P=0.007$). The area under curve (AUC) at ROC analysis for hepcidin in newly diagnosed subjects is 0.735 ($P=0.009$) with cut-off hepcidin value 48.8 ng/mL (sensitivity 0.52, specificity 0.95). Complete blood count parameters and Fe were significantly lower in de Quervain's patients and improved after achieving biochemical remission.
Conclusions
De Quervain's thyroiditis is characterized by increased hepcidin levels. With the cut-off value, establishment of the diagnosis of the disease is more likely. Hepcidin decreases after standard steroid anti-inflammatory therapy, which

favours this protein to be a practical monitoring tool facilitating the decision on tapering the dose of glucocorticoids and a potential predictive factor for the risk of the disease relapse. However, studies on larger group of de Quervain's patients are needed to confirm these observations.

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GP183

High-dose intravenous levothyroxine treatment as a successful, safe and clinically effective therapy option in severe hypothyroidism: a retrospective study

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Introduction
Treatment of hypothyroidism with levothyroxine is effective and simple; however, international guidelines advise starting with low doses in case of severe hypothyroidism, cardiac illness and aged population. Interestingly, and in contradiction to this dogma, high doses of levothyroxine have been given to patients with myxedema coma without untoward effects. The difference between myxedema coma, which deserves an intensive treatment, and longstanding severe hypothyroidism is often a matter of precipitating event or time.
Material and methods
Retrospective analysis of clinical evolution of 70 patients (49 females) with ages between 21 and 92 years (mean: 52.8) with severe hypothyroidism (mean TSH levels of 104.1 mUI/L ($\pm$ 34.6), ranging 52.63 mUI/L to 239.53 mUI/L) treated from 2004 to 2018 at our institution with intravenous levothyroxine at variable doses (most frequently 500 micrograms (divided in 400 and 100 micrograms the next day) with a mean dose of 433.3 micrograms and 2.1 ($+0.5$) days of treatment. Hormonal profile and cardiac safety were assessed daily with electrocardiogram studies. Data were analyzed with the Statistical Package for Social Science (SPSS), version 20.0.
Results

	Pre-treatment	2-3 days post	10-30 days post	>30 days post
TSH(mU/L)	104.1 ($\pm$34.6)	69.25 ($\pm$25.7)	18.49 ($\pm$5.7)	7.01 ($\pm$3.4)
Free T4(ng/dl)	0.39 ($\pm$0.16)	0.67 ($\pm$0.3)	1.02 ($\pm$0.3)	1.21 ($\pm$0.3)
Free T3(pg/ml)	2.24 ($\pm$0.6)	2.59 ($\pm$0.7)	2.72 ($\pm$0.6)	2.80 ($\pm$0.4)

Free T4 became normal in 6.33 days, free T3 in 8.4 days and TSH in 33.5 days. No statistical differences after treatment were observed in blood pressure or electrocardiogram studies after analyzing heart rate, PR, QRS and QT intervals Analysis of data in patients aging more than 65 years or with a previous history of cardiac illness did not differ from the entire population. No serious adverse effects were observed (palpitations, angina pectoris, or other cardiac events) despite 17.14% of patients had some kind of previous heart disease. Up to 97.1% of patients described a sudden non-specific improvement of symptoms during admission,and no new admissions or visits to the emergency room were recorded for one month after treatment.
Conclusions
Intravenous intensive levothyroxine treatment in patients with severe hypothyroidism provides a fast and safe relief in clinical symptoms and biochemical alterations with no evidence of serious events. Moreover, our study also provides evidence that it is safe to treat patients older than 65 years with hypothyroidism with a full replacement dose of levothyroxine.

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GP184

Effect of restoration of thyroid function on body composition, insulin resistance and visfatin concentrations in women with hypo- and hyperthyroidism

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Introduction
The adipose tissue secrets visfatin, that might have metabolic effect. Changes of visfatin serum concentrations have been observed in different thyroid pathologies. Thyroid hormones affect metabolism, thus, both hypo- and hyperthyroidism might significantly alter body composition.
Aims of the study
We aimed to investigate the effect of restoration of euthyroidism on serum visfatin in severe thyroid dysfunction, and its associations with insulin resistance and body composition. To limit the interference of individual factors, we have also analysed changes in three different thyrometabolic states in the same patients.
Patients and methods
The study was designed as an observational with consecutive enrollment. Newly diagnosed females with overt hypo- or hyperthyroidism caused by autoimmune thyroid diseases (Hashimoto's disease or Graves' disease, respectively) were included into the study. Laboratory parameters and body composition were assessed in each patient at the diagnosis and after restoration of thyroid function.
Results
Initially, 105 females were enrolled into the study: 49 hyperthyroid females (median age of 34 years) and 44 hypothyroid females (median age of 46) completed the study. In the hyperthyroid group, visfatin levels increased (<0.0001), while glucose levels decreased (<0.0001) after restoration of euthyroidism. Total body mass and fat mass in the trunk and limbs significantly increased during the treatment. In the hypothyroid group, significant weight loss after treatment resulted from decrease of fat and muscle masses in trunk and limbs. For pooled data of all women and all measurements, weak positive correlation between TSH concentrations and total body weight, as well as fat mass ($r=0.19$, $P=0.01$; $r=0.2$, $P=0.006$, respectively). There was also inverse correlation between FT4 and FT3 and total body weight ($r=-0.246$, $P=0.0008$; $r=-0.17$, $P=0.022$, respectively) and fat mass ($r=-0.16$, $P=0.026$; $r=-0.18$, $P=0.018$, respectively). Visfatin serum concentrations positively correlated with total fat mass ($r=0.19$, $P=0.01$) and insulin levels ($r=0.17$, $P=0.018$).
Conclusions
We may conclude that restoration of thyroid function is not associated with beneficial changes in body composition, especially among hyperthyroid females, reflected by the significant increase of fat mass followed by the increase of circulating visfatin concentrations.

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GP185

Thyroid-related adverse events in patients treated with Nivolumab and Pembrolizumab

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Introduction
Immune-Checkpoint Inhibitors (ICI) are frequently associated with thyroid-related adverse events (AE). Several studies analyzed thyroid disfunctions during ICI therapy, but many aspects remain to be characterized, especially for the most recent anti-PD-1 drugs. The aim of this study is to determine incidence and characteristics of PD-1 inhibitors associated thyroid dysfunction.
Methods
We retrospectively analyzed data of patients with advanced solid tumor treated with Programmed Death 1 (PD-1) inhibitors (Nivolumab, Pembrolizumab) in the Oncologic Unit B of Policlinico Umberto I of Rome, from January 2016 to December 2018. All patients performed baseline laboratory evaluations (TSH, FT3, FT4) that were repeated monthly over the duration of therapy.
Results
The cohort consisted of 126 patient, 66.7% males and 33.3% females with a mean age of 66.4 ± 9.7 years, treated for Non Small Cell Lung Carcinoma (73%), Renal Cell Carcinoma (16.7%), Metastatic Melanoma (7.9%) or other tumors (2.4%). 107 received Nivolumab, 19 Pembrolizumab. Thyroid AE occurred in 31.7% of patients and were asymptomatic in the majority (CTCAE grade 1). None of the patients developed grade 3–4 thyroid AE requiring therapy discontinuation. Hypothyroidism occurred in 17.5% of patients: in 15% it was subclinical (high TSH with normal free circulating hormones) and in 2.5% overt hypothyroidism. Mean TSH concentration at the time hypothyroidism was diagnosed was 10.7 ± 7.26 mUI/ml. Hyperthyroidism was observed in 14.3% of patients: in 9.5% subclinical and in 4.8% overt. The rate of thyroid AE was similar in Nivolumab (31.8%) compared to Pembrolizumab (31.6%). The median time of onset of thyroid AE was 6.5 ± 8.1 weeks (range 3–38): 6 ± 9.6 (4–38) for hypothyroidism, and 7 ± 5.7 (range 3–26) for hyperthyroidism. The majority of AE appeared

within the first 3 month (72.5%), none developed after 10 months. Of the 22 patients with hypothyroidism, 63.6% had received a previous treatment with tyrosine-kinase inhibitors (TKI). Logistic regression analysis showed that pre-treatment with TKI was the most potent predisposing factor (OR 8.19, 95%CI: 2.45 to 27.37, $P=0.001$) followed by female gender (OR 3.29, 95%CI: 1.26 to 8.57, $P=0.015$).
Conclusion
Thyroid AE are common during PD-1 inhibitors therapy and usually occur within the first 3 months of treatment, especially in subjects pretreated with TKI. Serial measurement of thyroid function is strictly recommended, especially in these patients, as thyroid disorders can be asymptomatic. No differences were found in thyroid effects between Nivolumab and Pembrolizumab.

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GP186

Metformin reduces risk of benign nodular goiter in patients with type 2 diabetes mellitus

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Background
Whether metformin might affect the risk of benign nodular goiter in patients with type 2 diabetes mellitus has not been investigated.
Methods
Patients with new-onset type 2 diabetes mellitus during 1999-2005 were enrolled from Taiwan's National Health Insurance database. Analyses were conducted in a propensity score matched-pairs of 20,048 ever users and 20,048 never users of metformin. The patients were followed until December 31, 2011 for the incidence of benign nodular goiter. Hazard ratios were estimated by Cox regression incorporated with the inverse probability of treatment weighting using the propensity score.
Results
Among the never users and ever users of metformin, 392 and 221 cases were diagnosed of benign nodular goiter during follow-up, with incidence of 457.88 and 242.45 per 100,000 person-years, respectively. The overall hazard ratio for ever versus never users was 0.527 (95% confidence interval: 0.447−0.621). When cumulative duration of metformin therapy was divided into tertiles, the hazard ratios for the first (<25.3 months), second (25.3–57.3 months) and third (>57.3 months) tertiles were 0.815 (0.643–1.034), 0.648 (0.517–0.812) and 0.255 (0.187–0.348), respectively. Sensitivity analyses estimating the overall hazard ratios for patients enrolled in each specific year from 1999 to 2005 consistently showed a lower risk of benign nodular goiter among users of metformin.
Conclusion
Metformin use is associated with a lower risk of benign nodular goiter.

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Adrenal and Neuroendocrine - Clinical

GP187

Primary adrenal insufficiency in children: results from a large nationwide cohort

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Background
Primary Adrenal Insufficiency (PAI) is a rare life-threatening disorder. Data on etiology and outcome of PAI in childhood are scanty, with the exception of Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD). The aim of our study is to evaluate etiology, morbidity and long-term outcome of PAI in a large cohort of children and characterize clinical presentation in subjects with PAI not due to 21OHD CAH.
Material and methods
802 children followed in 8 tertiary centers were retrospectively included.
Results
85% of patients ($n=682$) had 21OHD CAH and were not reviewed further. Different etiologies were found in 15% subjects ($n=120$): 37.5% had autoimmune PAI (10% isolated; 20.8% Autoimmune Polyendocrinopathy Syndrome type 1; 6.7% Autoimmune Polyendocrinopathy Syndrome type 2); 25% had steroid biosynthetic defects: 11-hydroxylase deficiency ($n=3$), 3β-hydroxysteroiddehydrogenase deficiency ($n=6$), 17α-hydroxylase deficiency ($n=1$), X-linked Adrenal Hypoplasia Congenita due to DAX1 mutations($n=13$), Familial Glucocorticoid Deficiency due to mutation in MC2R ($n=4$) or MRAP ($n=1$) and Glycerol Kinase Deficiency ($n=2$). 20.8% ($n=25$) had adrenoleukodystrophy; 6.7% ($n=8$) had rare syndromes (TripleA, Pearson); 2.5% ($n=3$) had a history of infection or hemorrhage. Finally in 7.5% of patients ($n=9$) no defined etiology was found. Mean age at diagnosis was 6.7 ± 5.2 yrs; time between onset and diagnosis ranged from 0 to 56 months. Common signs/symptoms were fatigue (76.7%), hyperpigmentation (48.3%), dehydration (31.7%), neurologic signs (32.5%) and hypotension (29.2%); most common biochemical finding was increased ACTH (89.2%), followed by hypocortisolism (64.2%) and hyponatremia (50%) whereas hyperkalemia and hypoglycemia were found in 28.3% and 25.8% of subjects, respectively. Overall mortality was <1%.
Conclusion
In our large cohort of pediatric patients with PAI, the most common cause of adrenal insufficiency is CAH due to 21OHD. Among patients with non 21OHD PAI we found that the second most frequent cause was autoimmunitiy, mostly represented by congenital autoimmune polyendocrine syndromes. Other causes were in order represented by rare steroid biosynthetic defects, adrenoleukodystrophy and rare congenital syndromes. 7.5% of our patients still remain without a definite diagnosis. With the exception of hyperpigmentation, which occurs late in the majority of cases, signs and symptoms at presentation of PAI in our cohort were highly aspecific leading to significant delay in diagnosis in particular in older children.

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GP188

Increased risk of infections in Addison's disease and congenital adrenal hyperplasia patients: a longitudinal study based on a United Kingdom primary care database

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Background
Primary adrenal insufficiency (PAI) can be of autoimmune origin (Addison's disease, AD) or due to inborn disorders of steroidogenesis (congenital adrenal hyperplasia, CAH). Prognosis of patients with PAI has improved considerably after glucocorticoid replacement therapy became available. However, even in recent years, an increased risk of death has been described in both AD and CAH patients. Moreover, even with the current state-of-the-art replacement therapy, PAI patients are at an increased risk of hospital admission for infections. However, the risk of primary-care managed infections is unknown.

Methods
We performed a retrospective longitudinal cohort study to estimate the risk of three specific infections (lower respiratory tract – LRTIs, urinary tract – UTIs, gastrointestinal – GIs) and the antimicrobial prescriptions rate in AD and CAH patients using data from a UK primary care database. Patients with a diagnosis of AD or CAH were compared with randomly matched unexposed patients (1:2 ratio).
Results
A diagnosis of AD and CAH was established in 1580 and 602 patients, respectively. Mean age was 51.7 years for AD patients and 35.4 years for CAH patients. All AD patients and 42% of CAH patients were prescribed glucocorticoids, most frequently hydrocortisone (82%) in AD and prednisolone in CAH (50%). Compared to controls, both AD and CAH patients exposed to glucocorticoids had a significantly increased risk of infection (LRTIs: AD adjusted incidence rate ratio (aIRR) 2.11 [95% confidence interval (CI) 1.64–2.70], CAH aIRR 3.33 [95% CI 1.22–9.11]; UTIs: AD aIRR 1.56 [95% CI 1.34–1.83], CAH aIRR 2.24 [95% CI 1.45–3.46]; GIs: AD aIRR 3.74 [95% CI 2.94–4.76], CAH aIRR 1.94 [95% CI 1.06–3.56]). This increased risk was also confirmed by an increased prescription rate for antibiotics (AD aIRR 1.74 [95% CI 1.70–1.78], CAH aIRR 1.44 [95% CI 1.38–1.50]) and antifungals (AD aIRR 1.85 [95% CI 1.71–2.01], CAH aIRR 1.63 [95% CI 1.38–1.91]) in both GC-exposed cohorts.
Conclusions
In this study we demonstrated for the first time a glucocorticoid-driven increase in LRTIs, UTIs and GI infections in AD and CAH patients in a primary care setting, with concurrently increased antibiotics and antifungal prescription rate. Future studies will need to address whether this increased infection risk could be reduced by more physiological GC replacement modes.

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GP189

Plasma renin concentration is associated with cardiac function and morphology in primary adrenal insufficiency

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Background
Despite adequate glucocorticoid (GC) and mineralocorticoid (MC) replacement therapy, primary adrenal insufficiency (AI) is associated with an increased mortality, mainly due to cardiovascular disease. The role of MC replacement is not known. Therefore we assessed whether renin concentrations during routine GC and MC substitution therapy are associated with cardiac function and morphology.
Methods
17 patients with AI underwent magnetic resonance (MR) spectroscopy and imaging measurements to assess cardiac function and morphology, ectopic lipid content in myocardium and liver, pericardial fat mass and the ratio of visceral/subcutaneous fat mass. Additionally, blood was drawn to investigate glucose and lipid metabolism. They were compared to 34 healthy controls matched for age and BMI. Patients were divided according to their actual plasma renin concentration at the study visit (Actual-$Renin_{low}$ *vs* Actual-$Renin_{high}$) and their median plasma renin concentration of previous visits (Median-$Renin_{low}$ *vs* Median-$Renin_{high}$).
Results
Ejection fraction was higher (67 ± 5 *vs* $55\pm3\%$; $P=0.001$) and left ventricular mass was lower (60 ± 9 *vs* 73 ± 10 g/m^2; $P=0.025$) in Actual-$Renin_{high}$. Median-$Renin_{high}$ was associated with lower cardiac mass (64 ± 9 *vs* 76 ± 11 g/m^2; $P=0.029$). Blood pressure, glucose and lipid metabolism, as well as ectopic lipid content, pericardial fat mass and visceral/subcutaneous fat were not different between the groups. Compared to controls ejection was significantly lower in patients with AI (56 ± 4 *vs* $63\pm8\%$; $P=0.019$). No differences were found in patients with $\leq$ 20 mg compared to $>$ 20 mg hydrocortisone per day.
Conclusions
Higher renin concentrations are associated with more favorable cardiac function and morphology in patients with primary AI.

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GP190

Management and outcome of pregnancies in women with adrenal insufficiency: experience from a retrospective European study

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Background and aims
Recommendations for the management of pregnancies in patients with adrenal insufficiency (AI) are scarce. The aim of this study was to analyse current clinical approaches in seventeen specialized centers across Europe with a particular focus on maternal and fetal outcome.
Patients
95 pregnancies in 86 patients with AI of different aetiology [Addison's disease ($n=37$), secondary AI ($n=22$), congenital adrenal hyperplasia (CAH) ($n=22$), or other reasons of AI including bilateral adrenalectomy ($n=5$)] were followed since 2013. Clinical and biochemical parameters and treatment details were assessed before and during pregnancy and maternal and fetal outcomes were recalled.
Results
66.3% (59/89) of the pregnancies were substituted with hydrocortisone in two or three daily doses while 14.6% (13/89) were treated with modified hydrocortisone, 9% with prednisolone, 5.6% with cortisone acetate and 6.7% with a combination of different steroids. The mean hydrocortisone equivalent dose before pregnancy was significantly lower in comparison to that during pregnancy (21.0 ± 7.7mg/day before vs. 23.1 ± 8.0 during 1st trimester, 25.5 ± 10.6 during 2nd trimester und 25.9 ± 8.3 during 3rd trimester) but did not differ significantly between trimesters. Fludrocortisone was used in 92.9% of the Addison's cases and in 39.1% of women with CAH before pregnancy and dosage was increased in 51% (23/45) of patients. Overall, in 63.1% of all cases glucocorticoid or mineralocorticoid dosage was adapted at least once during pregnancy. For delivery, in 55.3% (47/85) of all pregnancies caesarian section was performed while only in 8/47 cases the reason was clearly documented or was conducted as an emergency procedure. Hydrocortisone administration during delivery varied among different centers with no clearly standardized practice followed. Considering the outcome, 24 of 86 women (27.9%) had a documented history of at least one previous abortion with further three miscarriages taking place during the first trimester within the observation interval. While no maternal or fetal deaths occurred later during pregnancies, in 7/95 pregnancies minor complications for maternal and in 3/95 for fetal outcome were reported.
Conclusion
Overall, these retrospective data indicate good maternal and fetal outcome of pregnancies in AI patients. However, optimized treatment adjustments during pregnancy and appropriate approaches during delivery remain challenging, considering the lack of evidence-based guidelines. A remaining proportion of reported adrenal crisis during pregnancy and histories of abortion highlight the need for appropriate education of patients and treating physicians as well as early diagnosis of adrenal insufficiency in general.

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GP191

Pneumocystis pneumonia as a major complication of medical treatment for severe Cushing's syndrome linked either to ectopic ACTH secretion or to Cushing's disease

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Several cases of pneumocystosis developing after lowering cortisol serum level have been reported, mostly in patients with ectopic Cushing's syndrome. We report here 2 cases of pneumocystosis which developed after initiation of treatment with metyrapone, one in a patient with Cushing's disease, and the second in a patient with ectopic ACTH secretion by a prostate endocrine carcinoma. Both cases presented severe Cushing's syndrome. We then analyzed the periodic safety update report (PSUR) on metyrapone from 02/2012 to 06/2018 and the litterature Patient 1, a 39 year-old-woman, was diagnosed with severe Cushing's disease and metyrapone treatment was started to improve her condition before pituitary surgery. She developed respiratory symptoms 4 days after starting treatment. Patient 2, a 82 year-old-man, was diagnosed for an ectopic Cushing's syndrome due to endocrine prostate cancer, with diffuse bones metastasis. Respiratory failure occurred 30 days after metyrapone treatment initiation. In both cases, chest CT scan performed after development of dyspnea showed lesional pulmonary oedema and Broncho alveolar lavage (BAL) allowed identification of Pneumocystis jirovecii by PCR (in patient 2, co infection with CMV). Both patients were treated by trimethoprim-sulfametoxazole. Patient 1 was cured, but patient 2 died several days later from severe sepsis with multivisceral failure. Analysis of PSUR identified 5 cases of pneumocystosis, none of which were letal. Analysis of the literature identified 12 cases of pneumocystis jirovecii pneumonia linked to metyrapone in patients with very high levels of cortisol and other cases revealing several days after lowering cortisol levels either with ketoconazole, etomidate bromide or mifepristone. Physiopathology remains unclear but the hypothesis of immune reconstitution inflammatory syndrome is compelling: on the one hand, severe hypercorticism leads to an immunodepression state which favors the colonization by opportunistic organisms, and on the other hand it decreases inflammatory response, which delays apparition of symptoms. After lowering cortisol level, recovery of immunity might trigger an inappropriate host inflammatory response as part of a 'cytokine storm', which would make clinical features appear. These case reports should draw attention to the risk for a potentially letal pulmonary infection that may reveal only after initiation of medical therapy aimed at lowering cortisol levels, in patients with severe Cushing's syndrome who do not show any pulmonary symptoms initially. This risk might justify systematic prophylactic treatment with trimethoprim-sulfametoxazole in such patients, a treatment which is so far not clearly recommanded in the current guidelines.

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GP192

Diagnostic accuracy of captopril challenge test and saline infusion test in patients at high risk for primary aldosteronism

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Background and aim
Aldosterone-to-Renin Ratio (ARR) is recommended as initial test to screen for Primary Aldosteronism (PA), especially in high-risk hypertensive population. Endocrine Society (ES) Guidelines recommend that patients with an increased ARR should undergo one or more confirmatory tests in order to confirm or exclude PA diagnosis. Captopril Challenge Test (CCT) and Saline Infusion Test (SIT) are commonly used in routine clinical practice. The aim of our study was to evaluate the diagnostic accuracy of CCT and SIT in a large series of hypertensive patients with increased ARR.
Materials and methods
We retrospectively analysed data of 230 CCT and 120 SIT of 272 hypertensive patients (95 with PA and 177 with essential hypertension [EH]) with increased basal ARR (>30 ng/dL/ng/ml/h or >91 pmol/L/mU/L). Aldosterone was measured with radioimmunometric assay (RIA) and ARR calculated with Plasma Renin Activity (PRA) until April 2015; then Aldosterone was measured with electrochemiluminescence assay (ECLIA) and ARR calculated with Direct Renin Concentration (DRC). The accuracy of post-CCT ARR and post-SIT plasma aldosterone values for confirming PA was estimated with the area under the receiver operator curve (ROC), performed with SPSS, significance set at $P<0.05$.
Results
The median of post-CCT ARR, calculated both with PRA and with DRC, and post-CCT plasma aldosterone values, both in RIA and in ECLIA, were significantly higher in PA than in EH, as expected ($P<0.001$). Even the median of post-SIT plasma aldosterone values, both in RIA and in ECLIA, were significantly higher in PA than in EH ($P<0.001$). The ROC of post-CCT ARR and post-SIT plasma aldosterone values were 0.839 and 0.888, respectively, showing comparable diagnostic accuracy with a sensitivity of 75.8% and 83.3% and a specificity of 84.6% and 89.2, respectively. The optimal post-CCT ARR cutoff for identifying PA was 31 ng/dL/ng/ml/h, while the optimal plasma aldosterone cutoff value was 15.8 ng/dL post-CCT and 7 ng/dL post-SIT.
Conclusions
Post-CCT ARR, post-CCT and post-SIT plasma aldosterone values were all reliable for PA diagnosis, showing comparable diagnostic accuracy, especially to exclude rather than to confirm the PA. The optimal cutoffs were in line with those recommended by the ES.

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GP193

Comparison of whole-genome expression analysis in patients with secondary adrenal insufficiency treated with conventional treatment versus modified-release hydrocortisone

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Background
Conventional treatment (cortisone acetate or hydrocortisone) of adrenal insufficiency (AI) is potentially associated with glycometabolic alterations, bone loss and reduced quality of life. There is an increasing evidence of a more physiological replacement therapy with modified-release hydrocortisone (Plenadren).
Aim
The objectives of our study were: 1) to compare the gene expression profile of patients under conventional treatment and Plenadren versus healthy controls; 2) to evaluate the effects of Plenadren on glucose, lipid and bone metabolism and clinical parameters.
Materials and Methods
Eleven patients with primary (PAI) and 13 with secondary (SAI) AI were switched from conventional treatment to Plenadren at equivalent dose. Basally, 1 and 3 months after Plenadren, a whole-genome expression analysis was performed in PBMC of 6 patients with SAI and in 6 age and sex-matched healthy controls. Clinical and metabolic parameters (body weight, BMI, blood pressure, HbA1c, total, HDL and LDL cholesterol, triglycerides) and bone turnover markers (osteocalcin, bone alkaline phosphatase [BAP], serum cross-laps [CTX]) were measured, at baseline and 1, 3, 6, 12, 18 and 24 months after Plenadren in patients with PAI and at baseline, 1 and 3 months after modified-release hydrocortisone in patients with SAI.
Results
1) The number of genes differentially expressed (mainly involved in inflammation and immune response) in treated patients compared to healthy controls was higher in samples collected under conventional treatment (t0, $n=247$) than 3 months after Plenadren (t3, $n=114$) and the global gene expression profile after Plenadren was more similar to healthy subject. 2) On Plenadren treatment we observed a decrease of LDL-cholesterol (up to 27.4%), systolic (3.7%) and diastolic (11.2%) blood pressure, fat mass (13.5%) and an increase of lean mass ($+9.2\%$), CTX and BAP, mainly in patients with PAI at 24 months, while HbA1c and T-score remained stable and triglycerides tended slightly to increase.
Conclusions.
Modified-release hydrocortisone may restore a normal gene expression profile and improve metabolic and bone parameters in AI patients compared to the conventional therapy.

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GP194

New perioperative imaging techniques, immunohistochemistry and genetic analysis to investigate the suitability of laparoscopic partial adrenalectomy in primary aldosteronism

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Introduction & Objectives
A laparoscopic radical adrenalectomy is the standard treatment option for unilateral primary aldosteronism. Partial adrenalectomy for solitary adenomas has been suggested to be feasible and adrenal cortex-sparing. However, solitary adenomas may be rare. The purpose of this study was to assess whether partial adrenalectomy in patients with a seemingly solitary adenoma might be worthwhile by relating perioperative imaging to pathologic findings of excised adrenal glands.
Materials & Methods
Fifteen patients with unilateral primary aldosteronism, based on preoperative CT scan and adrenal vein sampling, were treated by laparoscopic total adrenalectomy. We compared findings of intraoperative EUS, ex-vivo MRI of the adrenal specimen (using a 11.7T MR system), immunohistochemistry (CYP11B2 and CXCR4, a recently described marker for aldosterone producing adenomas) and mutation analysis (KCNJ5, ATP1B2, ATP2B3, CTNNB1) regarding the presence of a solitary adenoma or multinodular hyperplasia.
Results
Considering the final pathology report as the gold standard, sensitivity and specificity to detect multinodular glands with EUS were 41.6% and 33.3%, respectively. Ex-vivo MRI identified thirteen of fifteen adrenals (87%) as multinodular where the pathologist initially classified seven of fifteen (47%) adrenals as multinodular. In the final pathology report, wherein the pathologist combined ex-vivo MRI and histology, the pathologist classified twelve of fifteen (80%) adrenals as multinodular. Immunohistochemistry showed in four of twelve (33%) multinodular glands more than one nodule positive for aldosterone synthase. All nodules positive for aldosterone synthase were also positive for CXCR4. In four of fifteen adrenals (27%) somatic mutations were present. In every gland with a mutation only one nodule harbored this mutation, irrespective of glands with multiple aldosterone synthase positive nodules.
Conclusions
In this study we show that intraoperative endoscopic ultrasound is not sensitive enough to detect multinodular glands. Ex vivo MRI and immunohistochemistry detect adrenal nodules that are frequently missed by routine histopathology. Some of these usually small nodules also produce aldosterone. The results from our study show that multinodular hyperplasia is common and questions suitability of partial adrenalectomy in primary aldosteronism because a solitary adenoma cannot reliably be proven pre- or intraoperatively, not even by EUS.

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GP195

Evaluation of clinical and biochemical cure and adrenal CYP11B2 and CYP11B1 immunostaining in primary aldosteronism operated after adrenal venous sampling

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Background
The cure of unilateral primary aldosteronism (PA) after adrenalectomy can result in complete, partial or absent biochemical and clinical improvement[1]. Histological findings from HE samples are of little assistance in determining if adenoma or hyperplastic adrenal tissue is hormonally overactive. Our aim in the present study was to compare immunohistochemical (IHC) CYP11B1 and CYP11B2 staining in adrenal slices to histological diagnosis based on H&E staining.
Methods
We identified prospectively 34 patients with confirmed PA[2]. Surgery was based on lateralization of aldosterone concentration in AVS in 33 patients and on lateralization of ^{11}C-metomidate PET and CT findings in one patient. Post-operatively, clinical and biochemical cure were evaluated at about 3 months. Both H&E and immunohistochemical expression of CYP11B1 and CYP11B2 (rat monoclonal anti-human CYP11B1–80–ndash;7 and mouse monoclonal anti-human CYP11B2–41–17 primary antibodies[3]) were analyzed in 3.5 μm thick adrenal slices in one representative slide from each case. In addition to IHC analysis of aldosterone-producing adenomas (APAs) and hyperplasia, small extranodular CYP11B2 positive cell clusters, so-called aldosterone-producing cell clusters (APCCs) were identified.
Results
After adrenalectomy, 32/34 showed clinical partial or complete cure and 31/32 (data missing for two) biochemical partial or complete cure. The mean aldosterone concentrations, ARR, BP and potassium concentration improved significantly ($P<0.001$ for all). The number of antihypertensive agents used decreased from 2.5 to 1.0 and DDD decreased by 50% ($P<.001$ for both). In H&E staining, 22/34 (65%) subjects were diagnosed with APA and 11/34 (32%) with hyperplasia. One subject did not reveal pathologic findings in H&E. All adrenal samples showed CYP11B2 positivity and most some CYP11B1 positivity. The IHC diagnosis was APA in 16/34 (47%), hyperplastic leading nodule 13/34 (38%) and hyperplasia presenting as APCCs in only 6/34 (18%) subjects. IHC staining with CYP11B2 changed the diagnosis from APA to hyperplasia in 6/34 (18%) and from no pathologic findings to APA in 1/34 (3%). One subject with cortical hyperplasia showed CYP11B1 but not CYP11B2 positivity in main nodule together with multiple CYP11B2 positive APCCs. The degree of biochemical cure did not differ between hyperplasia and APA subgroups.
Conclusions
With IHC staining for CYP11B2, the proportion of histological APA diagnoses decrease. APCCs may be significant source of aldosterone excess in some subjects with PA. IHC staining of adrenal tissue improves subtype diagnostics of PA.
References
1. Williams TA. Lancet Diabetes Endocrinol 2017;5:689
2. Funder JW. JCEM 2016;101:1889
3. Gomez-Sanchez CE. Mol Cell Endocrinol 2014; 5: 111
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GP196

Sexual function in adrenal insufficiency: data from the DREAM trial

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Introduction
Adrenal Insufficiency (AI) is characterized by absolute or relative deficiency of glucocorticoids and adrenal androgen precursors. Patients with AI show an impaired quality of life, metabolic status, immune function and dysregulated circadian genes. Data on sexual function are scarce and often contradictory. The aims of the present study are to evaluate sexual dysfunction (SD) in women and men patients with AI and to investigate the effects of restoring a more physiological circadian rhythm of glucocorticoid administration on sexual function.
Methods
Outcome assessors blinded, randomized, multicenter, active comparator clinical trial. 89 AI patients and 25 adrenal-sufficient matched controls were enrolled in the DREAM trial. AI patients on established multiple times a day glucocorticoid therapy were randomly assigned to continue their therapy or to switch to an equivalent dose of once-daily, modified-release hydrocortisone. 63 patients (34 women and 29 males) consented and completed sexual function evaluation (FSFI, IIEF-5 and AddiQoL questionnaires and hormonal evaluation) at enrollment and study completion (24 weeks).
Results
Sexual dysfunction was found highly prevalent in men (30%) and pre-menopausal AI women (45%); in menopausal AI women it was even more frequent (85.7%), but similar to the general population. In AI women, sexual health positively correlated with duration of disease ($P=0.008$) and estrogenic status ($P=0.007$). The questionnaire's domain for 'arousal' negatively correlated with age. In pre-menopausal women there was no correlation with androgen levels, while sexual function positively correlated with the 'Symptom' score of AddiQoL ($P=0.022$).

In post-menopausal patients there was a positive correlation of sexual function with testosterone levels ($P=0.008$). In males, erectile dysfunction significantly correlated with quality of life ($P=0.020$), while there was no correlation with age, androgen levels and metabolic profile. At 24 weeks there was no detectable difference in sexual function between randomization groups (standard *vs.* switch).
Conclusions
Young patients with AI show an increased prevalence of sexual dysfunction. Sexual health correlated with estrogen levels and duration of disease in women and with QoL in men. Restoring a better circadian profile of glucocorticoid therapy was not effective in improving sexual function. The lack of correlation with androgens in males and pre-menopausal women suggest that sexual dysfunction in AI has a more complex multifactorial etiology.

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GP197

Optimizing mineralocorticoid replacement therapy in patients with congenital adrenal hyperplasia and Addison's disease

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Background
Adrenal insufficiency (AI) results from deficient production/action of glucocorticoids (GCs), with or without deficiency of mineralocorticoids (MC) and adrenal androgens. GC treatment is essential but some patient needs MC therapy to allow sodium(Na^+) retention, potassium(K^+) excretion and to maintain normal plasma volume and blood pressure. Much attention has focused on optimization of GC replacement but no consensus exists for optimization of MC therapy in primary AI. Our aim was to explore the relationship between MC dose, Plasma renin concentration (PRC) and clinically important variables to determine the most helpful in guiding MC dose titration.
Design
We performed an observational, retrospective analysis on 1107 assessments from 281 patients (242 with salt-wasting CAH(SW-CAH) and 39 with Addison's disease(AD)) recruited from local databases and the international congenital adrenal hyperplasia registry (www.i-cah.org). Subgroup analysis was made in adult patients (age$>=$18years) and a longitudinal analysis performed in 92 patients with SW-CAH(median time between assessments 560 days,range 33–2082). PRC, electrolytes, BP and anthropometric parameters were assessed for their utility in optimizing MC replacement dose.
Results
PRC (normal range 11-32 μUI/mL) was low, normal or high in 30%,15% and 55% of patients respectively with wide variability in MC dose (37.7%, 16.6%, 15.4% and 11.7% of patients were on fludrocortisone 100.50.150 and 200 μg/day respectively) and PRC (median 47 μUI/mL, range 0.1–3166). Patients with high PRC had lower Na^+ levels (with no change in K^+), higher mean arterial pressure (MAP), BMI, age and were on the highest total daily MC dose. Univariate analysis demonstrated a direct relationship between MC dose and PRC ($P<0.001$), and an inverse correlation with potassium ($P<0.001$). Using multiple regression modelling, only Na^+ was able to predicted PRC. MC dose predicted K^+, but not MAP or PRC. In the longitudinal analysis, Na^+ concentration at final follow-up visit was associated with the change (Δ) in PRC (B$=$139.538, $P<0.001$). There was no relationship between ΔPRC and final MAP, K^+ or MC dose. No correlation was found between ΔMC dose and ΔPRC,K^+, Na^+ or MAP. Observations were similar in patients with SW-CAH and AD.
Conclusions
The lack of relationship between MC dose and PRC calls into question its utility as an aid to optimise and titrate MC replacement dose. This may reflect variability in sampling with respect to posture, timing and concomitant medications, but suggests that in clinical practice, emphasis should be placed on ensuring normalization of serum electrolytes in the optimization of MC replacement.

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GP198

Analysis of circulating microRNAs in primary aldosteronism

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Introduction
Primary aldosteronism (PA) is a major cause of secondary hypertension. The two major forms of sporadic PA (aldosterone producing adenoma – APA and bilateral adrenal hyperplasia – BAH) can only be reliably differentiated by adrenal venous sampling (AVS). Several mutations have been described for APA, but the pathogenesis of BAH is poorly elucidated. Differentiation of APA and BAH is clinically pivotal, as their treatment is different. There is no blood-borne marker for the differentiation of APA and BAH.
Aims
To determine and compare the circulating microRNA expression profiles of AVS-confirmed APA and BAH plasma samples, and to evaluate their applicability as minimally invasive markers.
Methods
81 AVS-confirmed plasma samples were included (43 APA and 38 BAH). Next-generation sequencing (NGS) on 30 EDTA-anticoagulated plasma samples (16 APA and 14 BAH) was performed by Illumina MiSDefault (discovery cohort) . Significantly differentially expressed microRNAs were validated by real-time RT-qPCR. The validation cohort included 30 samples of the discovery cohort (technical validation) and further 27 APAs and 24 BAHs.
Results
We have found relative overexpression of *miR-30e-5p, miR-223-3p, miR-30d-5p* and *miR-7-5p* in BAH compared to APA by NGS. Validation of 81 samples showed significant overexpression ($P=0.03$) of *miR-7-5p* in BAH samples compared to APA samples. A negative predictive value of 86.7% could be achieved to exclude BAH by a *miR-7-5p* dCT cut-off value of -18.9. No correlation between dCT values and hormonal parameters was found. APA samples displayed considerable heterogeneity in circulating microRNA expression, whereas BAH were much more homogeneous.
Conclusion
APA is more heterogeneous at the microRNA level compared to BAH. *miR-7-5p* was significantly overexpressed in BAH samples compared to APA samples, but its sensitivity and specificity values are not good enough for introduction to the clinical practice at present.

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GP199

LC-MS/MS measurement for urinary aldosterone improves primary aldosteronism screening

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Objective
Primary aldosteronism (PA) is the first cause of endocrine hypertension accounting for about 6% of all cases of hypertension. According to international guidelines, PA screening is based on plasma aldosterone-to-renin concentration ratio (ARR) computation. Nevertheless, measurement of urine aldosterone excretion may be of interest since it integrates aldosterone secretion over 24 hours. However, available urine aldosterone immuno-assays have poor specificity.
Design and method
In this context, we developed a new aldosterone assay using liquid chromatography and tandem mass spectrometry detection (LC-MS/MS) to recover specifically urine free aldosterone and glucuronide metabolites after 18-hour acid hydrolysis. Our method was validated according to FDA recommendations, and covers the expected range of aldosterone concentrations found in 24-hour urine collection (from 1.10 to 75 nM) with improved specificity. It has a within-run precision below 2% and a maximum between-run precision of 5.6%. The diagnostic performance of the assay was assessed in a cross-sectional retrospective study that included 234 subjects: 63 healthy volunteers (HV), 107 patients with essential hypertension (EH) and 64 PA patients. Final diagnosis was based on routine hormone measurements in accordance with international guidelines.
Result
Median (5th to 95th percentile) of 24-hour urine aldosterone excretion was 19.5 (5.2–53.4) nmol/24h in HV, 39.1 (13.3–97.4) nmol/24h in EH and 91.4 (40.6–225.3) nmol/24h in PA subjects. By ROC curve analysis (area 0.864), a cutoff value of aldosterone excretion of 65 nmol/24h yielded a 76.6% sensitivity and 78.5% specificity to discriminate PA from EH patients. 24-hour urinary aldosterone:creatinine ratio was more discriminant than 24-hour aldosterone excretion, with ratios (nmol/mmol) of 1.42 (0.5–3.9) for HV, 3.4 (1.3–7.9) for EH and 6.9 (2.5–30.0) for PA. By ROC curve analysis (area 0.867) a cutoff value of 24-hour urinary aldosterone:creatinine ratio of 5.0 nmol/mmol had 81.3% sensitivity and 81.3% specificity to discriminate PA from EH patients. Finally, 11% of our 64 PA patients showed a urinary aldosterone: creatinine ratio above this suggested cutoff value while ARR was below cut-off value.
Conclusion
In conclusion, LC-MS/MS measurement of urinary aldosterone is a specific, sensitive and effective method that could improve the screening of PA.

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Diabetes: Pharmacotherapy

GP200

A liver selective knockdown of Dpp4 by therapeutic siRNA affects lipid metabolism but fails to improve glucose control in diabetic mice

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Objective
The exopeptidase dipeptidyl peptidase 4 (Dpp4) selectively cleaves N-terminal dipeptides from several substrates, including cytokines, growth factors, neuropeptides, and the incretin hormones. The systemic inhibition of Dpp4 by the so-called gliptins (oral Dpp4 inhibitors) represents an effective and established treatment option for type 2 diabetes (T2D). In the current study we investigated in healthy as well as in obese and diabetic mice if a liver selective knock-down of Dpp4 by therapeutic siRNAs could be a novel, similarly effective treatment option for T2D. Liver selective inhibition of Dpp4 by therapeutic siRNAs could potentially reduce unwanted side effects which are induced by systemic inhibition and has the potential to exert a sustained, long-lasting effect compared to the established daily oral treatment regimen. Furthermore, effects on hepatic steatosis, inflammation and lipid metabolism were analyzed in mice after hepatoselective Dpp4 knock-down.
Methods
The knock-down efficacy and IC_{50} values of siRNAs targeting Dpp4 were analyzed in PC3 cells. Diabetic db/db, respective lean controls and lean C57BL/6J mice were injected intravenously with a liposomal formulation of siRNAs targeting Dpp4 (3 injections during 13 days for C57BL/6 mice and 5 injections during 30 days for db/db mice). Mice were metabolically characterized by standard procedures approx. 2 weeks after knockdown of Dpp4. Additional mice were treated with an oral Dpp4 inhibitor as a positive control.
Results
In both mouse models we observed a robust knock-down ~75% of hepatic Dpp4. As expected, the systemic inhibition of the enzymatic Dpp4 activity by an oral inhibitor significantly improved glucose handling and reduced circulating IL-6 levels in diabetic animals. In contrast, the reduction of hepatic Dpp4 production via therapeutic siRNAs does not affect circulating active GLP-1/GIP levels and consequently also no modulation of glucose metabolism was observed in mice (as demonstrated by oGTT and fasting glucose and insulin concentrations). Furthermore, treated db/db mice did not display significant improvements of hepatic steatosis. However, circulating cholesterol and hepatic mRNA expression of genes involved in lipid metabolism, namely *Acaca*, *Scd1*, *Fasn* and *Pparg* were significantly reduced after Dpp4 siRNA treatment.
Conclusion
These results point out that the major source for circulating Dpp4 is probably not the liver and therefore hepatic Dpp4 silencing seems to be not an appropriate tool for the treatment of T2D. However, hepatocyte-derived Dpp4 regulates liver lipid metabolism, potentially though paracrine mechanisms. Thus, targeting this pathway may have benefits that are distinct from those observed with systemic oral Dpp4 inhibitors.

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GP201

Blood intact incretin levels are related to beta-cell function and glycemia in patients with type 2 diabetes

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We performed this study to identify factors related to intact incretin levels in patients with type 2 diabetes (T2D). We cross-sectionally analyzed 336 patients with T2D. Intact glucagon-like peptide 1 (iGLP-1) and intact glucose-dependent insulinotropic polypeptide (iGIP) levels were measured in a fasted state and 30 min after ingestion of a standard mixed meal. The differences between 30 and 0 min iGLP-1 and iGIP levels were indicated as ΔiGLP-1 and ΔiGIP. After ingestion of a mixed meal, iGLP-1 (5.5 ± 3.0 to 10.4 ± 7.0 pmol/l; $P < 0.001$) and iGIP (3.8 ± 3.8 to 21.5 ± 7.1 pmol/l; $P < 0.001$) levels increased by 190% and 570%, respectively. In simple correlation analyses, fasting iGLP-1 was positively correlated with glucose ($r = 0.199$; $P < 0.001$), C-peptide ($r = 0.137$; $P < 0.05$), creatinine ($r = 0.124$; $P < 0.05$) and triglyceride ($r = 0.112$; $P < 0.05$) levels, and negatively correlated with eGFR ($r = -0.139$; $P < 0.05$). ΔiGLP-1 was positively correlated only with ΔC-peptide levels ($r = 0.194$; $P < 0.001$). Fasting iGIP showed positive correlations with HbA1c ($r = 0.146$; $P < 0.01$), fasting glucose ($r = 0.126$; $P < 0.05$) and C-peptide ($r = 0.153$; $P < 0.01$) levels, and negative correlations with ΔC-peptide ($r = -0.183$; $P < 0.01$) and HDL cholesterol ($r = -0.124$; $P < 0.05$) levels. ΔiGIP was negatively correlated with diabetes duration ($r = -0.118$; $P < 0.05$) and HbA1c ($r = -0.196$; $P < 0.001$) levels, and positively correlated with ΔGlucose ($r = 0.210$; $P < 0.001$) and ΔC-peptide ($r = 0.238$; $P < 0.01$) levels. In multivariate analyses adjusting for age, sex, and covariates, fasting iGLP-1 levels were significantly related to fasting glucose ($\beta = 0.189$, $P < 0.01$) and creatinine ($\beta = 0.158$, $P < 0.05$) levels, ΔiGLP-1 levels were positively related to ΔC-peptide levels ($\beta = 0.194$, $P < 0.001$), fasting iGIP levels were related to fasting C-peptide levels ($\beta = 0.160$, $P < 0.01$) and female sex ($\beta = 0.124$, $P < 0.05$), and ΔiGIP levels were positively related to ΔC-peptide ($\beta = 0.165$, $P < 0.01$) and Δglucose ($\beta = 0.138$, $P < 0.05$) levels. Taken together, intact incretin levels are primarily related to C-peptide and glucose levels. This result

suggests that glycemia and insulin secretion are the main factors associated with intact incretin levels in T2D patients.

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GP202

The growth hormone effect blocked with pegvisomant did not alter the free fat acid plasma concentration in pre-diebetic or type 2 diabetic patients treated with empagliflozin

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Context
Sodium-glucose cotransporter 2 (SGLT2) inhibitors induce glycosuria and improve glycemic control, β cell function and insulin sensitivity in type 2 diabetes mellitus (DM2). On the other hand, these drugs predispose to diabetic ketoacidosis by increasing the tonus of glucagon. Glucagon acts on the liver and has no relevant effect on peripheral lipolysis and release of free fatty acids (FFA) as a substrate for ketogenesis, an action attributed to growth hormone (GH). This study aimed to evaluate the role of GH in promoting FFA disposal for ketogenesis in pre-diabetic or DM2 patients treated with empagliflozin 25mg daily.
Design and methods
Seventeen individuals were included in the study. They were all over 18 years old, both sexes, with pre-diabetes or DM2 without use of any antidiabetic drug, excepted metformin; body mass index between 25 and 40 kg/m^2 and HbA1c $>$ 5.7 and $<$11%. Exclusion criteria were: presence of microalbuminuria or chronic renal disease, pregnancy, previous bariatric surgery, liver or heart disease that has repercussion on glycemic control and uncontrolled thyroid dysfunction. After an overnight fast, the participants were submitted to tests where blood samples were obtained at the times: -60, 0, 30, 60, 90, 120, 180, 240 minutes. At time -60 was administrated placebo (test 1) or empagliflozin 25 mg (test 2 and 3). All individuals ate a standard meal (1 boiled egg, parmesan cheese 50 g and bread 125 g) at time 0. After the test 1, all subjects were instructed to take empagliflozin 25 mg daily and the same procedure was done on day 21(test 2) and 28 (test 3). Thirty-six hours before the test 3, all subjects received pegvisomant 30 mg subcutaneous. Plasma concentrations of insulin, glucose, triglycerides, glucagon, GH, total cholesterol and fractions, FFA and IGF-1 were measured.
Result
When we compared to placebo (test 1), the treatment with empagliflozin diminished the plasma levels of glucose (-15.1, -16.7%, $P < 0.05$), insulin (-20.0, -23.3% $P < 0.05$), insulin/glucagon ratio (-21.6, -32.0%, $P < 0.05$) and FFA (-20.3, -23.4%, $P < 0.05$); and also increased the plasma glucagon levels (7.9, 10.7%, $P < 0.05$) - for test 2 and test 3 vs test 1, respectively for all. As expected, the plasma GH concentrations did not alter between test 1 and test 2, but increased dramatically at test 3 (3885%).
Conclusion
Blocking the effect of GH with pegvisomant did not alter the plasma concentrations of FFA in pre-diabetes or DM2 patients treated with empagliflozin.

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GP203

Effects of cardiovascular function of SGLT-2 inhibitos versus DPP–4 inhibitors in type 2 diabetes with coronary artery disease

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Objective
Randomized trials demonstrated a lower risk of cardiovascular (CV) events with sodium – glucose cotransporter-2 inhibitors (SGLT-2i) in patients with type 2 diabetes(T2D) at high CV risk. SGLT2-i should be considered as a valuable therapy in T2D with established atherosclerotic cardiovascular disease (ASCVD) or heart failure (HF). We analyzed the effects of cardiovascular function of SGLT 2 inhibitors in T2D with ASCVD or HF compared with dipeptidyl peptidase-4(DPP-4) inhibitors.
Methods
This is a retrospective, observational study, data from 89 patients with established ASCVD or HF 6 months of the SGLT-2 inhibitors and DPP-4 inhibitors therapy were analyzed, visited medical center from January 2018 to June 2018. We had divided into two groups: one group was SGLT-2 inhibitors and the other was DPP-4 inhibitors and check echocardiography and pro BNP.
Results
A total of 89 patients with T2D were identified as group of SGLT2 inhibitor ($n=41$) or a DPP-4 inhibitor ($n=48$). In SGLT2 inhibitors,mean baseline age was 59 years, duration of diabetes 10 years, HbA1C 7.8%, eGFR 81 ml/min per 1.73 m^2 and body mass index (BMI) 26 kg/m^2. In DPP4 inhibitors,mean baseline age was 65 years, duration of diabetes 13 years, HbA1C 7.6%, eGFR 67 ml/min per 1.73 m^2 and body mass index (BMI) 26 kg/m^2. The mean follow-up time was 2 years, with a total of 89 patient-years. SGLT2 inhibitors had improvement of left ventricular ejection fraction ($+2\%$ vs -2.7%), E/E' (3/40% vs 5/21%)and pro BNP (-374 pg/ml vs $+735$ pg/ml) compared with DPP-4 inhibitors.
Conclusion
SGLT-2 inhibitors improved LV systol, diastolic function and proBNP compared with DPP-4 inhibitors in type 2 diabetes with coronary artery disease.

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GP204

Fasting insulin levels correlate with the incidence of hypoglycemic events in patients with Type 2 Diabetes treated with sulfonylureas: a retrospective cross-sectional study

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Background
Sulfonylureas (SUs) are known to increase fasting insulin levels in patients with Type 2 Diabetes (T2D) treated with these agents. Whether this increase is related to a greater risk of hypoglycemia has not yet been sufficiently elucidated.
Methods
The study included 58 patients with T2D who had been on treatment with SUs, but not insulin, for more than 2 years. Confirmed hypoglycemic episodes during the past year were self-reported by the patients on a retrospective basis, by completing the 'Hypoglycemia Patient Questionnaire' weighted scoring system. Potential relationship of hypoglycemic event frequency with fasting insulin levels and received therapy was investigated.
Results
Fasting insulin concentrations were found to have a low positive and statistically significant correlation with the number of cases of mild hypoglycemia per year (rho$=0.279/P=0.034$), and a moderately positive and statistically significant correlation with the number of severe hypoglycemic events per month (rho$=$ $0.349/P=0.007$) and per year (rho$=0.39/P=0.002$). Patients on glimepiride had significantly higher number of mild hypoglycemic episodes during the previous month ($P<0.001$) and the previous year ($P<0.001$), compared to patients receiving gliclazide. Regarding the relationship between received treatment with SU and fasting plasma insulin levels, no statistically significant difference between gliclazide and glimepiride was observed ($P=0.591$).
Conclusions
The incidence of hypoglycemia in patients treated with modern SUs seems to vary, depending on the specific medication used. Fasting insulin levels could be a predictor of risk of hypoglycemia in patients with T2D on treatment with SUs.

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GP205

Metabolic changes in men undergoing androgen deprivation therapy for prostate cancer

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Introduction
Androgen deprivation therapy (ADT) is widely used around the world for the treatment various stages of prostate cancer. Androgen deprivation therapy (ADT) in men with prostate cancer (PCa) increased chance of developing metabolic disorders in insulin sensitivity, lipid levels, glucose metabolism, body composition (increases fat accumulation concurrently with a decrease in lean mass). These changes are the risk factors for the development of adverse cardiovascular events, including fatal ones.
Objective
To study the development of disorders in glucose metabolism during various regimens of ADT.
Materials and methods
The study included 115 patients with metastatic PCa, observed from 2014 to 2017 in the D.D. Pletneva State Clinical Hospital. Patients were randomised into 2 groups: group 1 ($n=62$) received monotherapy with gonadotropin-releasing hormone agonist (aGnRH), group 2 ($n=53$) received therapy with aGnRH and antiandrogens (maximal androgen blockade (MAB). Among the group 1 mean age was 64.2 years, among the group 2 mean age was 67.5 years. Evaluation of metabolic changes was performed before the start of therapy, 6 months and 1 year after the start of therapy, according to the following parameters: weight, body mass index (BMI), waist circumference (WC), fasting blood glucose level and oral glucose tolerance test.
Results
In both groups, comparable changes in the parameters were detected. After 12 months of therapy there was an increase in body weight by 6.56% in the aGnRH group ($P=0.041$) and by 6.87% in the MAB group ($P=0.045$). BMI increased by 6.19 ($P=0.054$) and by 7.62% ($P=0.036$), respectively, WC increased by 5.1 ($P=0.025$) and 4.48% ($P=0.013$), respectively. Changes in the parameters of glucose metabolism were estimated after 6 and 12 months of therapy. Fasting glycemia increased by 2% in the aGnRH group ($P<0.05$) and 2.36% ($P=0.055$) in the MAB group in 6 months, and in 12 months it increased by 4.07 and 3.7% ($P<0.05$), respectively. In the aGnRH group in 10% patiens diagnosed new cases of diabetes mellitus (DM) and in 10% impaired glucose tolerance during treatment period, therefore 20% of patients demonstrated glucose metabolism disorders during the year of therapy, in the MAB group DM manifested in 8% of patients, impaired glucose tolerance in 10%.
The conclusion
The MAB and monotherapy aGnRH therapy were associated with increase in body weight, WC, impaired of glucose metabolism in the early time (6 months of continuous therapy). It is important to initiate further prospective studies, to provide opportunities to manage these adverse changes.

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GP206

Antioxidant and hypoglycemic effects of gossitan

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Causing production of free radicals and reduction of antioxidant system activity, in the pancreatic β-cells, in particular, resulting in reduction in insulin production and consequently to hyperglycemia, oxidative stress could be a pathogenetic mechanism of morbidity in diabetes mellitus. Search for and development of medicines with antioxidant and hypoglycemic activity remains urgent.
Aim
The work was initiated to study antioxidant and hypoglycemic effects of gossitan.
Materials and methods
Produced from the polyphenol compounds isolated from the upland cotton *(Gossypium hirsutum L)* gossitan is a medicine with interferon-producing and antiviral effects effective against various influenza strains. Antioxidant effects of gossitan were examined in the models of adrenalin autoxidation and ascorbate-dependent lipid peroxidation. Experimental diabetes mellitus was induced by three-fold intraperitoneal administration of diabetogenic doses of alloxan. Gossitan was administered intragastrically in the dose of 4.9 mg/kg within 10 days until blood glucose was 11 mmol/l. Quercetine, a polyphenol, and gliclazide, were used as the controls.
Results
Gossitan was found to cause reduction in adrenaline oxidation by 35.7%, while quercetine reduced it by 37.7%, and twofold reduction in malondialdehyde in the liver homogenate of rats with experimental diabetes mellitus. Per oral administration of gossitan to the rats was found to decrease their blood glucose by 43.6%.
Conclusions
A polyphenol-based medicine, gossitan was found to possess antioxidant activity similar to the one of quercetine and to facilitate blood glucose decrease in rats with experimental diabetes mellitus, which seems to be associated with partial restoration of glucokinase activity in the rat liver and insulin level.

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GP207

Treatment with sitagliptin in patients with type 1 diabetes and type LADA diabetes

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Objective
Preclinical studies have shown that DPP-4 inhibitors (iDPP4) have beneficial effects on functional mass of beta cells and pancreatic insulin content. The aim of this study is to evaluate the efficacy of treatment with sitagliptin in monotherapy or in combination with insulin in person with type 1 diabetes (DM-1) or type LADA diabetes (DM-LADA) of recent diagnosis.
Patients and methods
Descriptive study: patients with DM-1 or DM-LADA in treatment with sitagliptin in monotherapy or in combination with insulin at diagnosis. Variables analyzed at baseline and at 6 and 12 months: type diabetes, age, sex, Body mass index (BMI), HbA1c, C-peptide, pancreatic autoimmunity (anti-GAD Antibody, anti-IA2 Antibody), treatment and adverse effects. Statistical analysis: ANOVA for comparison of means and McNemar for omparison of proportions.
Results
17 patients. 70.6% DM-1 (10 DM-1 patients with positive pancreatic autoimmunity and 2 negative pancreatic autoimmunity), 29.4% DM-LADA. Initial treatment: basal insulin + prandial insulin 35.29% ($n=6$), basal insulin + sitagliptin 29.41% ($n=5$), sitagliptin in monotherapy 35.29% ($n=6$). Treatment at 12 months: basal insulin + prandial insulin 29.41% ($n=5$), basal insulin + sitagliptin 23.52% ($n=4$), sitagliptin in monotherapy 47.05% ($n=8$). No adverse effects. Treatment at 12 months basal insulin + prandial insulin vs basal insulin + sitagliptin vs sitagliptin in monotherapy: age 39.60 ± 16 vs 37 ± 4.69 vs 32.5 ± 10.26 years ($P=0.54$); BMI initial 24.33 ± 3.59 vs 27.37 ± 4.75 vs 24.88 ± 2.76 Kg/m^2 ($P=0.41$); HbA1c initial 10.40 ± 3.55 vs 11 ± 2.12 vs 10.62 ± 3.04% ($P=0.95$); C-peptide initial 0.65 ± 0.36 vs 0.60 ± 0.53 vs 0.61 ± 0.20 pmol/ml ($P=0.96$); level of anti-GAD antibody 708.34 ± 822.51 vs 526.50 ± 982.59 vs 339.93 ± 733.16 U/ml ($P=0.32$); BMI at 12 months 24.44 ± 3.92 vs 27.54 ± 6.05 vs 24.54 ± 2.56 Kg/m^2 ($P=0.41$); HbA1c at 12 months 6.62 ± 0.37 vs 6.27 ± 0.45 vs 6.13 ± 0.60% ($P=0.36$). DM-1 with positive pancreatic autoimmunity 100% ($n=5$) vs 75% ($n=3$) vs 25% ($n=2$), DM-1 with negative pancreatic autoimmunity only sitagliptin in monotherapy 25% ($n=2$), DM-LADA 0% vs 25% ($n=1$) vs 50% ($n=4$)) ($P=0.89$); women 80% ($n=4$) vs 25% ($n=1$) vs 37.5% ($n=3$) ($P=0.19$).
Conclusions
Sitagliptin monotherapy achieves optimal metabolic control in almost half of patients with DM-1 or DM-LADA. The response to sitagliptin monotherapy is not related to any initial parameter. No adverse effects were observed in patients treated with sitagliptina in monotherapy.

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GP208

Effects of glucagon-like peptide 1 receptor agonist on short-chain fatty acids, carbohydrate and lipid metabolism in patients with type 2 diabetes

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Background
Type 2 diabetes (T2D) is a progressive disease. The gut microbiota has recently been identified as a new potential diabetes risk factor. Short-chain fatty acids (SCFAs) are organic fatty acids produced in the distal gut by bacterial fermentation of macrofibrous material that might improve T2D.
Aims
To examine the effectiveness of glucagon-like peptide (GLP)-1 receptor agonist treatment on SCFAs, carbohydrate and lipid metabolism in patients with T2D.
Materials and methods
Sixteen patients with T2D were enrolled in this prospective study. The mean age of patients was 45 (30–60) years. The levels of SCFAs, lipoproteins, serum fasting glucose, glycated hemoglobin (HbA1c), and body mass index (BMI) were examined at baseline and at 8 weeks on aGLP-1 therapy.
Results
At baseline the average glucose levels were 8.18 [5.3; 15.2] mmol/l, HbA1c – 6.7 [4.6; 9.8] %; total serum cholesterol (TC) – 5.46 [3.49; 7.83] mmol/l, low-density lipoprotein (LDL) – 4.26 [2.46; 6.65] mmol/l, high-density lipoprotein (HDL) – 1.17 [0.85; 1.76] mmol/l, triglycerides (TG) – 1.82 [0.56; 3.4] mmol/l and BMI – 39.35 [31.9; 51.0] kg/m^2. After 8 weeks of aGLP-1 treatment was detected a significant decrease in mean glucose levels by 18.2%, HbA1c by 5.22%, TC by 5.31%, LDL by 10%, TG by 12%, BMI by 3.43%, and no significant increase in HDL by 4% from baseline. SCFAs were analyzed in 7 patients. Despite the small number of patients, a significant positive relationship between acetate and BMI ($r(s)=0.31$; $P=0.039$), HbA1c ($r(s)=0.28$; $P=0.015$), LDL ($r(s)=0.26$; $P=0.039$), and negative relationship between butyrate and glucose ($r(s)=-0.41$, $P=0.014$), TG ($r(s)=-0.29$, $P=0.04$) were revealed at baseline. There was no significant correlation between propionate and above parameters. GLP-1 therapy was associated with significant decrease in acetate (from 3.48 [1.26; 7.149] to 2.61 [1.43; 3.5]) ($P<0.01$); no significant in propionate (from 1.29 [0.74; 1.39] to 1.06 [0.77; 1, 39] mg/g) ($P>0.05$) and increase in butyrate (from 0.76 [0.4; 0.98] to 0.86 [0.42; 1.4]) ($P>0.05$). Acetate decrease is associated with decrease in BMI for more than 3% at baseline and an improvement in glycaemia.
Conclusions
The preliminary results are indicating a positive effect of GLP-1 on weight, carbohydrate and lipid metabolism and short-chain fatty acids in patients with T2D.
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GP209

Efficacy and tolerability of dulaglutide in patients with type 2 diabetes: Experience on a secondary Hospital

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Introduction
Dulaglutide (Trulicity®) is a long-acting GLP-1 agonist that received US Food and Drug Administration (FDA) approval in 2014. Dulaglutide is a large sized molecule, which limits its renal clearance. This allows for once weekly dosing; which might improve patient compliance significantly. Extensive Phase III study data have been published with regard to dulaglutide, much of which was part of the AWARD studies, which provide evidence for its use in combination with several other antidiabetic agents.
Objective
The objective of the study was to evaluate the efficacy and tolerability of dulaglutide 1.5mg in patients with type 2 Diabetes, used in monotherapy and in combination with several agents including insulin.
Design and Methods
We present a restrospective, descriptive study. The included subjects were non pregnant adults with type 2 diabetes, who started on dulaglutide between March 2016 and September 2018. Patients were evaluated at 3, 6 and 12 months after the drug was started. Patients with less than 3 month follow-up were excluded.
Results
Data from 82 patients were analysed. Average age was 50.2 ± 9.09 years old with an average of diabetes duration of 9.87 ± 8.07 years. 13 patients (16.3%) were previously on treatment with another GLP-1RA and 52.4% were on insulin therapy. Patients enrolled were uncontrolled, with a baseline A1c of $8.6\%\pm1.5$. Throughout the 12-month study period great reduction in A1C was found (-1.5% at 3 month follow-up, which is mantained at 6 and 12 month follow up (-1.4 and -1.6% respectively)). An average weight reduction of -4.2 kg was observed throughout the study, specially at 6 month follow-up (-5.7 Kg). All results were statiscally significant ($P<0.01$). Only in 9.75% of the subjects ($n=8$), dulaglutide was discontinued due to nausea, vomiting, and diarrea, well-known dependent side effects of dulaglutide. In 4 subjets the drug was stopped because no efficacy was observed in terms of A1C and weight reduction.
Conclusions
Dulaglutide represents a well-tolerated and efficacious option in the treatment of T2DM. It is a viable second-line option after metformin, with demonstrated superior efficacy to other second-line agents. Ongoing trial data will better inform the future place in the therapy of dulaglutide considering the recent guideline emphasis on agents with beneficial effects on CV outcomes.
References
1. Thompson AM, *et al*. Advances in the treatment of type 2 diabetes: impact of dulaglutide. *Diabetes Metab Syndr Obes*. 2016;9:125–136.
2. Scheen AJ. Dulaglutide for the treatment of type2 diabetes. *Expert Opin Biol Ther*. 2017;17(4):485–496.
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GP210

Empagliflozin inhibits apoptosis of pancreatic beta-cells through amelioration of ER-stress.

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Introduction
Type 2 diabetes mellitus (T2DM) is characterized by progressive impairment/loss of pancreatic beta cell function Activation of endoplasmic reticulum (ER) stress by glucose variation has been suggested as an essential step towards beta cell dysfunction. Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are widely used in the treatment of T2DM considering their beneficial cardiometabolic sequalae. In the present study, we aimed to investigate the effect of Empagliflozin on ER stress-induced apoptosis in murine pancreatic islet/beta cell lines.
Material and methods
Hamster HIT-T15 (islet) and mouse BTC-6 (Beta) pancreatic cell lines were maintained in RPMI media, supplemented with 15% FBS.Both cell lines were seeded in 12 well plates and serum starved 16 hrs prior to treatments. After starvation cells were incubated with various concentrations of tunicamycin (5 ug/ml, 10 ug/ml, 20 ug/ml) or Empagliflozin (10^{-8}, 10^{-9} and 10^{-10} M) alone or co-incubated with both agents simultaneously. The expression levels of SGLT-1, SGLT-2, GRP-94, Bip, PERK, elf-2α and CHOP were measured by quantitative real time PCR while protein levels of GRP-94, Bip, p-PERK, elf-2α, P- elf-2α and CHOP were measured by western blotting. Cell proliferation and apoptosis were measured by XTT and Annexin V FITC assays respectively.
Results
SGLT-1 mRNA was detected only in BTC-6 cells while SGLT-2 mRNA was not detected in either cell line. Incubation of BTC-6 cells, but not HIT-T15, with Empagliflozin (10^{-8}, 10^{-9} M. $P<0.05$) resulted in significant increase in cell proliferation compared to untreated cells. Both Hit-15 and BTC-6 cells were sensitive to tunicamycin and underwent significant cell death after 48h treatment ($P<0.01$). Co-incubation of cells with Empagliflozin significantly inhibited tunicamycin (5 ug/ml and 10 ug/ml) -induced cell apoptosis with more robust effect observed in BTC-6 cell line ($P<0.01$) as compared with HIT-T15 cell line. Particularly, co-incubation of BTC-6 cells with tunacamycin and Empagliflozin reduced (ER) stress-induced apoptosis through down regulation of p-elf-2α ($P<0.01$) and CHOP ($P<0.01$) while in HIT-T15 the ER stress was reduced through reduction of Bip ($P<0.01$), p-PERK ($P<0.05$) and CHOP ($P<0.05$) protein expression. These results were in line with mRNA expression results.
Conclusion
Our data indicate that Empagliflozin increases proliferation and reduces cell apoptosis in beta-pancreatic cells, at least in part, via reducing ER stress. The effect of Empagliflozin on beta-cell apoptosis/survival could be mediated through SGLT-1. More studies are needed to verify the efficacy of this class of drugs in maintenance of pancreatic cells survival and function.
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GP211

New insights on strain-specific impacts of probiotics on insulin resistance

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Background and aims
Comparative animal study of efficacy of intermittent short courses administration of lyophilized single-, three- and alive multistrain probiotic on insulin resistance in rats with experimental obesity.
Methods
We included 70 rats divided into 7 groups ($n=10$ in each). Rats of group I were intact. Newborn rats of groups II-VII were injected with monosodium glutamate (MSG) (4 mg/g). Rats of group II (MSG-obesity group) were untreated. The groups III-V received lyophilized mono-probiotics *B.animalis VKL*, *B.animalis VKB*, *L.casei IMVB−7280* respectively. The group VI received the mix of these three probiotic strains. The group VII was treated with multi-probiotic 'Symbiter' which contains 14 alive probiotic strains (*Lactobacillus*, *Bifidobacterium*, *Propionibacterium*, *Acetobacter* genera).
Results
Neonatal treatment with MSG lead to the development of obesity in all MSG-obesity rats and up to 20–70% after probiotic administration. Supplementation of probiotic composition, with preference to alive strains (group VII), led to a significantly lower prevalence of obesity, decreasing of HOMA-IR (2.31 ± 0.13 vs 3.07 ± 0.3; $P<0.001$), proinflammatory cytokines levels (IL-1β, IL-12Bp40) and elevation of adiponectin (5.67 ± 0.39 vs 2.27 ± 0.36; $P<0.001$) as compared to MSG-obesity. Furthermore, significant changes were absent between alive probiotic group (VII) and intact rats ($P=0.098$). Single-strain analysis (group III-V) shows significant decreasing of metabolic parameters, but changes were less pronounced as compared to mixture groups and did not achieved intact rats level.
Conclusion
Multistrain formed mutualistic interactions in mixtures and therefore able to share with different metabolites, affect different receptors, which synergistic overall effect greater than the sum of the single effects.

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Gestational and Type 1 Diabetes

GP212

Prevalence of gestational diabetes during 14 pregnancies of acromegalic women

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Introduction
Abnormalities of glycoregulation are frequent in acromegaly (15-38%) secondary to insulin resistance related to GH/IGF-1 hyper-secretion. The frequency of gestational diabetes (GD) in women with acromegaly was reported in the French multicenter study (JCEM, 2010, 95, 4680) as increased mainly in the absence of pre-gestational control of GH/IGF-1 hyper-secretion. The aim of this study was to evaluate the frequency of GD in a cohort of acromegalic women, and compare characteristics of women with (GD+) or without GD (GD-).
Patients and methods
This is a descriptive monocentric study of 14 pregnancies in 11 women (mean age: 34.0 ± 3.6 years) followed for GH-secreting pituitary macro-adenomas. They were treated with first generation long-acting somatostatin analogues (octreotide LAR $n=3$, mean dose 30 mg/month; lanreotide Autogel $n=11$, mean dose 95 ± 26 mg/month) after a pituitary surgery ($n=6$) or as primary ($n=5$) treatment. Somatostatin analogues were discontinued during 1st trimester, at the time of pregnancy diagnosis. One acromegaly was diagnosed during pregnancy and was treated with octreotide LAR between 12 and 18 weeks of gestation. Before pregnancy, no woman had diabetes mellitus, and GH/IGF-1 hyper-secretion was uncontrolled in 6 women (mean IGF-1: 176% upper limit of normal range).
Results
A GD was diagnosed in 7 pregnancies (50%) on fasting blood glucose in 1st trimester ($n=5$) or an oral glucose tolerance test at 3rd trimester ($n=2$). Insulin treatment was necessary for 4 patients. Before pregnancy, IGF-1 was not controlled in 4 of GD+ and 2 in GD- women. Women with GD were older (GD+ 35.3 years, GD- 32.7 years, $P=0.20$), had increased pre-gestational BMI (GD+ 26 kg/m^2, GD- 20.7 kg/m^2, $P=0.02$), had frequently family history of type 2 diabetes mellitus (GD+3, GD- 0), no history of GD but a history of macrosomia for one patient. The percentile birth weight of newborns was on average 48.7 for GD + and 69.4 for GD- mothers ($P=0.15$).
Conclusion
In this cohort of acromegalic women, the prevalence of GD is increased compared to that reported in the literature, probably secondary to systematic GD screening and to the age of our women (73% were ≥35 years old). Therefore, routine screening of GD should be considered in all women with acromegaly, particularly those with risk factors for the occurrence of GD and with uncontrolled IGF-1.

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GP213

The impact of the intrauterine hyperglycaemia on the expression of genes related to cardio-metabolic diseases in human umbilical vein endothelial cells: results from a randomised, controlled study of different glycaemic targets during gestational diabetes treatment

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Background
Understanding the mechanism whereby the intrauterine hyperglycemia in women with gestational diabetes mellitus (GDM) affects the offspring' predisposition to metabolic and cardiovascular diseases may help prevent their intergenerational transmission. Our aim was to study the effect of the degree and duration of maternal hyperglycemia on the level of expression of genes associated with cardio-metabolic diseases in human umbilical vein endothelial cells (HUVECs) of newborns from women with GDM.
Materials and methods
HUVECs were isolated from 75 women with GDM and 28 women without GDM (control group). Women with GDM treated for GDM starting before 30-th week of gestation, were randomized to 2 groups per target glycaemic levels: GDM1 (tight glycaemic targets, fasting blood glucose <5.1 mmol/L and <7.0 mmol/L postprandial, N=34) and GDM2 (less tight glycaemic targets, <5.3 mmol/L and <7.8 mmol/L, respectively, N=29). Women with GDM who started treatment after 34-th week of gestation (N=11) were considered as late treatment group (GDM3). The level of ICAM1, VCAM1, ANGPTL4, ENG, TRIB1, MT-ND2, TFAM, PTGS1, MEST, PLAC8 and NR3C1 genes expression in HUVECs was determined by RT-PCR.
Results
The four groups did not differ by maternal age and pregestational body mass index. GDM groups (GDM1, GDM2 and GDM3) showed significantly reduced levels of ANGPTL4 gene expression compared to the control group (24.7 ± 26.1, 26.1 ± 40.1, 13.4 ± 11.9 vs 91.6 ± 100.5, respectively, $P=0.009$, 0.014 and 0.002) , but no difference was observed among GDM groups. NR3C1 gene expression also tended to be lower in all GDM groups compared to controls (4.6 ± 2.5, 4.6 ± 1.7, 3.4 ± 1.8 vs 6.0 ± 1.3, respectively, $P=0.093$, 0.051 and 0.006) with no difference among GDM groups. TRIB1 gene expression was lower in GDM3 compared to GDM1, GDM2 and control group (9.0 ± 4.9 vs 23.8 ± 23.9, 28.5 ± 27.2, 21.9 ± 4.1, respectively, $P=0.008$, $P=0.004$ and $P=0.001$) with no difference among GDM1, GDM2 and control group. GDM1 group achieved lower levels of 1 hour postprandial glucose compared to GDM2 during the whole period of the study (6.0 ± 0.4 vs 6.3 ± 0.5 mmol/L, $P=0.036$).
Conclusion
The decrease in ANGPTL4 and NR3C1 genes expression level has been detected in HUVECs of newborns from women with GDM compared to control group. However their expression was not associated with the intensity of glycaemic control and the duration of maternal hyperglycemia. The duration of maternal hyperglycemia was associated with TRIB1 gene expression which was decreased only in the late treatment group.

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GP214

Association between sleep disturbances and fear of hypoglycemia in adults with type 1 diabetes, data from VARDIA Study

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Aims
To assess the relationship between sleep quality and fear of hypoglycemia, glycemic variability and other diabetes-related outcomes in type 1 diabetes.
Methods
Our data were provided by the VARDIA Study, a multicentric observational cross-sectional study conducted between June and December 2015. Sleep characteristics were assessed by Pittsburgh Sleep Quality Index (PQ1I). Fear of hypoglycemia was measured with the Hypoglycemia Fear Survey version II (HFS-II). Glycemic variability was determined using the CV of three 7-points self-monitoring blood glucose profiles and the mean amplitude of glycemic excursion (MAGE). Comparisons between 'good' (PQ1I $\leq$ 5) and 'poor' (PQ1I $>$ 5) sleepers and correlation between PQ1I and these different parameters were tested.
Results
315 patients were eligible for PQ1I questionnaire analysis: 54% women, mean age 47 $\pm$ 15 years old, mean diabetes duration of 24 $\pm$ 13 years, HbA1c of 7.6 $\pm$ 0.9% (60 $\pm$ 7.5 mmol/mol). Average PQ1I score was 6.0 $\pm$ 3.3 and 59.8% of the patients had a total PQ1I score $>$ 5. HFS-II score was significantly higher among patients with sleep disturbances ($P<0.0001$) and global PQ1I score was positively correlated with HFS-II ($\beta=0.19$; 95% CI $=0.07;0.30$). GV evaluated by CV or MAGE did not differ between 'poor' and 'good' sleepers ($P=0.28$ and 0.54, respectively).
Conclusions
Adult patients with type 1 diabetes have disturbed sleep quality which correlate with fear of hypoglycemia. This study suggests that fear of hypoglycemia is a target for intervention to improve sleep quality in adults with type 1 diabetes.

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GP215

Brain volume and variability of glycemia in patients with type 1 diabetes mellitus

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Actuality
Currently, there is no doubt about the negative effect of diabetes mellitus (DM) on the state of the central nervous system. One of the pathological manifestations are anatomical changes in the brain, which in turn can lead to the development of functional disorders and cognitive decline. Conducting imaging research methods allows us to assess the presence or absence of brain atrophy at an early stage.
The aim
To identify the relationship between blood glucose indicators (including variability) and magnetic resonance imaging (MRI) of the brain in patients with DM type 1.
Materials and methods
58 patients with DM type 1 at the age of 29[25;32] and 20 people without diabetes (matched by sex and age) were examined. Using the EasyGV calculator was calculated the glycemia variability coefficients (standard deviation (SD), prolonged glycemic index (CONGA), glycemic lability index (LI), hypoglycemia risk index (LBGI), index risk of hyperglycemia (HBGI), mean daily differences (MODD),). Also MRI of the brain was performed to determine the volume of the gray matter of the cerebral cortex, white matter and hippocampus. Statistical processing - IBM SPSS Statistics 20.0.0 (significant differences - $P<0.05$).
Results
The average level of HbA1c in patients with type 1 diabetes was 8.4[7.5;8.9]%. Indicators of glycemia variability were: SD 6.25[3.1;7.7]mmol/l, CONGA 4.65[3.3;7.3]mmol/l, LI 4.25[3.3,5.1](mmol/l)^2/hour, LBGI 3.85[2.6,5.2], HBGI 7.75[5.6;12.5], MODD, 3.85[2.9;5.6]mmol/l. According to the results of MRI, the volumes of the brain structures of interest (patients with DM type 1/control group) were determined: the volume of the gray matter of the cerebral cortex, cm^3 – 516.95[504.71;542.1]/543.19[523.24;554.17] ($P=0.004$); white matter volume of the brain cm^3 – 675.37[661.33;687.68]/630.66[625.03;641.59] ($P=0.001$); the volume of the hippocampus on the left, cm^3 – 3.08[2.93;3.2]/3.09[3;3.24] ($P=0.325$); the volume of the hippocampus on the right, cm^3 – 3.09[2.92;3.23]/3.01[2.9;3.21] ($P=0.537$). Subsequently, the analysis of the relationship of the MRI results with the coefficients of glycemia variability was carried out. A positive correlation was found between the volume of gray matter of the cerebral cortex and HbA1c ($r=0.295$, $P=0.025$), as well as a negative correlation between the CONGA index and the left hippocampus ($r=-0.265$, $r=0.044$).
Conclusions
The study revealed the negative impact of chronic hyperglycemia on the state of the cerebral cortex. Atrophy of the cortex can be the cause of cognitive impairment, which is often found in patients with diabetes.

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GP216

Specific pattern of insulin delivery during pregnancy in tightly controlled type 1 diabetic patients treated with insulin pump; unchanged total daily insulin dose per kilogram with consecutive basal/prandial insulin ratio adjustment

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Introduction
Insulin is standard of care for the treatment of type 1 diabetes (T1DM). Constant insulin adjustment is necessary to keep up with the different insulin requirements of pregnancy. Rapid, flexible and precise dosing of basal insulin and advanced options of bolus calculator settings for prandial insulin make insulin pump optimal solution.
Aim
The aim of the study was to explore pattern of insulin dynamic in pregnancies of T1DM patients with tight glycaemic control treated with insulin pump.
Material and methods
Data from 14 women with T1DM were retrospectively analyzed. Patients were treated with insulin pump, monthly followed by same endocrinologist and obstetrician at University Hospital Centre Zagreb, Department of Endocrinology and Diabetes and Croatian State Referral Centre for Diabetes in Pregnancy. Average time from pump initiation to conception was 19 months (2–78). At the time of conception median age was 28.5 years (25–34), median body mass index 23.1 kg/m^2 (19–33) and median weight gain during pregnancy 13 kg (4–16).
Results
All patient were *successfully* delivered by *caesarean* section without peripartal complications; median week of delivery was 38 (37–39), median APGAR score 10 (7–10), median birth weight 3190 g (2670–4440). At the time of conception median A1C was 6.5% (4.8–7.0). In the last trimester A1C was significantly lower with median 5.25% (4.6–7.1%), (P 0.020). Median total daily insulin dosage (TDD) at time of conception compared to 32nd week of pregnancy increased significantly (P 0.006) from 34.7 IU (13.4–50.6) to 43.85 IU (17.5–87.0). Contrary, total daily insulin dose per kilogram of body weight (TDD/kg) did not significantly change; at the time of conception it was 1.88 IU/kg (1.27–4.53) and at 32nd week of pregnancy 1.72 IU/kg (1.08–4.0). Basal/prandial insulin ratio at the time of conception was 52/48 changing significantly to 38/62 in the third trimester, (P 0.001).
Conclusion
In this study TDD increased for 21% throughout the pregnancy. Surprisingly, TDD/kg remained the same. Having in mind specific insulin demands in second and third trimester due to postprandial hyperglycemia, consecutive changes in insulin pump setting (bolus calculator) were made. The setting adjustments resulted in decrease of carbohydrate-to-insulin ratio followed by increase of prandial component of insulin and decrease of the basal one. This study points to the importance of redistribution of insulin components beyond weight-based dosing in pregnant patients with T1DM. Our findings suggest that such approach

with steady TDD/kg of exogenous insulin during pregnancy enables tight glycaemic control without hyperinsulinisation.

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GP217

The rs2304256 A allele in the TYK2 gene is associated with protection for type 1 diabetes mellitus in a Brazilian population

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Background and Aims
Type 1 diabetes mellitus (T1DM) is caused by an autoimmune destruction of pancreatic beta cells, which renders patients insulin-dependent for life. The disease arises from a complex interaction among several genetic and environmental factors. To date, single nucleotide polymorphisms (SNPs) in >50 genes have been associated with T1DM, with *HLA class II* SNPs having the greatest impact on disease susceptibility. Other loci have minor effects on T1DM risk; however, the combination of *HLA* genotypes and non-HLA SNPs has been shown to improve disease prediction. Therefore, the identification of new non-HLA SNPs associated with T1DM might aid disease prediction. In this context, tyrosine kinase 2 (*TYK2*) is a new candidate gene for T1DM since it plays an important role in regulating apoptotic and proinflammatory pathways in beta cells through modulation of IFNα signaling. Accordingly, SNPs in *TYK2* gene have been associated with protection for autoimmune diseases. Thus, the aim of the present study was to investigate the association between a nonsynonymous SNP (rs2304256) in *TIK2* gene and T1DM in a Brazilian population.
Methods
This case-control study comprised 478 patients with T1DM (cases) and 522 non-diabetic subjects (controls) from Porto Alegre (Rio Grande do Sul, Brazil). The rs2304256 (C/A) SNP was genotyped by allele discrimination-real time PCR technique using TaqMan MGB probes (Thermo Fisher Scientific). In addition, *HLA class II DR/DQ* genotypes associated with high risk for T1DM were genotyped to control a possible association of the *TYK2* rs2304256 SNP with T1DM for these *HLA* genotypes.
Results
Genotype frequencies of the rs2304256 SNP differed significantly between T1DM patients and non-diabetic subjects (T1DM: C/C 59.4%, C/A 34.3%, A/A 6.3% *vs*. Controls: C/C 54.6%, C/A 32.2%, A/A 13.2%; P=0.001). The frequency of the minor allele (A) was 23% in T1DM group and 29% in control subjects, and this allele was significantly associated with T1DM protection under a dominant model of inheritance, adjusting for *HLA* high-risk genotypes, body mass index, ethnicity and hypertension (OR=0.60, 95% CI 0.39 – 0.95, $P=0.025$).
Conclusions
Our results demonstrated that the *TYK2* rs2304256 A allele is associated with protection for T1DM in a Brazilian population. No previous study has evaluated this SNP in Brazil.

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GP218

Effect of HbA1c and hyperglycemia on hemostasis in patients with type 1 diabetes

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Background and aims
Hyperglycemia can be a risk factor for adverse cardiovascular and cerebrovascular events. However, changes in platelets and coagulation hemostasis during hyperglycemia have not been extensively studied. The aim of this study was to assess the impact of level of fasting plasma glucose, HbA_1c on the platelet activity, the physiological anticoagulant activity and fibrinolysis in patients with Diabetes Mellitus type 1 (DM1).
Materials and methods
We examined 88 patients with DM1 (39 male and 49 female; age 27[23;33] years; HbA_1c 8.9[7.8;9.9]%). On the background euglycemia (fasting plasma glucose(fpg) $\leq$6.5 (5.7$\pm$1.06) mmol/l), and hyperglycemia (fpg $\geq$12 (13.2$\pm$2.35) mmol/l) were measured induced platelet aggregation (IPA) in whole blood using thrombin, collagen, ADF, arachidonic acid, ristocetin by multiple electrode platelet aggregometry (Multiplate); physiological anticoagulants (protein S, protein C, AT-III), von Willebrand factor, plasminogen activator inhibitor (PAI-1) and tissue plasminogen activator (tPA) were determined by ELISA. Hyperglycemia was achieved by correcting insulin therapy. On the moment of the study, none of the patient was taking antiplatelet therapy or anticoagulants; 20 patients were taking antihypertensive drugs and 15 patients were taking statins. Statistical analysis was performed with SPSS 22,0 for Windows, $P<0.05$.
Results
Platelet aggregation after adding collagen, thrombin, ADF, arachidonic acid, ristocetin was significantly increased on the background of hyperglycemia compared with euglycemia ($P=0.004$, $P=0.000$, $P=0.000$, $P=0.044$, $P=0.023$ respectively, *W-test).* Additionally, tPA was increased on the background of hyperglycemia as compared with euglycemia ($P=0.000$,*W-test).* Increased level of plasma glucose was correlated positively with tPA ($P=0.008$; $r=0.469$) and increased platelet aggregation after adding collagen ($P=0.001$; $r=0.394$), thrombin ($P=0.001$; $r=0.410$), ADF ($P=0.000$; $r=0.482$). Level of HbA_1c was correlated positively with PAI-1 ($P=0.001$; $r=0.541$), protein C ($P=0.032$; $r=0.374$) and increased platelet aggregation after adding collagen ($P=0.028$; $r=0.268$), ADF ($P=0.035$; $r=0.262$), arachidonic acid ($P=0.018$; $r=0.297$).
Conclusions
Hyperglycemia and increased level of HbA_1c are associated with platelet hyperactivity and a decrease in the systemic fibrinolytic balance via increased PAI-1 activity. However, these changes are compensated by the activation of free protein C, an increase of tPA and the preservation of increased concentrations of Protein S and AT-III.

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GP219

Impact of type 1 diabetes mellitus and its complications on markers of nitric oxide metabolism

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Background and aim
The role of derangements of nitric oxide (NO) metabolism in the pathogenesis of complications of type 1 diabetes mellitus (T1D) is not sufficiently clear. There is little data on simultaneous measurements of NO metabolites nitrite and nitrate (NO_2/NO_3) in urine and serum in T1D. Data about the measurement of NO production by electronparamagnetic spectroscopy (EPR) in whole blood in T1D were never published. To fill this gap we have characterised NO production and NO_2/NO_3 concentration in the biological fluids of patients with and without complications of T1D.
Methods
Two hundred and seventy-one patients with T1D duration > 1 year and 69 healthy volunteers were included. NO_2/NO_3 was measured by Griess reaction. Production of NO in whole blood was detected by EPR spectroscopy. Statistical analysis was performed by programme R.
Results
In T1D group *vs* control subjects, blood NO was higher, but serum NO_2/NO_3 was lower. There was a trend of higher serum NO_2/NO_3 in patients with diabetic nephropathy and chronic kidney disease (CKD), with concentrations reaching those of healthy subjects. Diabetic retinopathy, diabetic polyneuropathy, cardiovascular disease and arterial hypertension did not cause further changes in serum NO_2/NO_3 and whole blood NO as compared to the median value of T1D patients. Urine NO_2/NO_3 was lower in patients with microvascular T1D complications compared with milder phenotypes. In T1D, estimated glomerular filtration rate (eGFR) correlated with urine NO_2/NO_3 and whole blood NO.
Conclusions
Whole blood NO, serum NO_2/NO_3 and urine NO_2/NO_3 are affected differently by T1D and its complications. Decreased NO_2/NO_3 urine, but not in serum, is a marker of microvascular complications of T1D.

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GP220

Definition of a third-trimester HbA1c cut-off point for an increased risk of Large-for-Gestational-Age in mothers with Gestational Diabetes

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Introduction
Gestational diabetes mellitus (GDM) is associated with important neonatal risks and a higher incidence of large-for-gestational-age (LGA) newborns and fetal macrosomia. The aim of our work was to define a third-trimester HbA1c cut-off point for increased risk of fetal morbidity, macrosomia and LGA newborns.
Methodology
Observational retrospective study of all singleton pregnant women with GDM, followed at our Diabetes and Pregnancy Clinic between 2011 and 2017. Excess gestational weight gain was defined by the IOM guidelines. Adverse neonatal outcome included: neonatal respiratory distress, neonatal hypoglycemia, neonatal jaundice, shoulder dystocia, fractures, Erb's palsy and admission to neonatal intensive care unit. ROC curve was used to define the third-trimester HbA1c cut off point for increased risk of fetal morbidity, macrosomia and incidence of LGA.
Results
A total of 1085 singleton pregnant women were evaluated during the study period; their mean age was 32.9 ± 5.3 years and mean body mass index (BMI) of 26.5 ± 5.6 Kg/m^2. During the pregnancy, 36.3% (n = 395) of the women were started on insulin therapy and 31.5% (n = 337) had excess gestational weight gain at the time of the delivery. Mean gestational age at delivery was 38.5 ± 1.5 weeks. In 729 cases, third-trimester HbA1c was determined and mean third-trimester was HbA1c 5.3 ± 0.4%. Of the 1085 newborn, mean neonatal birth weight was 3188.5 ± 49.5 g, 4.5% (n = 49) of these were LGA, 4.8% (n = 52) were macrosomic and 19.1% (n = 208) had at least one adverse neonatal outcome. On univariate analysis, third-trimester HbA1c presented a 13.6 higher risk of LGA (CI95% 6.1 – 30.5, P < 0.001), 4.8 higher risk of fetal macrosomia (CI95% 2.4 – 9.6, P < 0.001) and 1.9 higher risk of fetal morbidity (CI95% 1.2 – 3.1, P = 0.006). ROC curves showed a cut-off point of third-trimester HbA1c > 5.4% for identifying newborns with a greater probability of LGA (Sensitivity: 82.8%; Specificity 72.0%; AUC 0.824; P < 0.001); cut-off point of third-trimester HbA1c > 5.6% for macrosomia (Sensitivity: 85.1%; Specificity 42.1%; AUC 0.664; P < 0.001) and a cut-off point of third-trimester HbA1c > 5.3% for fetal morbidity (Sensitivity: 50.4%; Specificity 62.4%; AUC 0.592; P = 0.026).
Conclusion
In this study, a cut-off point of third-trimester HbA1c > 5.4% was found to have a good sensitivity and specificity for the identification an increased risk of LGA.

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GP221

Insulin requirements during lactation in women with diabetes mellitus type 1 in comparison with pre-pregnancy levels – a retrospective study

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Introduction
Lactation is a period of particular importance regarding the management of glycemia in women with Diabetes Mellitus type 1 (DM1), the aim being to prevent hypoglycemia during breastfeeding. The purpose of this study was to investigate the variation of insulin requirements during lactation in comparison with pre-pregnancy levels in women with DM1 and to find potential correlation factors.
Materials-methods
We conducted a retrospective case file study of women with DM1, on singleton pregnancies who breastfed. We assessed medical records in the last 8 years with data regarding management of their glycemic profile before pregnancy, during pregnancy and when breastfeeding for at least 3 months. Fourteen women were included in the study (mean age ± s.d. 38.6 ± 3.6 years; mean BMI ± s.d. 24.8 ± 3.8 kg/m^2; mean duration of pregnancy 37.8 ± 0.7 weeks). Seven women had a vaginal birth and 7 underwent a caesarian section (newborn mean weight was 3352.1 ± 729.8 g). We used non-parametric analysis of covariance to assess the mean daily insulin dosage during lactation, regarding the way of breastfeeding (exclusive or part-time) as a co-factor, in relation to age, duration of pregnancy, mean weight gain in pregnancy, the newborns' mean weight, hypoglycemic episodes in lactation and insulin requirements before and during pregnancy.
Results
Regarding the glycemic profile variability, the mean HbA1c before pregnancy was 7.5 ± 1.5%, with an average daily insulin dosage of 54.7 ± 14.1U. During pregnancy the average daily insulin requirements were increased at 98.8 ± 31.0U, with a mean HbA1c of 6.6 ± 0.5% and a mean weight gain of 15.78 ± 5,4 kg. Seven women breastfed exclusively and 7 part-time. At the first trimester of breastfeeding the average daily insulin dosage was 44.4 ± 12.6U with a mean HbA1c of 7.7 ± 1.9%. In the group of women who breastfed exclusively, a 26% reduction of median daily insulin dosage was noted compared to pre-pregnancy levels. In the group of part-time breastfeeding the insulin dosage reduction was 13,5% respectively. During breastfeeding, 42.8% (6/14) of women experienced repeated episodes of hypoglycemia, with an equal distribution (50%) in relation to the type of breastfeeding (exclusive/part-time). A trend (P = 0.10) was noted between exclusive breastfeeding with the need for slightly lower insulin dosage in correspondence with weight gain in pregnancy.
Conclusions
The expected changes in caloric needs, diet, timeline, and consequently of the metabolic profile of women with DM1 during breastfeeding, lead to a reassessment of their therapeutic algorithm, mainly to prevent hypoglycemic episodes.

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GP222

The impact of gestational weight gain on subclinical atherosclerosis, placental circulation and neonatal complications

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Objective
Vascular atherosclerotic changes, mediated by environmental and genetic factors, develop years before an event. Detection of vascular damage, using ultrasonographic measurement of carotid IMT, is predictive of future cardiovascular events. The present study was designed to investigate the impact of gestational weight gain (GWG) on early atherosclerotic changes during late pregnancy, using intima media thickness (IMT), as well as placental vascular circulation and inflammatory lesions and pregnancy outcome.
Design and methods
59 women who gave birth at Wolfson Medical Center during 2018 were divided into two groups according weight gain during pregnancy: Group 1 included 32 women with pregnancy weight gain within recommended range, Group 2 included 27 wonen with exessive weight gain during pregnancy. IMT was measured by High-resolution B-mode ultrasound (Sonosite Titan/Sonosite, Inc., Bothell, Washington, USA). Placental histology was performed for vascular circulation, as well as inflammatory lesions of maternal and fetal origin. Metabolic measures such as fasting glucoe, lipids, hs-CRP, HOMA-IR were determined. Maternal and neonatal outcome parameters were collected.
Results
Weight gain during the pregnancy was significantly higher in Group 1, compared to Group 2 (17.5 ± 6.2 vs 6.8 ± 5.7, P < 0.0001), whereas pre-gestational BMI did not differ significantly between groups (P = 0.059). IMT levels differed between groups and was significantly higher in group 1 compared to Group 2 (0.7 ± 0.1 vs 0.6 ± 0/1, P = 0.028). In regression analisys, pregnancy weight gain remained a significant independent predictor of IMT. Rate of macrosomia was significantly higher in Group 1 than in Group 2 (P = 0.014). Maternal vascular supply (MVS) abnormalities of the placental bed did not differ significantly between groups (P = 0.297). Among placental lesions related to fetal vascular malperfusion, villous changes consistent with fetal thrombo-occlusive disease (FTOD) were significantly higher in Group 1 than in group 2 (P = 0.034).
Conclusion
In the present study, excessive weight gain during pregnancy was significantly and independently associated with an increased IMT. Among placental vascular lesions, villous changes consistent with fetal thrombo-occlusive disease (FTOD) were significantly higher women with excessive weight gain during pregnancy. Among neonatal complications, rate of macrosomia was significantly higher in women with excessive weight gain during pregnancy.

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Adrenal and Neuroendocrine - Clinical

GP223

Small molecule allosteric agonist of relaxin receptor ML290 demonstrates antifibrotic properties in liver fibrosis

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The beneficial effects of relaxin peptide treatment have been demonstrated in animal models of liver fibrosis. However, the low stability of peptide *in vivo* prevents using it in chronic treatments. We have identified a series of small molecule allosteric agonists of the human relaxin receptor, RXFP1. The therapeutic effects of lead compound ML290 was tested in various models of liver fibrosis. To analyze the anti-fibrotic effects of ML290 on gene expression, we used primary human hepatic stellate cells followed by RNAseq analysis of ML290 treatment in an established human stellate cell line, LX-2. We then tested the effects of ML290 in fibrotic human liver organoids and in a carbon tetrachloride model of mouse liver fibrosis. We demonstrated that RXFP1 expression is increased in fibrotic mouse liver, specifically in activated hepatic stellate cells. The lead compound, ML290, was selected based on its effects on the gene expression profile associated with fibrosis in primary human stellate cells. RNA-Seq analysis of TGFβ1-activated LX-2 cells showed that about 500 genes were misregulated by ML290. Gene Ontology analysis demonstrated that ML290 treatment primarily affects extracellular matrix remodeling and cytokine signaling. ML290 treatment in human liver organoids with lipopolysaccharide-induced fibrotic phenotype resulted in dramatic reduction of type I collagen. The pharmacokinetics of ML290 in mice after multiple daily injections demonstrated its high stability *in vivo*, as evidenced by the sustained concentration of compound in the liver. In mice expressing human RXFP1 gene treated with carbon tetrachloride, ML290 significantly reduced collagen content, alpha-smooth muscle actin expression, and cell proliferation around portal ducts. In summary, ML290, the small molecule agonist of relaxin receptor, has anti-fibrotic effects in liver fibrosis.

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GP224

Caffeine upregulates hepatic SHBG production by increasing adiponectin in white adipose tissue

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Epidemiological studies have shown that caffeine increases plasma SHBG levels and also reduce the risk of type 2 diabetes. There are no reports describing any molecular mechanism by which caffeine regulates hepatic SHBG production. The aim of the present study was to explore whether caffeine regulates SHBG production and to determine the associated molecular mechanisms. For this purpose, *in vitro* and *in vivo* studies were performed using human HepG2 cells and human *SHBG* transgenic mice. Our results showed that caffeine treatment did not change SHBG production in HepG2 cells. By contrast, caffeine treatment increased significantly both plasma and hepatic mRNA SHBG levels in human *SHBG* transgenic mice when compared with control mice. Caffeine treatment increased adiponectin mRNA levels in epididymal adipose tissue of human *SHBG* transgenic mice and in differentiated 3T3-L1 mouse adipocytes. This caffeine-induced increase in adiponectin in turn upregulated the hepatic levels of HNF-4a in human *SHBG* transgenic mice. Our results showed for the first time that caffeine upregulates hepatic SHBG expression by increasing adiponectin production in the adipose tissue. These results suggest that the beneficial effects of caffeine in preventing type 2 diabetes development could be mediated by increasing SHBG plasma levels.

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GP225

Activation of the ATM/Akt/CREB/eNOS expression signaling axis by aphidicolin increases nitric oxide production to attenuate endothelial cell death

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Previously, we reported that aphidicolin acutely increases nitric oxide (NO) production in bovine aortic endothelial cells (BAECs) by increasing phosphorylation of endothelial nitric oxide synthase at serine 1179 (p-eNOS-Ser^{1179}) and decreasing phosphorylation at serine 116 (p-eNOS-Ser^{116}) without altering eNOS protein expression. Here, we demonstrate that prolonged treatment with aphidicolin (over 24 h) also increased NO production in BAECs. Unlike the acute effects of aphidicolin, however, prolonged treatment increased expression of eNOS protein and dimerization with elevated level of tetrahydrobiopterin, an essential cofactor for eNOS dimerization. The NOS inhibitor, Nω-Nitro-l-arginine methyl ester hydrochloride (L-NAME), completely reduced aphidicolin-induced NO production, despite no change of eNOS protein. Prolonged treatment with aphidicolin increased mRNA expression of eNOS. A promoter assay using 5′-serially deleted eNOS gene promoters (−1600 to +22; −962 to +22; −873 to +22; −428 to +22) revealed that the Tax-responsive element (TRE) site, a cAMP response element (CRE)-like site, located at -962 to -873 of the eNOS promoter, was responsible for aphidicolin-stimulated eNOS gene expression. Ectopic expression of a dominant-negative inhibitor of CRE binding protein (CREB), A-CREB, repressed the stimulatory effects of aphidicolin on eNOS gene expression and its promoter activity. We also found that aphidicolin increased CREB activity, as evidenced by increased level of p-CREB-Ser^{133}. Co-treatment with LY294002, a phosphoinositide 3-kinase inhibitor, but not H-89, an inhibitor of protein kinase A, decreased the aphidicolin-stimulated increase in p-CREB-Ser^{133} levels, eNOS expression, and NO production. Furthermore, ectopic expression of a dominant-negative Akt construct attenuated aphidicolin-stimulated NO production. Aphidicolin also increased phosphorylation of ataxia telangiectasia mutated kinase (ATM) at Ser^{1981} (p-ATM-Ser^{1981}) and the knockdown of ATM using small interfering RNA (siRNA) attenuated all stimulatory effects of aphidicolin on p-Akt-Ser^{473}, p-CREB-Ser^{133}, eNOS expression, and NO production. Lastly, aphidicolin significantly decreased BAEC viability, which was further decreased by co-treatment with the NO scavenger, 2-phenyl–4, 4, 5, 5,-tetramethylimidazoline-1-oxyl 3-oxide or the NOS inhibitor, L-NAME. Similarly, the knockdown of eNOS using siRNA further aggravated EC damage, suggesting a protective role for NO in EC death caused by aphidicolin. Taken together, our results suggest that aphidicolin increases NO production in BAECs by increasing eNOS expression via an ATM/Akt/CREB signaling cascade, which contributes to the attenuation of aphidicolin-induced EC death.

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GP226

Evaluation of the CCK-2 receptor agonist 177Lu-PP-F11N for radionuclide therapy of medullary thyroid carcinoma – final Results of the phase 0 'Lumed' Study

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Objectives
Despite the introduction of new molecular targeted therapies, there is still an unmet need for an effective systemic therapy for advanced medullary thyroid carcinoma (MTC). As MTC expresses cholecystokinine-2 (CCK-2) receptors at a high incidence and density, targeting the CCK-2 receptor with radiolabelled gastrin analogues is a potential approach for radionuclide therapy. Unfortunately, kidney and bone marrow toxicity precluded therapeutic applications of CCK-2 receptor specific radiotracers until now. The aim of this prospective clinical study is to test the proof of principle that the novel gastrin analogue [^{177}Lu-DOTA-(DGlu)$_6$-Ala-Tyr-Gly-Trp-Nleu-Asp-PheNH$_2$] (^{177}Lu-PP-F11N) targets effectively metastases of MTC (ClinicalTrials.gov: NCT02088645).

Methods
Six patients received two injections of 1 GBq ^{177}Lu-PP-F11N, one injection with and the other without Physiogel (Gelofusin = plasma expander for nephroprotection) infusion. Planar scintigraphy and SPECT/CT scans were performed at several time points for up to 72 h post injection in order to calculate tumor- and organ doses using 3D volume based MIRD dosimetry (Dosimetry Research Tool v5.2, Siemens Medical Solutions, USA). Blood samples were taken for bone marrow dose calculations. ECG, blood count and blood chemistry were measured up to 12 weeks after the second administration of ^{177}Lu-PP-F11N in order to evaluate adverse events.
Results
Adverse reactions (mainly hypotension, flushing and hypokalemia) were self-limiting and not higher than grade 1, according to CTCAE version 4.03. In all patients, ^{177}Lu-PP-F11N accumulation was visible in tumor tissue, in the kidneys, stomach and the colon. Altogether, 13 tumors were eligible for dosimetry. The median (range) radiation dose for tumors, stomach, kidneys and bone marrow was 0.88 Gy/GBq (0.38–8.04), 0.42 (0.13–2.07), 0.1 (0.05–0.15) and 0.010 (0.008–0.016). These resulted in median tumor-to-kidney dose ratios of 12.3 (6.8–27.6) (without Physiogel) and 13.0 (6.4–21.8) (with Physiogel), which was not significantly different (Wilcoxon test $P=0.19$). The median tumor-to-bone marrow dose ratio was 77.7 (52.8–398.5).
Conclusions
The administration of the novel CCK-2 receptor ligand ^{177}Lu-PP-F11N was safe in all six examined patients. Visualization of metastasized/recurrent disease in all patients provides evidence that CCK-2 receptor targeting with ^{177}Lu-PP-F11N is feasible in patients with MTC. The dosimetry results indicate tumor doses that could enable radionuclide therapy. Dosimetry results for kidneys and bone marrow revealed low organ doses, as well as excellent tumor-to-kidney and tumor-to-bone marrow ratios. Further studies will be necessary to evaluate the theranostic potential of ^{177}Lu-PP-F11N in patients with CCK-2 receptor expressing tumors.

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GP227

Multikinase inhibitors for the treatment of progressive, metastatic parathyroid cancer

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Introduction
The treatment of choice for parathyroid carcinoma (PC) is a radical en bloc resection. Treatment options for patients with metastatic PC are limited especially if a complete tumor removal cannot be performed. We present four cases of PC patients with multiple metastasis and refractory hypercalcemia that eventually received a multikinase inhibitor with different response on therapy.
Clinical cases
The first patient was a 27-year-old woman with metastatic PC in the right lung (2.9 cm and 2.2 cm). Five months after the thoracoscopic resection of the lung lobe, PTH was 720 pmol/l, (15-65), ca – 2.74 mmol/l (2.10–2.55). Diffusional MRI (DW-MRI) showed multiple lesions in both lungs (0.2–0.5 cm). Based on the reports of successful sorafenib treatment in metastatic PC by Dr. Lerario A.M. we started a targeted therapy with 400 mg of sorafenib 2 times a day. The therapy showed good results: over the next three years of sorafenib treatment, we've observed stabilization of the metastatic process according to PET/CT (lesions in lungs without uptake of the 18-fluorodeoxyglucose) as well as normocalcemia and significant reduction of PTH in lab tests. The second and the third cases are very similar. Both patients (76 and 61 years old woman underwent 5 surgeries on the neck because of the recurrent disease and both had metastasis in lungs. Based on our own experience we started the sorafenib therapy. After a year, despite persistent elevated levels of PTH (2000–2500 pg/ml) and Ca (2.7–2.9 mmol/l) the PET/CT showed the significant reduction in metastases size regarded as the stabilization of the process. So we decided to continue the sorafenib therapy. The fourth patient (64-years old woman) had the most aggressive PC course with multiple metastases in the neck lymph nodes, lungs, liver, left clavicle, C6-7 and L4 vertebras. She referred to our centre after 6 reoperations on the neck, 3 sessions of radiation therapy (SOD 87.4 Gy), ineffective chemotherapy with capecitabinum (Ca− 3,10 mmol/l, PTH- 2090 pg/ml). 4 weeks after we initiated sorafenib therapy and noted a dramatic decrease in PTH to 98.2 pg/ml and Ca to 2,15 mmol/l (tested twice). However three months after the start treatment PET/CT showed the increase in metastasis size and the newly formed lesions. The sorafenib therapy was stopped because of the ineffectiveness.
Conclusions
Sorafenib seems to be a promising drug for targeted therapy in some PC cases.

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GP228

Serine-threonine PAK1 as a novel common node for estrogen- and prolactin-dependent pathways in breast cancer

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Even though serine-threonine kinase PAK1 is activated by estrogen and plays an important role in breast cancer, the role of PAK1 in estrogen response is not fully understood. We have shown that estrogen activates PAK1 through both ERα and GPER1 plasma membrane receptors and that cytoplasmic Etk/Bmx directly phosphorylates Tyr153-PAK1 and activates PAK1 in response to estrogen. We have described a signaling complex composed of pTyr-PAK1, Etk, the heterotrimeric G-protein subunits, Gβ1, Gγ2 and/or Gγ5, βPIX (PAK-associated guanine nucleotide exchange factor) and PKA (protein kinase A) which, upon formation, activates PAK1 through positive feed-back manner. The PKA catalytic subunit (PKA-Cα) directly phosphorylates PAK1 while the PKA RIIβ subunit is a direct target of PAK1. In response to estrogen, activated pTyr-PAK1 complex reciprocally potentiates PKA activation. PKA phosphorylates Ser305-ERα in response to estrogen. However, in response to prolactin (PRL), Ser305-ERα is phosphorylated by pTyr-PAK1. Our data suggest that in cells exposed to both PRL and estrogen, Ser305-ERα is phosphorylated by both PKA and pTyr-PAK1 resulting in maximal signal. Furthermore, S305-ERα activation leads to enhanced phosphorylation of Ser118-ERα, and promotes cell proliferation and tumor growth. Together, our data strongly support a critical interplay between PRL and estrogen via PAK1. Ligand-independent activation of ERα suggests that PRL/PAK1 may contribute to resistance to anti-estrogen therapies. Thus, we propose that PAK1 serves as a common node for estrogen- and PRL-dependent pathways, making it an attractive target for anti-cancer therapy.

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GP229

Melatonin prevented beta cell senescence against glucolipotoxicity

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Beta cell senescence is being regarded as the one of the mechanisms of beta cell dysfunction. Melatonin secreted primarily from the pineal glandregulates a variety of physiological functions, such as sleep, circadian rhythms, and neuroendocrine actions. Melatonin has also very strong anti-oxidant effects. The effects of melatonin on the pancreatic beta cell senescence induced by glucolipotoxicity have not been studied. INS-1 cells were exposed to 33mM glucose with palmitate 200uM (glucolipotoxicity: HG + palmitate (HGP)) with or without melatonin. Cell viability and apoptosis were assessed by MTT assay and Annexin V staining. We compared senescence β-Galactosidase (SA-β-Gal) staining and $p16^{INK4a}$immunostaining depending on melatonin treatment against HGP. We assessed phospho-p38 MAPK, Sirt1 and p16 protein expression with and without melatonin. CDK4 protein and anti-oxidant enzyme were assessed in both conditions. Melatonin increased INS-1 cell viability and decreased apoptosis against HGP. SA-β-Gal and $p16^{INK4a}$ immunostaining were increased in HGP, and melatonin significantly reversed them. Melatonin decreased phospho-p38 MAPK and $p16^{INK4a}$ protein expression in 24 hours. Melatonin increased Sirt1, Mn-SOD and catalase expression against HGP. In conclusion, we found that melatonin prevent beta cell senescence induced by metabolic stresses like glucolipotoxicity. The effects of melatonin on beta cell aging may be related with phospho-p38 MAPK and $p16^{INK4a}$ pathway, and anti-oxidant system.

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GP230

Low-dose pollutant mixture triggers metabolic disturbances in ovariectomized mice and comparison with the effects of 17β-estradiol (E2) treatment

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Introduction
Environmental pollutants especially those endowed with endocrine disrupting activities have been shown to contribute to metabolic related diseases suggesting that hormonal deficit conditions as observed in post-menopausal women may constitute aggravating conditions. To explore this hypothesis, we used the model developed in the laboratory which consists in a chronically exposure of mice to low-dosed chemicals in mixture incorporated in a high-fat-high-sucrose diet (HFHSD). Within the present study, mice were ovariectomized to mimic hormonal deficit.
Methods
Five week-old C57Bl6/J mice fed a HFHSD were divided in sub-groups depending on surgery (sham, ovariectomy (Ovx), Ovx + E2 implants) performed by week 7. Half of the Ovx and Ovx + E2 were exposed to a mixture of 2,3,7,8-TCDD (dioxin), polychlorobiphenyl (PCB)153, DEHP (phthalate) and bisphenol A at doses resulting in mice exposure at the Tolerable Daily Intake dose range (TDI) for each pollutant. The other half received vehicle only. Protocol lasted 15 weeks. A glucose tolerance test was performed and we measured several blood parameters and hepatic TG and cholesterol accumulation. Gene expression studies were performed by RT-qPCR in the liver and adipose tissues.
Results
Ovariectomised mice exhibited enhanced body weight and fat pads, glucose intolerance and insulin resistance (normalized by E2 replacement) but no hepatic TG accumulation. A set of estrogen-regulated genes was also identified in the liver and the adipose tissues at the mRNA level. Exposure to the mixture of pollutants did not impact body weight or glucose tolerance but adiponectin levels were altered. In addition, it resulted in enhanced hepatic lipid deposition and in changes in the mRNA level of genes related to lipid metabolism. Specifically, genes impacted included Nr1h3, Nr0b2, Cd36 and Cyp7a1 but not Esr1 in a direction distinct from the one triggered by E2 replacement. Pollutant exposure also differentially impacted the subcutaneous and visceral adipose tissues at the gene expression mRNA level, especially estrogen receptors reproducing part of the effects elicited by E2 treatment.
Conclusion
These data support the concept of the cocktail effect if considering that the dosage of the pollutants in the mixture is based on the TDI dose, thus not expected to generate an adverse effect. Interestingly, we found that the pollutant mixture triggered effects distinct or mimicking E2 treatment, depending on the metabolic tissue considered. These findings may have implications for the understanding of the potential role of environmental contaminants in the development of metabolic diseases, especially in females during the menopausal transition.

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GP231

In vitro effects of bisphenol A and its analogs on human melanocortin 4 receptor

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Bisphenol A (BPA) is a widely used chemical and belongs to the list of metabolism-disrupting chemicals. BPA is banned in several countries and replaced by others BPA-analogs. We investigate the effects of BPA and 6 BPA-analogs (BPS, BPAF, BPF, BPB and BADGE) on the response of the human melanocortin 4 receptor (MC4R), a receptor involved in food intake and weight control, to its natural ligands. We used HEK293 cells line transiently transfected with human MC4R to determine the impact of bisphenols on MC4R-dependent cAMP production. BPAF (10^{-11}M) and BPF (10^{-11}M) were the most potent positive modulators of α Melanocortin-Stimulating Hormone (MSH) response, followed by BPB (10^{-9}M) = BADGE (10^{-9}M) > BPS (10^{-8}M) = BPA (10^{-8}M). Moreover, BPA (10^{-8}M) impaired the response of MC4R to the Agouti-related Peptide (AgRP), a natural inverse agonist of the receptor. In HEK293 mock-transfected cells, bisphenols had no effect on basal or adenosine induced cAMP response. Thus, the potentiating effect of bisphenols was dependent on and specific of the MC4R. In opposite, we showed that BPA and BPA-analogs reduced by half the response of melanocortin 3 receptor to α MSH. In conclusion, our *in vitro* findings suggest that human MC4R is a target for both BPA and BPA-analogs. These findings highlight that BPA analogs retain an activity similar to that of BPA and thus they may still remain potential metabolism-disrupting chemicals.

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GP232

Can phthalates impair liver function?

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Introduction
The impairment of liver function and enhancement for NAFLD development may be attributed to the ubiquitous exposure to endocrine disrupting chemicals such as phthalates. In this study the urinary levels of monoethyl phthalate (MEP) and mono-(2-ethylhexyl) phthalate (MEHP) were compared with the parameters of hepatic function and lipids in overweight, diabetic patients and normal weight population.
Methods and patients
In 305 volunteers of both genders who were divided into three groups based on the body mass index, waist circumference and glucose levels: I -obese with central obesity, II -patients with diagnosed type 2 diabetes mellitus (T2DM) treated only with medical nutrition therapy and III-control, normal weight healthy volunteers, phthalate metabolites concentration was determined in the morning spot urine.
Results
The urine samples from 66 volunteers were positive on MEP while 72 were positive on MEHP. Aspartate Aminotrasferase (AST) and Alanine Aminotransferase (ALT) concentrations differed significantly between MEP+ and MEP-normal weight healthy volunteers ($P=0.02$ and $P=0.01$, respectively) while significantly higher Gamma-Glutamyl transferase GGT levels were observed in MEHP+ control subgroup ($P=0.017$). The positive correlation was observed between AST, ALT and $\log_{10}$MEP levels in obese patients ($P=0.02$ and $P=0.05$). GGT positively correlated with MEP concentration in T2DM patients ($P=0.048$). Negative correlation was found between $\log_{10}$MEP values in the control group and both total cholesterol and LDL levels ($P=0.0051$ and $P=0.0015$, respectively) while in obese group MEP was positively associated with serum triglycerides ($P=0.024$). The $\log_{10}$MEHP in the control group was correlated negatively with serum HDL ($P=0.0035$). BMI was significantly increased ($P=0.044$) in BMI in MEHP+ control subgroup compared to MEHP-.
Conclusions
The ubiquitous exposure to phthalates may be related to the impairment of normal liver function according to the results obtained in this study.

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Anterior and Posterior Pituitary

GP233

Evaluation of postoperative copeptin concentration as a predictive factor of diabetes insipidus after pituitary surgery. preliminary results

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Introduction
Central diabetes insipidus (DI) is observed in up to 34% of patients undergoing pituitary surgery. Early postoperative diagnosis of DI is critical because its detection allows early treatment, reducing morbidity and hospital stay. AVP levels measurement is not commonly used to diagnose DI. As an alternative, copeptin determination has been proposed, but its usefulness has only been validated in one series.

Objective
To define the threshold and optimal measurement time of serum copeptin for early prediction of DI after pituitary surgery in an independent series.
Design
Observational, prospective study in a unique center. *Subjects*: Patients operated by endonasal surgery from 2017 to 2018, excluding those with pre-surgery DI. *Variables*: serum copeptin, sodium, potassium, glucose, creatinine, urea, plasma and urinary osmolality, and glomerular filtration before and at 4-6h, 24h and 48h after surgery, preoperative basal serum cortisol, TSH and free thyroxine, sex and tumor features (size, invasion, chiasmatic compression and functionality). *Statistical analysis*: SPSSv.21. Kolmogorov-Smirnov test to evaluate normality of the distribution. Descriptive of quantitative variables: mean and standard deviation in parametric distributions, median and *P*25–75 in nonparametric ones. Calculation of the best cut-off point by Receiver Operating Characteristic (ROC) curves in each time. Calculation of sensitivity (Se), specificity (Sp), negative (NPV) and positive predictive value (PPV).
Results
27 patients, 32% women. Age 49 ± 17years. Maximum diameter 20.3 ± 9mm. Clinical diagnosis: 55% non-functioning adenomas, 15% Prolactinomas, 19% acromegaly, 7% Cushing's disease, 4% pituitary apoplexy. Eight (30%) patients developed post-surgery DI. Copeptin concentrations at 4–6h after extubation was significantly lower (7.7 vs 16.5 pmol/L, $P = 0.037$) in patients who developed postoperative DI than those who did not. No other significant differences between groups were found in any of the studied variables, except for the development of cerebrospinal fluid leak ($P = 0.006$). The greater diagnostic validity of copeptin for the detection of DI in the postoperative period was obtained 24h after surgery, with a threshold point of 3 pmol/L (Se 62.5%, Sp 95%, PPV 83.3%, NPV 86.3%). All patients who presented DI normalized their neurohypophyseal function during the follow-up, except one with persistent DI two months after surgery.
Conclusions
The prevalence of post-surgery DI in the studied series (30%) agrees with that described in the literature. Our preliminary results suggest that copeptin measured 24h postoperatively may be a useful tool for early diagnosis of DI, although the optimal threshold differs from that previously reported.

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GP234

Is the molecular study of pituitary transcription factors useful in the identification of Pituitary Neuroendocrine Tumor subtypes according to the new WHO 2017 criteria?

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Introduction
Recently we have demonstrated the contribution of the quantification of expression of adenohypophyseal hormone genes in the identification of the different Pituitary Neuroendocrine Tumor (PitNET) subtypes according to the 2004 WHO criteria.
Aim
The aim of the present study was to evaluate the contribution of the quantification of expression of pituitary transcription factor genes to the identification of PitNETs according to 2017 WHO criteria.
Methods
From our collection of 300 PitNETs, we selected 93 tumors with complete clinical, immunohistochemical and molecular information with sufficient quality and quantity of remmanent biological material. In this study, we are reporting preliminary results of 41 tumors analyzed to date. The series analyzed include 6 corticotropinomas (CT), 7 somatotropinomas (3 mixed GH-PRL), 3 thyrotropinomas (TT), 14 gonadotropinomas (GT), 4 plurihormonal tumors (PH), 5 null cell tumors and 2 samples initially considered as normal pituitary gland. We quantified the gene expression of *TBX19* (Tpit), *POU1F1* (Pit1), *SF1, GATA2 and ESR1* by quantitative real-time-PCR (qRT-PCR). The relative differences in gene expression were expressed as fold change and were obtained with the $2^{-\Delta\Delta Ct}$ method. We relied on the dominant gene expression in the qRT-PCR of the transcription factors to identify the different subtypes of PitNETs.
Results
All ST (pure and mixed) and TT PitNETs predominantly expressed *POU1F1* (Pit1), confirming the previous molecular identification. Thirteen out of 14 GT expressed dominantly *GATA2*, confirming the GT lineage. The remaining tumour expressed *NEUROD1* suggesting a CT cell origin. Five out of 6 CT expressed *TBX19* (Tpit), verifying the CT origin. One CT expressed *GATA2*, suggesting a GT cell origin. t Two out of 5 null cell tumors, expressed *SF1* and 1 expressed *GATA2* suggesting a GT origin. The last two expressed both, *NEUROD1* and *GATA2*, indicating a CT-GT lineage. Among the 4 PH tumors, 3 expressed *POU1F1* (Pit1) and one expressed *GATA2*. Finally, one of the 2 samples initially considered as normal pituitary gland was identified as GT, since it predominantly expressed *GATA2*, while the other sample was confirmed as normal tissue.
Conclusion
In conclusion the molecular quantification of pituitary transcription factors validates the strength of our previous results of the contribution of the study of the expression of the adenohypophyseal hormone genes in the identification of PitNET subtypes. Moreover, allows us to reclassify the null cell and plurihormonal tumors and suggest the existence of a corticotroph-gonadotroph subtype. The complete series with molecular an immunohistochemical results will be presented in the congress.

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GP235

The effect of previous optic chiasm compression on the post-illumination pupil response in pituitary patients

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Rationale
A history of optic chiasm compression in patients treated for sellar tumors is associated with alterations in sleep-wake rhythm. The optic chiasm contains axons of intrinsically photosensitive retinal ganglion cells (ipRGCs) that mediate photoentrainment of the suprachiasmatic nucleus. Compression could disrupt this entrainment leading to desynchronization with the 24-hour light-dark cycle. The post-illumination pupil response (PIPR) after blue light exposure is a unique indicator of ipRGC function. PIPR measurement presents a promising tool to evaluate ipRGC impairment due to compression of the optic chiasm. This study is the first to compare the PIPR between pituitary patients with and without a history of chiasm compression.
Methods
Adult patients with at least one centrally impaired endocrine axis and normal ocular health were eligible for inclusion. Patients in the chiasm compression group all had visual field defects prior to treatment. Groups were matched for age, gender and BMI. The PIPR was assessed using a validated chromatic pupillometry protocol of five 5-minute blocks, ensuring reliable pupil measurements. The primary outcome parameters were defined as the absolute (PIPR-mm) and the relative (PIPR-%) difference between baseline and post-blue-stimulus pupil diameter averaged over the 2nd-4th minute of the corresponding block. For sufficient power, 25 patients were included in each group.
Results
For this analysis, pupillometry results of 23 patients in the chiasm compression group (CC+) and 22 patients in the control group (CC−) were available. Groups did not differ in relevant clinical characteristics or in baseline pupil diameter. No significant differences were found in PIPR-mm (mean ± SD, CC + 1.70 ± 0.74mm and CC− 2.14 ± 0.88mm; $P = 0.07$) and PIPR-% (CC + 36.80 ± 10.97% and CC− 41.62 ± 9.24%; $P = 0.12$). On further examination of the normalized (i.e. relative to baseline) pupil diameter data, a less sustained PIPR in the CC+ group was observed. The difference in PIPR-% reached significance during the last minute of the post-blue block (CC + 32.23 ± 12.34% and CC− 40.87 ± 8.23%; $P = 0.009$), suggesting at least partial impairment of ipRGC function.
Conclusion
These preliminary results do not show significant differences in our primary PIPR outcomes. However, a less sustained PIPR was demonstrated in the CC+ group, which might correspond to less robust ipRGC transduction. The study identifies the PIPR as a potential tool to evaluate dysfunction of ipRGCs in patients with optic chiasm compression.

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GP236

Characteristics and natural history of a large cohort of non-functioning pituitary incidentalomas: a two-centers study

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Context
Available data on the natural history of pituitary incidentalomas (PI) are not strong enough to draw any evidence-based conclusion on timing and length of follow up of these masses, due to heterogeneity and low sample sizes.
Objective
To describe the characteristics and the natural history of PI using data from a large cohort of patients investigated in two Italian Pituitary Centers.
Patients and methods
Retrospective study on patients diagnosed with PI with imaging characteristics and/or histology compatible with non-functioning pituitary adenoma between 1980 and 2018.
Results
371 patients were included (microadenomas 50.9%, males 35.6%). Men were older and were more likely to have a macroadenoma at diagnosis ($P < 0.01$). At the first hormonal evaluation, hypopituitarism was present in 23.7% of patients, with a higher percentage of deficit in males, older patients and macroadenomas. Follow up data were available for 294 patients; 86 (29.2%) required surgery after first evaluation; 208 patients were initially managed conservatively. During follow up, 14.7% adenomas increased in size (more macroadenomas). 5.2% of patients developed new deficits (4.8% micro and 5.3% macro; more males); 7 of 10 patients showed a deterioration of pituitary function not associated with an increase in the size of the adenomas. 14 additional patients (6.7%) required surgery during follow up (1 microadenoma), bringing the number of patients requiring surgery to 100 (34.1%).
Conclusion
Size at diagnosis $\geq$10 mm, male gender and age are risk factor for hypopituitarism in pituitary incidentalomas at diagnosis; a pituitary deficit is present in more than 1 in 5 patients, underlying the importance of correct evaluation at baseline in these patients. During follow up, macroadenomas tend to grow more often; however, deterioration of pituitary function occurs in both micro and macroadenomas, and it is not always related to a change of the size of the adenoma. Overall, a third of patients requires surgery.

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GP237

Diagnostic accuracy of copeptin in the diagnosis of diabetes insipidus after pituitary surgery

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Background
Routine clinical use of arginine-vasopressin (AVP) is limited by its small molecular size and pre-analytical errors. In contrast, copeptin – a peptide of 39 amino acids co-secreted with arginine-vasopressin (AVP) - is a stable protein and its measurement represents a reliable measure of AVP concentration. The aim of this study was to analyze diagnostic role of copeptin in diagnosis of diabetes insipidus (DI) in patients treated for hypothalamic-pituitary diseases.
Materials and methods
This study included patients who underwent pituitary surgery by a dedicated neurosurgical team and followed at our center. Daily assessment of polyuria-polydipsia signs/symptoms and fluid balance was performed. DI was defined as emission of high volume ($>$40 ml/kg/die) of hypoosmotic urine. Copeptin was measured: i) 24 hours before surgery; ii) at second post-operative (PO) day; iii) at discharge; iv) 6–8 weeks after surgery. A complete assessment of pituitary function was performed before and 6–8 weeks after surgery. Patients with DI before surgery were excluded.
Results
We selected 47 patients (F/M 27/20, mean age 55 ± 15 years). 44 patients were affected by pituitary adenoma, 2 patients by craniopharyngioma and one patient by meningioma. 16 patients (34.0%) developed DI, which was transient in 9 (56.3%) and permanent in 7 (43.7%). DI occurred shortly after surgery (median [range]: 2 [1–3] day). Patients with Cushing's disease presented a higher risk of post-surgical DI. An inverse correlation between tumor diameter and development of DI was found (24 ± 8 vs 12 ± 9 mm, $P=0.002$), while pituitary insufficiency and radiologic invasiveness at baseline did not show any significant difference. Median (IQR) copeptin levels was significantly lower at second PO day, at discharge and at follow-up in patients who developed DI in respect to those who did not [3.25(2.45–3.7) vs 4.5(3.6–7.4), 2.2(1.8–3.3) vs 3.8(3.2–5.6) and 3(2.5–4) vs 4.45(3.2–7) pmol/l, respectively, for all $P<0.05$). No difference in copeptin levels between patients with transient and permanent DI was found. Unadjusted binary logistic regression did not show a significant association between copeptin levels and DI development at baseline and at second PO day.
Conclusion
Consistently with diagnosis, postoperative copeptin levels is lower in patients who develop DI. However, in our restricted cohort of patients and at time points evaluated, copeptin did not represent an accurate marker for postoperative DI.

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GP238

Immune checkpoint inhibitors therapy-induced hypophysitis is frequently associated with previous thyroid disorders: results from ImmuCare study

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Context
The immune checkpoint inhibitor (ICI) therapy is frequently used to treat advanced cancers. Autoimmune adverse events have been reported, such as endocrine side effects including frequent thyroid disorders and more rarely hypophysitis. The aim of this study was to describe retrospectively the association thyroiditis-hypophysitis.
Patients and method
From 99 patients with endocrine side effects of the ImmuCare cohort, 18 patients with hypophysitis were included from 2014: eight patients with hypophysitis alone (H group) and ten patients with association thyroiditis-hypophysitis (ATH group). The median age was 59 years, sex ratio M/F was 14/4. Thirteen patients received anti PD1, four patients anti CTLA4 and one patient a combination of both.
Results
Hypophysitis occurred after a median of five courses and 120 days (72 to 323 days). Ten cases were grade $\leq$2 and eight cases were grade 3. The discovery was clinical in 14 cases (77%). MRI was available in 17 cases and showed pituitary enlargement in two cases (11%). ACTH deficiency was present in 100% of cases and eight patients (44%) had another associated deficiency (4 gonadotropic deficiency, 3 somatotropic deficiency, 3 thyrotropic deficiency). After a median time of 13 months follow-up, ACTH recovery was observed in one case (5%) at 2 months. Thyroiditis occurred after a median of three courses and 42 days (20 to 180 days). All cases were low grade. The thyroid dysfunction was new-onset hypothyroidism for five patients (50%), sub clinical transient hyperthyroidism for one patient (10%) and hyperthyroidism progressing to hypothyroidism for four patients (40%). Antithyroid peroxidase and antithyroglobulin antibodies were positive for three patients. Levothyroxine therapy was introduced and continued after a median time of 20 months follow-up in 70% of cases. Hypophysitis occurred after the primary thyroid dysfunction in 70% of cases, within a median time of 65 days. In two cases the discovery was simultaneous and in one case hypophysitis occurred 80 days before thyroid dysfunction. Hypophysitis occurred earlier in the ATH group (108 vs. 143 days). The use of anti CTLA4 or combination was more frequent in the ATH group (40% vs 12.5%). In addition to the ACTH deficiency, four patients had another deficiency in the ATH group (40%, vs 50% in the H group). The sex ratio, median age and clinical presentation were not different between groups.

Conclusion
In our cohort, hypophysitis was frequently preceded by a primary thyroid dysfunction. Hypophysitis occurred earlier when it was associated with thyroiditis.

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GP239

Peptide receptor radionuclide therapy (PRRT) in patients with giant aggressive pituitary tumors: experience of an Italian referral center and review of literature

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Background
Pituitary tumours (PT) are generally benign, but they can rarely show an aggressive behaviour, invade surrounding structures and/or grow/recur despite multimodal treatment, making their management extremely challenging. According to the latest guidelines, temozolomide (TMZ) can be an option after failure of standard therapies in aggressive PT, while little data are available on alternative approaches such as peptide receptor radionuclide therapy (PRRT). Herein we report on the effectiveness, safety and long-term outcome of PRRT in three patients with aggressive giant PT, also reviewing data from literature.
Patients and methods
Two patients (1 F, 1 M) were affected by giant prolactinoma, and one (F) by a non-functioning pituitary adenoma (NFPA). Patient #1 received 5 cycles of ^{111}In-DTPA-octreotide (total dose 37 GBq) over a 23-month period, after unsuccessful surgery and long-term dopamine-agonist treatment. Patient #2 underwent 2 cycles (12.6 GBq) of PRRT with ^{177}Lu-DOTATOC, after failure of multiple surgeries, radiosurgery and TMZ. In Patient #3, five cycles (29.8 GBq) of ^{177}Lu-DOTATOC were administered after five unsuccessful trans-sphenoidal approaches, radiotherapy and TMZ. A systematic review of the current literature retrieved nine more cases of aggressive PT treated with PRRT.
Results
PRRT was successful in patient #1, leading to significant shrinkage of the tumor (from 63 to 3.1 cc) and remarkable visual/neurological amelioration over an eight-year follow-up period. Patient #2 and #3 did not take advantage from treatment, since PT continued to grow leading to blindness and neuro-cognitive disorders in patient #2, and monolateral amaurosis in patient #3. No PRRT-related adverse effects were reported in any subject. Overall, also including 9 patients reported in literature (3 carcinomas and 6 adenomas), PRRT induced tumor shrinkage and clinical/biochemical improvement in 4/11 patients (36.3%). Response to PRRT did not correlate with gender or age of patients, neither with radionuclide or peptide used for treatment, but PRRT failure was significantly associated with previous TMZ treatment. Overall, PRRT was well tolerated and significant adverse effects were reported only in 2 patients (18.2%).
Conclusions
PRRT induced PT shrinkage and clinical and/or biochemical improvement in one-third of patients with aggressive PT overall, and in 80% of those not previously treated with TMZ. PRRT is a safe therapeutic option when surgery and radiosurgery fail to control PT progression. However, at present, considering the few available studies, PRRT should be proposed for aggressive PT only in an experimental setting, after conventional therapies.

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GP240

Adrenal axis deterioration in the families/sporadic patients with PROP1 mutation, over 30 years of single center longitudinal observation

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Introduction
The time, degree and mode of pituitary function deterioration in patients with PROP1 mutation is not fully known and understood.
Aim
To investigate the time and mode of pituitary function deterioration in the families/sporadic patients with PROP1 mutation during longitudinal observation.
Methods
We performed a retrospective longitudinal (33 years, SD = 12) analysis of 22 patients (11M/11W) with PROP1 mutation, including 5 families (13/22, 59% of investigated population), with 2–3 affected siblings who were under medical supervision of the pediatric/adult endocrinology departments of our university.
Results
All patients initially presented with growth failure at mean age (MA) 7.4 years (SD = 4,3). 14/22 patients were first diagnosed with GH and TSH deficiency occured simultaneously and replacement therapy was instituted MA 6.6 years (SD = 3.0). 5/22 (older patients) received delayed/intermittently GH treatment. Gonadal deficiency was diagnosed in 22/22 patients MA 15.6 years (SD = 5.1). 20/22 (91%) patients developed adrenal deficiency MA 23.3 years (SD = 15.0). In 2 patients with low morning cortisol/symptoms of adrenal insufficiency hydrocortisone supplementation was implemented during the transition period however reevaluation of the gonadal axis at age 21 revealed normal adrenal function. The age of deficiencies determination in siblings are given in the Table 1.

Table 1

Families Sex/ Actual age	Age when insufficiency was diagnosed	HGH	TSH	LH/FSH	ACTH
1	F/25	5	5	16	7
	M/19	4	1	12	12
2	M/35	9	8	16	16
	M/33	5	5	15	No
	M/29	4	2	14	21
3	M/52	5	5	5	46
	F/42	3	3	19	29
	F/40	5	16	16	31
4	F/39	8	8	15	No

Conclusions
The pituitary function deteriorates progressively in patients with PROP1 mutation, however there is no specific order of deterioration even among affected siblings. The adrenal axis can deteriorate long after other axis insufficiencies, however there are patients with no adrenal insufficiency even during lifelong observation. Patients with PROP1 mutation should be carefully monitored for possible adrenal insufficiency including stimulation tests regardless of the time of observation.

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GP241

Inflammatory response to osmotic stimulus in healthy volunteers

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Context
Osmotic stimulus or stress results in release of vasopressin. Animal studies have shown that inflammatory parameters such as interleukin-6 (IL-6) and interleukin-8 (IL-8) increase in parallel, mainly in central brain regions. Whether osmotic stimulation leads to an inflammatory response in humans is unknown. We therefore investigated the influence of osmotic stimulation on the inflammatory system in healthy volunteers.
Method
In this prospective cohort study, 44 healthy volunteers underwent a standardized test protocol leading to an osmotic stimulation into the hypertonic range by hypertonic-saline infusion (serum sodium > 150 mmol/l). Copeptin, a marker to

indicate vasopressin activity, sodium, osmolality, IL-6, IL-8 and TNF-a was measured at baseline and directly after osmotic after stimulation.
Results
Median serum sodium increased from 141 mmol/l (IQR 140, 142) to 151 mmol/l (IQR 150; 153) (*P*-value <0.01), median serum osmolality increased from 295 mmol/l (IQR 291; 298) to 315 mmol/l (312; 317) (*P*-value <0.01). Copeptin increased form 4.3 pg/l (IQR 3.3; 6.7) to 28.8 pg/l (19.9; 43.4) (*P*-value <0.01). IL-8 levels decreased from 0.79 pg/ml (IQR 0.65; 1.1) to 0.7 pg/ml (IQR 0.57; 0.9) (*P*-value 0.09) and TNF-a decreased from 0.53 pg/ml (IQR 0.38; 0.69) to 0.45 pg/ml (IQR 0.3; 0.5) (*P*-value 0.036). There was no significant change in IL-6 levels.
Conclusions
Contrary to animal data, inflammatory markers remain unchanged or decrease in human serum after osmotic stimulation. Increased vasopressin/copeptin seems not to stimulate inflammatory markers; whether a negative feedback exists remains unclear.

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GP242

Copeptin levels in SIADH – a marker of malignant disease?

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Context
Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a very common condition in hospitalized patients. It is crucial to establish the cause of SIADH especially in order to exclude or detect an underlying malignancy. As SIADH can be caused by paraneoplastically produced arginine vasopressin (AVP), we hypothesized that its stable surrogate marker copeptin may be used as a diagnostic tool.
Methods
We analyzed data from 146 patients with SIADH from two prospective observational studies, conducted in Switzerland and Germany, who were included while presenting at the emergency department. Patients underwent a standardized diagnostic assessment at admission including the measurement of copeptin levels.
Results
39 patients (median age: 63 years, 51% female) were diagnosed with cancer-related and 107 (median age: 73 years, 68% female) with non-malignant SIADH. Serum sodium levels were higher in cancer-related versus non-malignant SIADH: median (IQR) 124 mmol/l (120; 127) versus 120 mmol/l (117; 123) ($P < 0.001$). Median (IQR) copeptin levels of patients with cancer-related SIADH were 11.1 pmol/l (5.2; 37.1) and 10.5 pmol/l (5.2; 25.2) with non-malignant SIADH ($P = 0.21$). Among different cancer entities, patients suffering from small cell lung cancer showed the highest copeptin values, but overall no significant difference in copeptin levels between cancer types was observed ($P = 0.47$).
Conclusion
We found no difference in copeptin levels between cancer-related and non-malignant SIADH. Copeptin is not suitable as diagnostic tool to exclude or detect an underlying malignancy in SIADH.

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GP243

Histological classification of pituitary neuroendocrine tumors: genomic insights on cell lineage

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The 2017 World Health Organization (WHO) classification of pituitary adenomas is based on cell lineage and transcription factors (TFs). Pituitary progenitors expressing Pit-1 are driven towards the somato-lacto-thyrotroph differentiation, T-Pit towards corticotroph, and SF-1 towards gonadotroph. We recently generated a multi-genomic classification of pituitary neuroendocrine tumors (PitNETs) (abstract submitted to ECE2019 by Neou M.). Transcriptome classification identified six groups: corticotroph overt Cushing; lactotroph; silent corticotroph; gonadotroph and null-cell; thyrotroph, Pit-1 plurihormonal and sparsely-granulated somatotroph; somatotroph and mixed GH-PRL.
Aim
To characterize the lineage differentiation in PitNETs.
Methods
Transcriptome of 134 PitNETs (RNA sequencing) was used to determine TFs expression at mRNA level, and to provide a canonical transcriptome signature for each cell-type (cortico-, lacto-, somato-, thyro- and gonadotroph). Pathological study of the present serie of PitNETs included the histological examination and the immunohistochemical tests for all pituitary hormones, proliferation markers and TFs including GATA3.
Results
Pit1 lineage. As expected, Pit1 mRNA showed expression exclusively in somatotroph (23/23), mixed GH-PRL(8/8), thyrotroph (6/6), lactotroph (16/16) and Pit-1 plurihormonal (9/9) PitNETs. Immunohistochemistry confirmed this observation. Based on transcriptome classification, accurate thresholds of immunoexpression for GH, PRL and TSH were established in order to define the different Pit-1 subtypes:
PRL >10%, with GH ≤5% for lactotroh
GH >10%, with PRL ≤5% for somatotroph
TSH >10%, with GH and PRL <5% for thyrotroph
PRL and GH positivity >5% for mixed GH-PRL
Combined PRL, GH, TSH, FSH, and LH positivity for Pit-1 plurihormonal.
T-Pit lineage
T-Pit mRNA showed the expected expression in corticotroph PitNETs (35/35), lower in silent ones (Wilcoxon $P < 10–5$). Immunohistochemistry confirmed this profile.
SF1 lineage
SF1 mRNA expression showed the expected high expression in gonadotroph PitNETs (29/29), but also in a subset of somatotroph PitNETs (9/21). SF1 immunopositivity was confirmed in this somatotroph subgroup.
The cell-type specific transcriptome signatures revealed an unexpected gonadotroph signature in silent corticotroph PitNETs, accounting for 40% (median) of silent corticotroph signature. GATA3 TF was one of the gonadotroph signature genes. Immunohistochemistry for GATA3 confirmed positivity in gonadotroph (29/29) and in silent corticotroph PitNETs (6/8).
Conclusion
This study showed for the first time on a large series of PitNETs the correlation between pathological and molecular classifications. The Pit1 and T-Pit TFs are strong determinants of PitNETs molecular classification. In contrast, gonadotroph lineage is more complex, with possible transdifferentiation in silent corticotroph and in a subset of somatotroph PitNETs.

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GP244

Tomosyn negatively regulates arginine vasopressin secretion in embryonic stem cell-derived neurons

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Arginine vasopressin (AVP) is secreted via exocytosis; however, the precise molecular mechanism underlying the exocytosis of AVP is unknown. To better understand the mechanisms of AVP secretion, here we study to identify proteins that bind with a 25 kDa synaptosomal-associated protein (SNAP25), a protein that plays a crucial role in exocytosis, in the posterior pituitary. Embryonic stem (ES) cell-derived AVP neurons were established to investigate the functions of the identified proteins. Using glutathione S-transferase (GST)-pulldown assays and proteomic analyses, we identified tomosyn as a SNAP25-binding protein in the posterior pituitary. Coimmunoprecipitation assays indicated that tomosyn formed N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complexes with SNAP25 and syntaxin1. Immunohistochemistry showed that

tomosyn localized to the posterior pituitary. Mouse ES cells self-differentiated into AVP neurons (mES-AVP) that expressed tomosyn and two transmembrane SNARE proteins, including SNAP25 and syntaxin1. KCl increased AVP secretion in mES-AVP, and overexpression of tomosyn reduced KCl-stimulated AVP secretion. Downregulation of tomosyn with siRNA increased KCl-stimulated AVP secretion. In addition, pituitary adenylate cyclase-activating polypeptide (PACAP) increased the PKA-catalysed phosphorylation of tomosyn and thus increased AVP secretion. These results suggest that tomosyn negatively regulates AVP secretion and that phosphorylation of tomosyn by PKA is involved in tomosyn-regulated AVP secretion in mES-AVP.An important next step would be to screen for gene mutations in tomosyn in patients with idiopathic CDI. We anticipate our methods of mES-AVP culturing to provide a more sophisticated *in vitro* model of secretion of AVP, including application to studies of CDI-specific human samples and induced pluripotent stem cells.

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Disturbances of Reproduction

GP245

MRI detection of aortic anomalies in 204 adult patients with Turner syndrome: a longitudinal study

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Mortality is 3 fold higher in patients with Turner syndrome (TS) than in the general population, primarily due to cardiovascular complications. Recent clinical guidelines (Gravholt et al. EJE 2017) underlined the need of a lifelong cardiovascular follow-up. However, prospective studies evaluating the aortic natural history in clinical practice are scarce. We performed a monocentric longitudinal study including 204 adult TS patients, between 2005 and 2018. Inclusion criteria were a karyotype $\geq$10% 45,X cells and a 1.5 Tesla magnetic resonance imaging (MRI). Aortic root diameters were measured at the 5 recommended levels: annulus, valsalva sinuses, sino-tubular junction, tubular ascending aorta and aortic cross. Aortic dilatation (AD) was defined by a diameter $>$32 mm or $>$ 20 mm/m^2 when indexed to body surface area (BSA). History of cardiovascular surgery, valvular abnormalities and cardiovascular risk factors were recorded. Kaplan-Meier curves and uni/multivariate cox regressions were performed using SAS-V9.3 software. TS patients' median age was 25.4 [P25; P75: 19.5; 34.2]. Their median BMI was 22.9 [20.3; 25.6] Kg/m^2. A 45,X monosomy was present in 82/204 (40.2%) of cases. Cardiovascular surgery had been performed at a median age of 13.0 [1.5; 24.0] in 5.9% of cases. Bicuspid aortic valve (BAV) and coarctation were detected in 22.1% and 8.8% of cases, respectively. Treated diabetes, dyslipidemia, and hypertension were found in 5.9%, 5% and 4.9% of cases, respectively. At baseline and at last follow-up, AD was observed in 65/204 (31.9%) and 85/204 (41.7%), respectively. Age at detection of AD $>$ 20 mm/m^2 and $>$ 25 mm/m^2 was 29.3 [21.5; 36.8] and 35.8 [24.8; 58.2] years. Kaplan-Meier modelization showed a median age of survival without AD of 35 years. Univariate cox regression showed that age of the patient (P $<$0.001); age at diagnosis of TS (P 0.006); presence of BAV (P $<$.001); coarctation ($P<.001$); hypertension (P 0.02); history of cardiovascular surgery (P 0.008) were significantly associated with AD. After multivariate cox modelization, only age at diagnosis ($<$.0001) and BAV ($<$.004) remained associated with AD. Preliminary data found a mean aortic progression of 0.17 mm/year over this period. Overall, AD risk is increased by 2.15 [IC95% 1.27–3.64] in presence of BAV. In conclusion, our prospective study on a large cohort of adult TS patients identified risk factors for aortic dilatation. Our results should help identifying TS patients with a higher risk of AD. It should therefore optimize the timing of MRIs during the patients' lifelong follow-up.

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GP246

Is monosomia related to poorer cardiometabolic state in Turner syndrome?

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Introduction
45,X karyotype is known to be related to more severe phenotype disorders, still comparative analysis of the karyotypes and phenotypes in Turner syndrome (TS) is difficult, even in the largest studies, mainly due to differences in patient's age and variability in the definition of clinical features (1). We aimed: to assess if monosomia in Turner syndrome patients is related to their cardiometabolic features.
Methods
75 females with confirmed TS $\geq$18 yrs were enrolled into the cross-sectional study. Patients were divided into 2 groups: 45,X group and non-45,X group (mosaicism, isochromosome, etc.). Standard clinical evaluation was performed (height, weight, body mass index (BMI), blood pressure (BP), heart rate (HR)). Levels of plasma glucose and lipids were assessed. Size of ascending aorta (adjusted for body surface area (BSA)) was evaluated by means of thoracic magnetic resonance angiography (1.5T) in four positions: aortic sinus (D1), sinotubular junction (D2), ascending aorta at the bottom edge of the right pulmonary artery (D3) and ascending aorta at the right proximal brachiocephalic artery (D4).
Results
45,X karyotype was identified in 65.3% of the TS cohort. Age at investigation was similar in monosomia vs. non-45-TS groups ($P=0.075$). Lower BMI was found in non-45,X compared to 45, X patients (23.0 vs. 25.6 kg/m^2, respectively, $P=$ 0.028), they were significant taller (155 cm vs. 150 cm, respectively, $P=0.004$). Duration of Growth hormone treatment was comparable in both study groups ($P=$ 0.105). The diameter of aorta in D2 and D3 positions was larger in 45,X group (16.4 mm/m^2 vs. 14.8 cm/m^2, $P=0.046$ and18,2 mm/m^2 vs. 15.9 mm/m^2, $P=$ 0.028, respectively). The prevalence of congenital cardiovascular anomalies (bicuspid aortic valve, coarctation of aorta) was higher in 45,X patients (28.6% vs. 0%, $P=0.001$). No difference in BP, HR, levels of glucose and lipids was observed between the groups.
Conclusion
High prevalence of 45,X was found in Lithuanian Turner syndrome cohort. Monosomia was related to larger size of ascending aorta and higher body mass index.

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GP247

The efficacy of long-term metformin treatment in overweight and obese women with PCOS: A 10-year database study

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Context
Metformin is an established therapy for women with PCOS and pre-diabetes or diabetes when lifestyle modification is insufficient. Metformin should also be considered in women with PCOS with BMI$\geq$25 kg/m^2 independently of the presence of metabolic disturbances. However, its long-term efficacy in this subset of patients is inadequately studied.
Aim
We analyzed collection data of 10 years for the efficacy of metformin on body mass (BM), menstrual frequencies (MF), metabolic and hormonal outcomes in women with PCOS and BMI$\geq$ 25 kg/m^2.
Methods
Collection data from endocrine outpatient clinic at the university medical centre for 10 years comprising 800 patients with PCOS defined by Rotterdam criteria including 180 patients with PCOS and BMI$\geq$25 kg/m^2 (age 28.8$\pm$6.6 years, BM 96.4$\pm$18.7 kg, BMI 34.8$\pm$6.4 kg/m^2) all receiving uniform monotherapy with metformin 1000 mg BID.
Results
The registry contained 7143 time-points with a subset of anthropometric, reproductive, hormonal and metabolic parameters. The drop out rate in the 1st year was 13%, in the 2nd 24%, in the 3rd 26%, in the 4th 32% and in the 5th year

40%. Only 18% of patients continued with metformin for 10 years. After the 1st year BM decreased for 4.2 ± 1.1 kg ($P < 0.001$) and remained in a steady state until the 10th year in those that continued with the therapy. MF increased from 7.5 ± 3.8 to 10.7 ± 2.9 bleeds/year ($P < 0.001$) after 1st year to over 11 bleeds/year in the following years. The total testosterone and androstendione decerased for 25% after the 1st year, with further decrease in androstendione for 50% from the initial values within the 5 years. LH, FSH and fasting glucose did not changed significantly over the treatment period. Increased MF correlated with the decreases in BM and total testosterone, with no correlation with the change in LH/FSH ratio. Initially, 10% had pre-diabetes and 1.7% had diabetes. After the 1st year 5.7% had pre-diabtes and 1.9% diabetes, after 3rd year 2.2% of women that continued with metformin had pre-diabetes and none had diabetes. The remission rate from pre-diabetes to normal glucose homeostasis in the 1st year was 72%.
Conclusions
Long-term metformin treatment of women with PCOS and BMI ≥ 25 kg/m^2 independently of their initial metabolic status resulted in maximum treatment response after the 1st year, with the improvements in BM, MF and androgen profile. A great drop out was seen after the 3rd year. In women that subsequently remained on therapy an overall beneficial steady state was observed up to the 10th year.

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GP248

Gut microbiota-dependent cardiometabolic risk and oral contraceptive use in polycystic ovary syndrome: A prospective study

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Context
Polycystic ovary syndrome (PCOS) is associated with an increased cardiometabolic risk that might not necessarily translate into adverse cardiovascular outcome later in life. Recently, alterations in gut microbial composition have been reported in the syndrome. Microbiota-dependent metabolite trimethylamine N-oxide (TMAO) and its precursors are closely linked with development of atherosclerotic cardiovascular disease, independently of traditional risk factors.
Objective
To assess whether TMAO and its precursors are altered in PCOS and to determine potential impact of oral contraceptive (OC) use on these metabolites**.**
Materials and methods
The study included 27 overweight/obese patients with PCOS and 25 age- and BMI-matched healthy control women. At baseline, fasting serum TMAO and its precursors were measured after a 3-day standardized diet. Patients received dienogest-ethinylestradiol (2 mg/0.03 mg) therapy along with general dietary advice for three months after which all measurements were repeated. Four patients were excluded from the second analysis due to antibiotic use during the study period.
Results
The median age and BMI of patients and controls were 21 (IQR: 19–22) versus 23 (IQR:20.5–27) years and 30.7 (IQR:27.8–33.3) versus 31.5 (IQR:27.8–37) kg/m^2 respectively (P=NS for both). Patients had higher total testosterone (T) and free androgen index (FAI) whereas whole body fat mass, fasting plasma glucose, insulin and lipids were similar between the groups. PCOS group showed significantly higher serum levels of TMAO and its precursors: TMAO (2.39 [IQR:2.15–4.49]vs 2.05 [IQR: 1.36–3.33][Mol/L, $P=0.042$), choline (43.2 [IQR:39.5–48.9] vs. 36.6 [IQR:29.85–41.3][Mol/L, $P=0.001$), betaine (49.4 [IQR: 38.3–53.3]vs. 39.8 [IQR: 33.8–50.9][Mol/L, $P=0.034$), and carnitine (10.7 [IQR: 9.9–12.3]vs. 9.7 [IQR:8.15–11.6][Mol/L, $P=0.024$). TMAO and choline showed correlations with T ($r=0.292$, $P=0.037$, and $r=0.353$, $P=0.010$). After 3 months of OC use, there were decreases in BMI (30.3 [IQR: 27.5–33.3]vs. 29.4 [IQR:25.8–31.4] kg/m^2, $P<0.001$) and FAI levels(11.2 [IQR: 5.6–15.5]vs. 1.74 [IQR:0.76–2.53] ng/dl, $P<0.001$). TMAO and all its precursors significantly reduced after therapy: TMAO (3.35 [IQR: 2.18–4.93]vs. 2.05 [IQR:1.7–2.93][Mol/L $P=0.002$), choline (43.6 ([IQR: 39.5–49]vs. 33.8 [IQR: 31.5–36.9][Mol/L, $P<0.001$), betaine (49.4 [IQR: 39.9–57.1]vs 24.4 [IQR:20.2–32.6][Mol/L $P<0.001$), and carnitine (10.7 [IQR: 9.9–12.3]vs 8.9 [IQR: 8.2–9.7][Mol/L $P<0.001$).
Conclusion
This study reports for the first time that TMAO and its precursors are elevated in PCOS which might contribute to increased cardiometabolic risk of the syndrome and that OC use is associated with reduction of these microbiome-dependent metabolites.

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GP249

Maternal 3rd trimester cortisol status was associated with offspring sex and PCOS status. Odense Child Cohort

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Background
Maternal circulating cortisol and 24-h urinary free cortisol levels are up to three times higher in third trimester pregnant women compared to non-pregnant women. Maternal cortisol status could be associated with offspring sex, maternal PCOS and testosterone levels.
Aims
To determine predictors of maternal serum (S) and urinary (U) cortisol and cortisone levels during 3rd trimester and to examine associations between maternal cortisol status, offspring sex, and maternal PCOS status.
Methods
The study is part of the prospective Odense Child Cohort. This study cohort included 1489 women (PCOS, $n=145$ and controls, $n=1{,}344$). Fasting morning S-cortisol and 24h U-cortisol/U-cortisone (24h U-C/C) were collected at gestational week 28 and measured by liquid chromatography-tandem mass spectrometry.
Results
Maternal S-cortisol levels were significantly higher in women pregnant with girls ($n=702$) vs. boys ($n=787$): 833 (643; 1,077) vs. 799 (588; 1,084) nmol/L, $P=0.014$. In multiple regression analyses, maternal S-cortisol was positively associated with female offspring, maternal testosterone levels and inversely associated with maternal age and parity. When women were divided according to PCOS status, 24h U-cortisone was higher (467 (334; 652) vs. 415 (286; 604) nmol/24 h) and 24h U-C/C was lower in women with PCOS compared to controls.
Conclusions
Maternal 3rd trimester S-cortisol levels were positively associated with female offspring and circulating testosterone levels. Cortisol metabolism was higher in women with PCOS vs. controls.

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GP250

Diagnostic potential of a 'mouse azoospermia' gene panel in human azoospermia: identification of novel genetic causes of meiotic arrest

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Purpose
Non-Obstructive Azoospermia (NOA), occurring in approximately 1% of men, has an unknown etiology in the majority of cases. This study aims at evaluating the diagnostic efficiency of a gene panel contemplating all known genes associated with azoospermia in mice.
Subjects and methods
Design of a 'mouse azoospermia' gene panel through the consultation of MGI; selection of 175 mouse azoospermia genes with human orthologues; selection of 31 idiopathic NOA patients from a total of 1300 infertile patients and selection of a familial case (2 brothers) of NOA. Next-Generation Sequencing in the 33 selected NOA men. Characterization of the discovered gene defects in human testis tissue: i) meiotic studies in carriers of *RNF212* and *STAG3* mutations; ii) *RNF212* and *STAG3* expression profile through qPCR.
Results
Homozygous pathogenic *RNF212* variant was identified in two brothers (consanguineous parents) and biallelic variants in *STAG3* in a sporadic patient. Meiotic studies in the siblings revealed normal meiotic entry/XY body formation but an increase of apoptotic metaphases while in the *STAG3* mutation carrier normal meiotic entry but no XY body formation.
Conclusion
By using a hypothesis-driven approach which consisted in the sequencing of 175 genes, for the first time, we report biallelic variants in *STAG3* in one sporadic patient, and a homozygous *RNF212* variant in the two brothers as the genetic cause of NOA. Meiotic studies allowed the detection of the functional consequences of the mutations and provided information on the role of STAG3 and RNF212 in human male meiosis. Our approach was relatively successful since we could diagnose a candidate gene mutation in 9% of idiopathic NOA

cases (2/33). This proportion increases up to 40–50% if we consider only patients affected by meiotic arrest. Our study represents an additional step towards elucidating the genetic basis of early spermatogenic failure. We propose the inclusion of *RNF212* and *STAG3* in a future male infertility diagnostic gene panel. More than half of the 175 sequenced genes are reported to affect also female reproduction in mice (among them Rnf212 and Stag3) and *STAG3* mutations were first described as a cause of female infertility (POI) and ovarian cancer. Hence, our results stimulate further research on shared genetic factors causing both POI and NOA. The diagnosis of such genetic factors implies that genetic counselling for NOA has relevance not only to the male family members and male descendants but also to female relatives.

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GP251

Free Testosterone (FT) is inversely related to frailty in Human Immunodeficiency Virus (HIV)-Infected Men

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Background
HIV-infection is associated to several age-related comorbidities, such as a premature decline of serum testosterone (T). There is evidence about the relationship between health status, represented by frailty and comorbidities, and serum T levels in general population, while only one previous retrospective study investigated it in HIV-infected men.
Aim
To investigate the association between frailty and gonadal status by assessing serum total T (TT) with Liquid Chromatography tandem Mass Spectrometry (LC-MS/MS) in a cohort of HIV-infected men.
Methods
Prospective, cross-sectional, observational study on HIV-infected men (age <50 years) with ongoing Highly Active Antiretroviral Therapy (HAART). Serum TT was assessed by the gold standard ID-LC-MS/MS. Sex hormone-binding globulin (SHBG) was measured by chemiluminescent immunoassay. Free T (FT) was calculated by Vermeulen equation. Frailty was calculated through 38-items multimorbidity frailty index. *Statistical analysis:* Parameters were not normally distributed and Mann-Whitney *U* test was used to compare continuous variables. Correlations were performed using linear regression models.
Results
315 consecutive HIV-infected men were enrolled (mean age 45.56 ± 5.61 years; average duration of HIV-infection 16.30 ± 8.57 years). 17 patients (5.4%) had TT below 320 ng/dl and 31 patients (9.8%) had calculated FT below 64 pg/ml. Overall, 37 patients (11.7%) had T deficiency defined by low TT levels and/or low FT. 56 patients (17.8%) showed SHBG above the normal range (>71.4 nmol/l). Frailty score ($P=0.031$), age ($P=0.001$), duration of HIV-infection and of HAART ($P<0.0001$) significantly differed between eugonadic and hypogonadic patients, while no difference was found for BMI ($P=0.209$). FT inversely correlated with frailty score ($P=0.038$, $R^2=0.014$), while TT did not ($P=0.235$). At stepwise multivariate regression analysis, FT showed an inverse relation with age ($P<0.0001$, $R^2=0.150$), years of infection (-0.339, $P<0.0001$, $R^2=0.125$) and years of HAART (-0.346, $P<0.0001$, $R^2=0.117$), but not with frailty score and BMI of patients.
Conclusions
To the best of our knowledge, this is the first properly-designed prospective study aiming to investigate the relationship between general health status and gonadal function in a cohort of HIV-infected men. FT is inversely related to frailty score, suggesting an impairment of gonadal function in those patients affected by more multimorbidities in this setting as well as in general population. At the same time, the age of patient and the duration of HIV-infection seem to be more potent predictive factors for serum FT levels than frailty score. In clinical practice it is important to check for testosterone in these patients due to frequent alterations of SHBG.

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GP252

Prolactin and prostate: an observational case-control study in men with prolactinoma under cabergoline treatment

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Prolactin (PRL) exerts independent hypertrophic effects on prostate in *in vivo* and *in vitro* experimental models, and prostatic PRL receptors are known to activate cell proliferation pathways such as MAPK and STAT. Nevertheless, in men with hyperprolactinemia the risk of prostate cancer has been found reduced suggesting a role of concomitant hypogonadism. Chronic cabergoline treatment generally normalizes PRL treatment and improves gonadal function. The current study aimed at investigating prostate morphology in patients with prolactinoma under cabergoline treatment as compared to healthy control subjects. Twenty men with prolactinoma on chronic cabergoline treatment (CAB, 6–12 months, median dose 0.5 mg/week), including 6 (30%) on testosterone replacement therapy (TR, 6 months, median dose 30 mg/day) and 20 healthy age-matched controls entered the study. In patients and controls, hormonal levels (PRL, FSH, LH, testosterone) were evaluated and transrectal prostate ultrasound was performed. In patients, LH ($P=0.04$) and testosterone ($P=0.026$) levels were significantly lower than in controls, with no significant difference in PRL levels. Prostate volume was slightly but not significantly lower in patients than in controls. Prevalence of normal prostate morphology was significantly higher ($P=0.05$) in controls as compared to patients, whereas ultrasound signs of prostatitis resulted significantly more frequent in patients ($P=0.027$) as compared to controls. Prevalence of prostate adenoma and carcinoma was similar in patients and controls, with two cases being recorded in each group. PRL levels ($r=-0.44$, $P=0.05$), but not testosterone levels and CAB or TR dose, significantly and inversely correlated with prostate volume. In conclusion, in men with prolactinoma on chronic CAB treatment the risk of prostate hypertrophy is lower compared to healthy subjects, whereas prostatitis is more prevalent in patients than in controls. Concomitant testosterone deficiency, together with the known action of PRL as regulator of inflammation and autoimmune pathology, might represent potential mechanisms responsible for these findings. Further studies are required to better elucidate the burden and the role of PRL, hypogonadism, CAB and TR on prostate morphology in prolactinomas.

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GP253

Genetic architecture of greek patients with isolated GnRH deficiency

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Introduction
Isolated Gonadotropin Releasing Hormone (GnRH) Deficiency (IGD) is a rare disease with a wide spectrum of reproductive and non- reproductive clinical characteristics and is mainly characterized by hypogonadotropic hypogonadism with anosmia (Kallmann Syndrome) or normal olfactory function (Normosmic Idiopathic Hypogonadotropic Hypogonadism- nIHH). Apart from the phenotypic heterogeneity IGD is also highly genetically heterogeneous with >35 genes implicated in the disease. Despite this genetic heterogeneity, genetic enrichment in specific subpopulations has been described.
Methods
A cohort of 87 IGD patients underwent Sanger and Whole Exome Sequencing (WES) with the goal to discover rare sequence variants (RSVs) in genes that cause IGD. Sanger sequencing was performed in 14 known IGD genes, whereas WES expanded the analysis to 37 genes. All patients were phenotyped in detail and segregation of the detected variants was performed in family members via Sanger Sequencing.
Results
The cohort consisted of 58 male and 29 female probands and was represented by a large number of normosmic patients (57 nIHH probands) compared to patients with Kallmann Syndrome (30 probands) suggestive of a phenotypic enrichment of the normosmic feature. The majority of cases were sporadic (79/87) and most patients carried non- reproductive features. Even though, Sanger sequencing detected RSVs in 25% (21/81) of IGD patients in 7/14 IGD genes without any evidence of oligogenicity, WES revealed that 31% (27/87) of IGD patients carried

a rare genetic change in a total of 15 genes with 4 IGD cases being oligogenic (i.e. carrying RSVs in more than 1 genes).
Discussion
This is the first analysis on the largest IGD Greek cohort that has ever being studied. Our findings suggest that next generation sequencing (NGS) techniques can discover previously undetected variation, making them the standardized method for screening patients with rare and/or more common disorders.

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Thyroid Nodules and Cancer 2

GP254

Recurrent laryngeal nerve liberation technique for phonation recovery

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Introduction
Recurrent laryngeal nerve (RLN) dysfunction is a major complication in thyroid surgery, caused commonly by thermal damage, transection or misplaced ligations. It can also be caused by RLN distension by thyroid tumors or thyroid goiter. Permanent paralysis decreases significantly quality of life and should be treated. Some surgical techniques can provide improvement in phonation, even complete recovery. The aim of this study was to analyze usefulness of RLN liberation technique in patients with RLN paresis/paralysis of various origins, based on symptoms improvement and laryngoscopy.
Materials & methods
From 2000 to 2018, 19 patients with RLN paresis/paralysis on laryngoscopy had RLN liberation as a part of thyroid surgery for various indications. If RLN dysfunction was caused by nerve distension over the enlarged thyroid lobe, the nerve was liberated during primary surgery from the lobe and repositioned. If RLN dysfunction was a consequence of previous surgery, misplaced ligation or postoperative adhesions were removed from the nerve, with its preservation. If patients had bilateral RLN paralysis, RLN liberation was performed in a two-step surgery, to avoid the risk for tracheostoma. Patient's recovery was assessed by laryngoscopy and qualitative scoring scale (QSS) at 4 time points: preoperatively, in 1st, 6th and 12th postoperative month. This *original Dzodic's liberation technique* was first reported in 2008 and published in *World J Surg* in 2016.
Results
One patient with RLN paralysis due to distension by a large follicular adenoma restored normal vocal cord mobility after lobectomy with RLN liberation (score 5 on QSS). In remaining 18 patients RLN liberation was done in a reoperation 2 months to 16 years after primary surgery – in 12 of them thyroid cancer was a primary surgical indication, in 6 reoperation was performed for alleviating the symptoms of severe dysphonia or stridorous breathing. Fifteen patients with redo surgeries scored 4 on QSS. Three patients with RLN liberation 6 months, 3 and 16 years after primary surgery restored normal vocal cord mobility on laryngoscopy (score 5 on QSS).
Conclusion
The *original Dzodic's technique of RLN liberation*, accompanied by phono-rehabilitation, enables patients with RLN paresis/paralysis a significant improvement in phonation, even complete voice recovery. It is possible to achieve complete vocal cord mobility many years after RLN injury.

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GP255

Are clinicopathological features of isthmic thyroid nodules different from nodules located in thyroid lobes?

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Aim
Although thyroid nodules located in isthmus were less frequent, papillary thyroid cancer in this location was reported to be more aggressive in some studies. Our aim was to evaluate hormonal, ultrasonographic, and cytopathologic features of nodules located in isthmus (isthmic nodules).
Material and methods
Data of patients who underwent thyroidectomy between 2006–2014 were reviewed retrospectively. Hormonal, ultrasonographic, and cytopathologic features of patients with isthmic and with lober (non-isthmic) nodules were compared.
Results
Patients with isthmic nodules (Group-1) and non-isthmic nodules (Group-2) consisted of 260 and 2171 patients, respectively. Age and gender distributions were similar. AntiTg positivity was higher in Group-1 (28.6% vs 21.2%; $P=0.018$). Subsequently, 268 isthmic (10.7%) and 5347 non-isthmic (89.3%) nodules were compared. Although ultrasonographical features such as presence of microcalcification and halo, nodule diameters, echogenicity, texture, margin, and vascularity were similar between groups, macrocalcification rate was lower in isthmic nodules (19% vs 27%; $P=0.004$). Furthermore, cytologic results were also similar. However, malignancy rate was lower in isthmic nodules (6.0% vs 11.4%; $P=0.006$), type of thyroid cancer was similar in isthmic and non-isthmic nodules. When malign isthmic ($n=16$, 2.6%) and malign non-isthmic nodules ($n=605$, 97.4%) were compared, diameter and type of tumor, lymphovascular and capsular invasion, extrathyroidal extension and multifocality rates were statistically insignificant. Malign isthmic nodules ($n=16$, 6%) had smaller size [10.05(4.00–34.50)mm vs 20.05(8.40–74.10)mm; $P=0.002$], higher hypoechogenity (31.2% vs 5.6%, $P<0.001$) and exophyticity rates (28.6% vs 4.9%; $P=0.007$) compared to benign isthmic nodules ($n=251$, 94%).
Conclusion
Although isthmic nodules had lower malignancy rate compared to non-isthmic ones, histopathologic features were similar in isthmic and non-isthmic nodules. Relatively small, hypoechoic, and exophytic nodules located in isthmus should be evaluated immediately for malignancy.

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GP256

Impact of age at the diagnosis of radioiodine resistance in differentiated thyroid cancer patients

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Background
Clinical predictors of survival of radioiodine-refractory differentiated thyroid cancer (RR-DTC) are poorly described. Age has been identified as a major prognostic factor in differentiated thyroid cancer. We asked whether age was a valuable predictor of poor prognosis in RR-DTC.
Patients and method
This single centre, retrospective study enrolled all patients diagnosed with a RR-DTC between 1991 and 2017. The primary end point was overall survival. Secondary endpoint was progression free survival. Log-rank test was used to compare population.
Results
Between 1991 and 2017, 155 patients was diagnosed with a RR-DCT. Diagnosis of RR-DTC was done before the age of 65 (younger group) in 71 cases and in 84 cases after 65 years-old (older group). Mean follow-up was 50 months (1–231). During follow up, 75 patients died, 35 in younger group and 41 in older group. Median overall survival was 4.19 years for younger group and 4.22 years for older group, with no statistical difference ($P=0.5$). Progression free survival was 1.5 years in younger group and 0.98 years in older group, but without statistical difference ($P=0.2$). There was no difference between the two groups especially regarding sex, histological subtype, or number of distant metastases. Therapeutic management did not differ between the 2 groups. Forty eight patients received tyrosine kinase inhibitor (TKI), 20 (28%) in younger group and 28 (33%) in older group ($P=0.5$). There was also no difference for radiotherapy ($P=0.6$), cervical surgery ($P=0.391$) or local treatments (cementoplasty, radiofrequency, metastases' surgery ($Ps=$ns)).
Conclusion
In RR-DTC patients, age was not predictive of the outcome. Continual progress made in the management of RR-DTC, especially in the last 15 years with the implementation of systemic therapies (i.e. TKI) should probably make reconsider the natural history and conventional prognostic factors of RR-DTC.

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GP257

Effects of hospital volume on clinical outcomes after thyroidectomy - a Swiss nation-wide study

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Background
Epidemiologocal data suggest an continuous increase in thyroid carcinoma diagnosis. Therefore, thyroidectomy rates are projected to increase world-wide in exponential scale. In Switzerland, the institutional number of thyroidectomies varies, however there is no data yet on the association between institutional thyroidectomy volume and clinical outcome.
Methods
Cross-sectional analysis of adult inpatients in Swiss hospitals using a nation-wide inpatient database covering the years 2011–2015. The study population consisted of adult ($\geq$18 years) inpatients who underwent total thyroidectomy or hemithyroidectomy as the primary procedure. Hospitals were stratified into very low ($<$20 thyroidectomies per year), low (20–100 thyroidectomies per year), intermediate (101–200 thyroidectomies per year) and high ($>$200 thyroidectomies per year) thyroidectomy volume institutions. Multivariate regression models were used to determine complications, length of hospital stay (LOS), intensive care unit admission (ICU), 30-day readmission rates, and mortality in relation to hospital volume.
Results
A total of 17,410 patients were included whereof two-thirds (11,613; 66.7%) of thyroidectomies were performed at very low and low volume hospitals and one-third (5,797, 33.3%) at intermediate and high-volume hospitals, respectively. Operations of malignant thyroid diseases were more frequent among high-volume hospitals compared to low-volume hospitals (27.7% vs. 17.4%; $P<0.001$). Rates of hypocalcemia following thyroidectomy were lowest in high-volume hospitals (very low 6.7%, low 9.5%, intermediate 9.7%, and high 3.7%) with an overall adjusted odds ratio of 0.34 (95% CI, 0.29–0.42; $P<0.001$). Rates of recurrent laryngeal nerve paralysis were overall low at 2.1% (SD 14.5) for both total and hemithyroidectomies, just as mortality rates which did not show significant differences in relation to institutional number of thyreoidectomies (overall 8 deaths (0.05%). Length of stay revealed a bell-shaped curve and was lowest among high-volume hospitals when compared to other hospital volume with a mean difference of 0.61 days (95% CI; ($-$0.72)–($-$0.50); $P<0.001$).
Conclusions
Despite higher rates of malignant thyroid diseases, high-volume hospitals had less or comparable complications and shorter length of stay following thyroidectomy when compared to hospitals with low thyroidectomy volume. Mortality rate was low and independent of institutional thyroidectomy volume.

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GP258

Predictors of malignancy in thyroid FNA classified as high-risk indeterminate lesions (TIR3B): combining ultrasonographic and cytology features

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Introduction
The new Italian cytological classification of thyroid nodules published in 2014 has replaced the TIR3 'indeterminate' category into two subcategory with different risk of thyroid cancer (TC): TIR3A, low-risk indeterminate lesion and TIR3B, high-risk indeterminate lesion. The aim of our study was to describe the incidence of TIR3B in a large prospective cohort of patients, the risk of TC, and its correlation with anamnestic, ultrasonographic (US) and cytological features.
Methods
Anamnestic, US and cytological features from all thyroid nodules undergoing FNA from June 2014 to January 2019 have been prospectively recorded. All patients receiving a cytological diagnosis of TIR3B have been referred to surgery and patients for whom histological examination was available have been divided into two groups: 1) TC; 2) benign lesions. Anamnestic, US and cytological features have been compared between the two groups.
Results
From June 2014 to January 2019, 1844 thyroid nodules underwent FNA in our institution and among these 96 (5%) have been diagnosed as TIR3B. Histological examination was available for 66 patients and among these 28 (42%) had TC and 38 (58%) had a benign lesion. At univariate analysis, patients aged $\leq$54 yrs had a significantly higher risk of TC than older ones (OR = 7.9, 95% CI 2.45–25.42, $P<0.001$), as well as patients with family history for extrathyroid malignancy (OR = 2.8, 95% CI 1.00–7.58, $P=0.04$) and for any malignancy (thyroid + extrathyroid) (OR = 3.1, 95% CI 1.09–8.73, $P=0.02$) as compared to those with negative family history. At US, nodule size $\leq$20 mm (OR = 5.6, 95% CI 1.84–17.10, $P=0.02$) and hyperechoic spots (OR = 5.7, 95% CI 1.72–18.96, $P=0.003$) were significantly associated with TC. Among cytological parameters, nuclear grooves (OR = 3.4, 95% CI 1.21–9.75, $P=0.017$), nuclear inclusions ($P=0.002$) and 'frosted-glass core' appearance (OR = 5.1, 95% CI 1.69–15.45, $P=0.003$) had a significantly higher risk of TC. After multivariate analysis, age $\leq$54 yrs was found an independent risk factor for TC (OR 8.84, 95% CI 1.75–44.58, $P=0.008$).
Conclusions
Thyroid nodules with a TIR3B FNA diagnosis that turned out to be thyroid cancer at the histological examination were not larger than those who were benign at final diagnosis, but more often presented hyperecoic spots at US. Cytologically, these nodules more frequently exhibited nuclear grooves, inclusions and 'frosted-glass core' appearance. Patients harboring a malignant lesion were younger and had a family history for any malignancy. The combination of anamnestic, US and cytological features could help in discriminating which high-risk indeterminate specimens should effectively be referred to surgery.

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GP259

Sentinel lymph node biopsy using methylene blue dye in clinically N0 papillary and medullary thyroid carcinomas for decision on one-time lateral neck dissection

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Introduction
Surgical management of clinically N0 (cN0) patients with thyroid carcinomas remains debatable due to various reported frequencies of lymph node (LN) metastases. The aim of this paper was to present usefulness of sentinel lymph node biopsy (SLNB) of jugulo-carotid regions after methylene blue dye (MBD) mapping in intraoperative selection of cN0 patients with papillary and medullary thyroid carcinomas for one-time lateral neck dissection (LND).
Materials & methods
We present results of three studies from our Surgical Oncology Clinic that analyzed usefulness of *Dzodic's original SLNB method for LN staging in thyroid carcinomas* (published in *Word J Surg, 2006*): the first with 153 cN0 papillary thyroid carcinomas (PTC), the second with 111 cN0 micro-PTCs and the third with 17 cN0 medullary thyroid microcarcinomas (micro-MTC) with serum calcitonin levels $<$1000 pg/ml. All patients underwent injection of 1%-MBD subcapsullary in both lobes, total thyroidectomy, prophylactic central neck dissection and SLNB of jugulo-carotid regions. All sentinel-LNs were examined by frozen section analysis (FSA). One-time LND was performed only in patients with sentinel-LN metastases on FSA. Otherwise, surgery was not extended.
Results
None of the patients had allergic reactions to MBD. LN metastases were histologically verified in 40.9% of cN0 PTCs and 25% of cN0 micro-PTCs. Only one patient with hereditary micro-MTC had LN metastases in central and both lateral regions. *Dzodic's SLNB method* enabled detection of LN metastases in lateral neck compartments in 21% of patients. Skip metastases were detected in about 4% of patients with PTCs and micro-PTCs, while there were no skip metastases in micro-MTCs. Method's overall accuracy was high in all studies, but the highest in the study with micro-MTCs (100%).
Conclusion
Dzodic's SLNB method with MBD mapping and FSA of sentinel-LNs from jugulo-carotid regions is accurate in detection of lateral LN metastases in cN0 patients with papillary and medullary thyroid carcinomas and microcarcinomas. It prevents over-treatment of patients without metastases in sentinel-LNs and helps in decision for one-time LND in patients with histologically proven sentinel-LN metastases. This method additionally facilitates central neck dissection and diminishes the possibility of accidental removal of parathyroid glands (that remain non-colored), even in less experienced surgeons' hands.

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GP260

Factors influencing nodular goiter – An analysis of the growth rates in long-term follow-up patients

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Background
Nodular goiter (NOD) is one of the most common disease (69% in our thyroid clinic). Although the nodular growth is generally slow, it may be influenced by thyroid hormones, autoimmunity or other factors. The analysis may contribute to predict the outcomes.
Patients and methods
2,213 Japanese patients (2007–2018; Fukushima coast area) with NOD were enrolled in this study. Mean observation period was 6.4 years with 7 visits (1–50). They consist of female (80%, mean age 57) and man (20%, 66). Serology was performed for thyroid peroxidase antibody (TPO), anti-thyroglobulin antibody (TgAb), thyroid stimulating hormone receptor antibody (TSH-RAb) and, in some patients, thyroid stimulating hormone antibody (TSAb). Hormonal assay was performed for free thyroxine (F-T4), free triiodo-thyronine (F-T3), thyroid stimulating hormone (TSH) and thyroglobulin (Tg). Nodules were examined by ultrasonogram to estimate total volumes of nodules (VOL). Pathological diagnosis was made by a fine needle aspiration cytology. Growth rates of nodules (VR%) were calculated from a formula; (current VOL/initial VOL)/ years.
Results
1. VR: 33% of NOD remained unchanged after 2 years of follow-up period, whereas 29% reduced and 38% enlarged. 2. TSH: TSH decreased from 1.46 IU/ml (mean) to 0.79 IU/ml after 8 years ($P<0.05$). 3. TSH and NOD: VR (/year) yearly decreased from 7% (0–2 years) to 0.9% (16 years). Patients with high TSH(>3 IU/ml) showed high VR (26–68%). 4. Thyroid antibodies: Positive (+) rates were 28% in TPO and 22% in TgAb. Both were associated with reduction of VR: no increase of VR in TPO+, whereas an increase (up to 3–8%) in TPO- ($P<0.05$). TSH-R was associated with an increase of VR (from 2% to 11%). 5. Cytology: VR was highest in cancer ($P<0.001$). 6. Physical states: VR was high in youth (age 10–30) and decreased in aging ($P<0.001$). Female had higher VR (3.9) than man (0.13, $P<0.05$). 7. Drugs: Patients treated with Levothyroxine showed low VR (−2%), whereas those with Methimazole showed high VR (+20%).
Conclusions
Growth of NOD was associated with various factors including TSH, thyroid autoantibodies and age. The activity appeared to be lost according to the follow-up periods.

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GP261

Evaluating effects of thyrotrophin receptor antibody positivity on cytology and histopathology in patients with graves disease

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Aim
It has been reported that thyrotrophin receptor antibody (TRAb) is associated with frequency and aggressiveness of thyroid cancer in patients with Graves disease (GD). However, there is not any data regarding the effects of TRAb on cytology and histopathology results of patients with nodular GD. Thus, the aim of the present study is to evaluate the effects of TRAb on cytology and histopathology results in patients with nodular or multinodular thyroid disease on the basis of GD.
Materials and methods
Clinical data of patients with GD who had thyroidectomy and preoperative TRAb levels were reviewed retrospectively. The cytology and histopathology results of 548 nodules from 598 patients with GD were evaluated for the present study.
Results
Of 598 patients, 189 (31.6%) were men and 409 (68.4%) were women. However 352 patients did not have nodular disease on preoperative thyroid ultrasound, 74 had only one nodule and 172 had ≥ 2 nodules. 517 (86.5%) patients had benign and 81 (13.5%) had malignant final histopathology. In malignant group, 77 (95.1%) patients had papillary throid carcinoma, 2 (2.5%) had follicular thyroid carcinoma, 1 (1.2%) had thyroid tumor of uncertain malignant potential, and 1 (1.2%) had hurthle cell thyroid carcinoma. However, TRAb was detected as positive in 359 (60%) patients, it was found as negative in 239 (40%) patients. There were 185 nodules in TRAb positive group and 363 nodules in TRAb negative group, and there was no significant difference in cytology results between groups ($P=0.181$). Malignancy was detected in 48 (13.4%) and 33 (13.8%) patients with TRAb positive and negative patients, respectively ($P=0.878$), and there was not any difference in histopathology results between groups ($P=0.161$). Furthermore, there was no difference in features of carcinoma such as capsular, vascular, and lymphatic invasions between TRAb positive and negative groups ($P>0.05$).
Conclusion
In the present study, it was found that malignancy rate was similar in TRAb positive and negative patients. Contrary to literature, TRAb positivity was not associated with increased malignancy rate and also had no effect on cytology and histopathology results in patients with GD.

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GP262

Classification of thyroid nodules by ultrasound in clinical practice: the added value of the judgment of the skilled endocrinologist

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Background and aim
Several ultrasound (US) classifications for thyroid nodules have been proposed. Since most of them are hardly applicable in clinical practice, we set up the Modena US Thyroid Classification (MUT) that stratifies the risk of malignancy considering both knowledge derived from scientific literature and clinician subjective impression. The aim of the present study was to test the diagnostic accuracy of different thyroid US classification systems, AACE/ACE-AME, American Thyroid Association (ATA), British Thyroid Association (BTA), and MUT, and to evaluate inter-classification agreement.
Methods
We prospectively enrolled 111 patients (33M, 78F; age 19–75) candidate for surgery because of indeterminate, suspicious or malignant cytology. All patients underwent neck US before surgery and a score according to MUT was assigned: 1 not certainly nodular; 2 not suspect; 3 indeterminate; 4 suspect; 5 very suspect. Then, we retrospectively classified nodules according to AACE/ACE-AME, ATA and BTA, thanks to the detailed collection of each nodule US features in a preformed checklist. US pattern was related to histology. Sensitivity, specificity, diagnostic cut-off value and accuracy of each classification were calculated. The overall agreement between classifications was quantified by Bland-Altman test. The agreement between single nodule analysis by different classifications was evaluated considering Weighted Cohen's Kappa.
Results
Fifteen patients had uninodular and 96 multinodular goiter, for a total of 457 nodules. MUT has the highest accuracy (AUC 0.808) and specificity (89%), followed by ATA and BTA, and finally by AACE/ACE-AME. ATA and BTA are highly interchangeable and MUT is comparable to both of them. AACE/ACE-AME is the least interchangeable with all the other classifications. Considering agreement between single nodule analyses by different classifications, ATA and BTA had the best ($\kappa=0.723$); AACE/ACE-AME showed slight agreement with BTA ($\kappa=0.177$) and MUT ($\kappa=0.183$), and fair agreement with ATA ($\kappa=0.282$); MUT had fair agreement with both ATA ($\kappa=0.291$) and BTA ($\kappa=0.271$).
Conclusions
Our data analysis to quantify the agreement between different classification systems confirms the reliability and reproducibility to classify malignancy. However, results bring out the limit in specificity of the current reference classifications, which improves when the subjective impression of the clinician is considered.

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GP263

Predictive factors of short and long-term vandetanib response in locally advanced or metastatic medullary thyroid cancer: a single center experience

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Objectives
Vandetanib (V) is an important drug in the metastatic medullary thyroid cancer (MTC) treatment. The objective of this study was to evaluate the presence of predictors of V response, in short and long period, in locally advanced or metastatic MTC patients (pts).
Methods
Seventy-nine locally advanced or metastatic MTC pts with progressive or symptomatic disease, referred to our Center between 2007 and 2018 and already treated surgically and with other systemic therapies, were treated with V. During follow-up it was performed clinical examination, biochemical and morphological evaluation. Twenty-five pts were treated with V for less than 12 months (short responders, Group 1), 54 patients were treated with V for at least 12 months (long responders, Group 2).
Results
The genetic screening showed that in the Group 1, 4/25 (16%) pts were inherited forms and 21/25 (84%) pts were sporadic cases. In the Group 2, 8/54 (14.8%) pts were inherited forms and 46/54 (85.2%) pts were sporadic cases. The evaluation of somatic mutations showed that RET mutation was present in 82.3% and in 95.3% of pts in Group 1 and in Group 2, respectively. However, the presence of RET mutations, it wasn't a predictor of response to treatment. The metastases site wasn't correlated with the outcome. Otherwise, we observed that in long responders group, 47/54 (87%) pts showed at least one adverse events (AE) during V treatment with a correlation between AE and V response ($P=0.02$). In this group we also observed a statistically significant correlation between the younger age (<45 yrs) at screening and a greater response to V ($P=0.01$) and between the absence of progression disease at screening and response to V ($P<0.0001$). In the long term outcome, considering the last CT scan performed at the data cut-off during the treatment, 29/54 (53.7%) pts showed a persistent response to V after a median follow-up of 41 months. Moreover, we observed that the pts in the Group1 had a more aggressive disease and a more advanced age at screening than pts in Group 2. The estimated median Progression Free-Survival of all patients was 47 months.
Conclusions
In our study, it was observed that the appearance of AE during V treatment, the younger age and the absence of progression disease at screening were predictive factors of long-term response to V in MTC pts. Moreover, RET somatic mutations were very frequent in the metastatic MTC patients but it wasn't a predictor of response to V.

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GP264

Assessment of different ti-rads systems using computer-aided detection technology

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Aims
Different guidelines of Thyroid Imaging, Reporting, and Data System (TI-RADS) have been published to determine whether FNAC is required. Most of the guidelines recommended observation for nodules less than one centimeter and FNAC for nodule larger than two centimeters. In this study, we focus on the management of nodules size between one and two centimeters. We aim to evaluate the different guidelines on the treatment of thyroid nodules with the computer-aided detection (CADe) technology. We also propose a novel guideline for FNAC to reduce unnecessary procedures.
Methods and materials
The thyroid ultrasound pictures database collected prospectively were used. From July 2008 to December 2015, 369 patients with 422 nodules size between one and two centimeters were recruited, which were pathologically proven. (191 benign and 231 malignant) Eight guidelines, i.e., ACR (2017), ATA (2015), AACE (2016), Russ (2016), Seo (2016), BTA (2014), Kwak (2011) and Kwak (2013), were evaluated with sonographic features computerized by a USFDA-cleared CADe software device (AmCAD UT Detection). This CADe device quantifies and visualizes six sonographic features: hypoechogenicity, echogenic foci, heterogeneous texture, irregular margin, anechoic area, and taller-than-wide features, to assist physicians in making their diagnostic decisions with structural reports. The novel guidelines for the recommendation of FNAC were proposed using the quantified sonographic features.
Results
The ultrasound images were further divided into two groups, one is the size less 1.5 cm (1–1.5 cm) and the other is the size larger than 1.5 cm (1.5–2 cm). For group (1–1.5 cm), we presumed that the sensitivity above 90% was acceptable. The BTA (2014) had the sensitivity of 91%, with the specificity 23%. For group (1.5–2 cm), higher sensitivity is demanded. The Russ (2016) had the sensitivity of 96%, with the specificity 19%. The novel guideline was proposed and tested. For group (1–1.5 cm), if either one of US features including hypoechogenicity, calcifications and taller than wide was present, then sensitivity is 91% and specificity is 26%. For group (1.5–2 cm), if either one of US features including hypoechogenicity, calcifications and heterogeneity were present, the sensitivity is 95% and specificity is 21%. The guideline is simple and effective in reducing unnecessary FNAC procedures.
Conclusion
The CADe device is an effective tool to assist physicians in following the TI-RADS guidelines. With the proposed novel guideline, it's shown that 91% of malignant nodules (1–1.5 cm) and 95% of malignant nodules (1.5–2) could be successfully identified and proceed to FNAC for further treatment with better specificity compared to other guidelines.

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Poster Presentations

Adrenal and Neuroendocrine Tumours 1

P1

A novel heterozygous mutation in exon 3 of VHL gene leading to Von Hippel-Lindau disease in a Turkish family

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Background
Von Hippel-Lindau disease (VHL) is an autosomal dominant disease, characterized by haemangioblastomas of the retina and CNS, renal cell carcinomas (RCC) and renal cysts, pheochromocytomas, pancreatic neuroendocrine tumors and cysts, and endolymphatic sac tumors. VHL is associated with a germline mutation of the *VHL* tumor suppressor gene on the short arm of chromosome 3. The type-1 disease is caused by mutations, leading to severe disruption of protein activity, including deletions, missense and nonsense mutations, and other microdeletions/insertions. However, the type-2 disease is generally associated with missense mutations in approximately 96% of the cases. Herein, we report a family with pheochromocytomas in 3 generations and 4 affected members. The family had recurrent pheochromocytomas with retinal angiomas and spinal cord hemangioblastomas. However, none of the family members had RCC. A novel heterozygous class-2 mutation in exon3 of VHL gene (c.572_574delACC/p.His191del) was determined by DNA sequence analysis in all affected family members.
Cases
The first case is a 63 years old female who had been operated for bilateral pheochromocytomas when she was 38. MRI of the spinal cord demonstrated a 19×68 mm hemangioblastoma at the T12-L1 vertebra levels. The second case is a 38 years old female who had been operated for bilateral pheochromocytomas when she was 16. Ophthalmological examination demonstrated an optic nerve and a peripheral angioma. Abdominal and spinal cord MRI demonstrated a 14× 6 mm hemangioblastoma at the T12-L1 vertebra levels and a 45×35 mm broad ligament cyst. The third case is a 42 years old male who had been operated for bilateral pheochromocytomas when he was 22. An asymptomatic recurrent 3.5× 14 mm right adrenal pheochromocytoma was diagnosed by high plasma normetanephrine and serum chromogranin A levels and confirmed by abdominal MRI and GA-68 DOTATATE PET/CT. The fourth case is a 17 years old male, who had been operated for bilateral pheochromocytomas when he was 9. He admitted for hypertension 9 months before. His plasma normetanephrine, and serum chromogranin A level was high. A 2×15 mm mass at the right adrenal area was determined by MRI and GA-68 DOTATATE PET/CT. Ophthalmological examination demonstrated a peripheral retinal angioma.
Conclusions
In this family, we found a novel class-2 heterozygous mutation in the VHL gene in all family members, that has not previously been reported. This mutation leads to the development of recurrent bilateral pheochromocytomas at a very young age, spinal hemangioblastomas, and retinal angiomas, but probably doesn't lead to RCC.

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P2

Long evolution of Connshing syndrome?

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Introduction
Primary hyperaldosteronism is the main endocrine cause of secondary hypertension. Its association with an autonomous cortisol secretion is rarely described in the literature. Here we report the case of a patient having a unilateral adrenal adenoma responsible for both mineralocorticoids and glucocorticoids excess.
Observation
A 54-years-old female diagnosed at the age of 26 years with hypertension. She received up to four antihypertensive treatments including thiazide diuretics without prior investigation. At the age of 52 years, she was admitted for angina with normal coronary arteries where a severe hypokalemia was detected and treated with potassium supplementation in addition to the withdrawal of diuretics. The diagnosis of renal artery stenosis was ruled out and the CT scan revealed a 2 cm unilateral left adrenal adenoma. The patient was hospitalized later in our department for hormonal investigation. At admission she presented clinical symptoms of tetany, U wave in electrocardiogram with low serum potassium (2.5 mmol/l). The hypokalemia required up to 20.8 g per day of oral and IV potassium supplementation in order to maintain normokalemia. Renin dosage was low (3.6 mIU/l) despite the use of ACE inhibitor which cannot be stopped due to the severity of hypokalemia and hypertension. Once spironolactone (50 mg per day) was introduced in addition to captopril (150 mg per day) and amlodipine (10 mg per day), blood pressure and potassium was stabilized and the patient didn't require additional supplementation. 1 mg overnight dexamethasone suppression and 2-day low-dose dexamethasone tests were elevated 20 and 24 ng/ml successively. The patient didn't have catabolic signs. ACTH level was incompletely suppressed (14.9 pg/ml) and the pituitary imaging was normal. Surgical treatment was chosen due to the glucocorticoids excess in addition to prediabetes and bone demineralization.
Discussion
Connshing syndrome is a challenging disease characterized by overproduction of mineralocorticoids and glucocorticoids from adrenal adenoma. Hypercortisolism, although generally mild, is able to increase the risk of developing diabetes mellitus and osteoporosis. Medical treatment could normalize hypertension and hypokalemia but it has no effect on glucocorticoids excess which requires adrenalectomy to be cured. The long evolution of resistant hypertension in our patient without clinical feature of Cushing syndrome may rise the question whether the overproduction of glucocorticoids is concomitant or not to primary hyperaldosteronism.

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P3

Effect of Glucocorticoid receptor antagonist administration in a Cushing's syndrome model rat

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In Cushing's syndrome (CS), hypercortisolemia due to cortisol-producing adrenal adenomas suppresses the hypothalamic-pituitary-adrenal (HPA) axis, so the normal adrenal tissue is atrophied without ACTH stimulation and its function impairs. As a result of surgical resection of cortisol-secreting adenoma, postoperative adrenal insufficiency occurs. Therefore, we thought that administering glucocorticoid receptor antagonist (mifepristone) in order to release suppression of HPA axis caused by hypercortisolemia enables early recovery of adrenal function due to stimulation of ACTH for normal adrenal glands. We thus compared adrenal function in a dexamethasone (DEX)-induced CS model rat ($n=4$) with or without mifepristone (MIF). In this study, MIF-treated rats demonstrated less suppression of plasma ACTH levels (55.13 ± 15.87 pg/ml) and increased adrenal weight (26.3 ± 5.3 mg). In addition, we confirmed that atrophic changes were less on pathological findings in the adrenal glands of MIF-treated rats. These results suggest that preoperative mifepristone administration may improve the residual adrenal function for CS. Our group is currently conducting experiments to investigate the levels of mRNAs for *CYP11B1* in adrenal glands as assessment of the recovery of adrenal function.

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P4

Ectopic adrenocorticotropic hormone (ACTH-ectopic) syndrome and osteoporosis: Rare cases and difficult treatment

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Objective
Ectopic adrenocorticotropic hormone (ACTH-ectopic) syndrome (EAS) is a rare cause of ACTH-dependent endogenous hypercortisolism. The objective of this study was to analyze the clinical, biochemical, and radiological features, management, and treatment outcome of patients with EAS.

Methods
It was a retrospective case-record study of 47 patients with EAS. Clinical, biochemical, and radiological features and response to therapy and survival rate were measured.
Results
The median follow-up was 7 years. (range, 1–13 years.). None of the dynamic tests achieved 100% accuracy. Imaging correctly identified the lesion at first investigation in 80.9% of cases. Bronchial carcinoid tumors were the most common cause of EAS ($n=27$; 57.5%), followed by other neuroendocrine tumors ($n=11$, 23.4%). In 19.1% (9) of patients, the source of EAS was never found. Tumor histology and the presence of distant metastases were the main predictors of overall survival ($P < 0.05$). It is interesting that 40 patients (85,1%) have steroid osteoporosis. 10 patients were treated with calcium and vitamin D, 35 patients by bisphosphonates, 2 patients by denosumab and 3 by teriparatide.
Conclusions
ACTH-ectopic syndrome is a very rare condition with severe complications. There is no significant data and guidelines for osteoporosis treatment in such disease. So we need to improve our to improve the quality of life of such difficult patients.

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P5

Paraganglioma of the urinary bladder wall: 2 cases with 2 different presentations

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Objective
We present two cases of patients with Paraganglioma of the urinary bladder wall, illustrating the differences in diagnosis and management.
Case 1: An 80-year-old female known to have diabetes and hyperthyroidism (treated) presented to her urologist with painless hematuria. Cystoscopy was done and bladder polyps were biopsied. Results of the tumors sampled showed paraganglioma of the urinary bladder wall, although patient was asymptomatic. She presented to the endocrinology clinic to rule out pheochromocytoma. She has long-standing hypertension well-controlled with three medications (CCB, ARB, BB). She denied headaches or syncope especially upon micturition. No flushes or palpitations. Plasma metanephrines, dopamine and normetanephrines were checked and were negative, ruling out secretory pheochromocytomas. She underwent TURBT later for complete resection of the tumor, the pathology of which was consistent again with Paraganglioma of the urinary bladder wall. Patient remains asymptomatic afterwards with good control of her blood pressure despite the diagnosis.
Case 2: A 32-year-old male previously healthy presented to the urology clinic with 9 months history of headaches and palpitations following micturition. He denied any obstructive or irritative lower urinary tract symptoms. Family history was unremarkable for any related conditions. Patient had his vital signs monitored before and after micturition, and were found to be: Blood pressure and heart rate were 130/80 mmHg and 75 bpm before voiding, rising to 170/100 mmHg and 100 bpm upon bladder emptying. His urinalysis showed microscopic hematuria. Pelvic ultrasound revealed a left bladder wall polyp measuring 35 × 23 mm seen also on CT scan. Cystoscopy showed a submucosal pulsating mass 3 cm in size. He had elevated plasma free normetanephrines (1.90 nmol/l; normal < 0.93). His 24 h urine catecholamine and metanephrine levels were within normal limits. Iodine 131-MIBG scintigraphy showed no other sites involved. Patient received an α-adrenergic blocker as a preparation for surgery, along with vigorous hydration. A successful partial cystectomy was done and was uneventful, without blood pressure fluctuations. Immunostaining was strongly positive for synaptophysin and chromogranin, in favor of a paraganglioma. Patient remained asymptomatic upon long term follow-up.
Conclusion
Bladder wall paragangliomas are variable in their nature and their presentation. Tumors range from non-secretory masses in asymptomatic individuals to excessively secreting catecholamine leading to life threatening hypertension and tachycardia.

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P6

Adrenal insufficiency secondary to bilateral adrenal diffuse large B-cell lymphoma: a case report

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Introduction
Primary adrenal lymphoma is extremely rare. It accounts for <1% of extranodal lymphoma. It affects typically old males with bilateral adrenal gland involvement that leads to adrenal hypofunction. Prognosis is very poor due to the lack of optimum chemotherapeutic regimens.
Case Report
A 71 yearr old man with prior history of non insulin dependent diabetes, was admitted to the emergency department with symptoms of progressive weakness, fatigue, anorexia, and 15 kg weight loss in the previous 6 months. These symptoms were associated with hypotension, nausea, vomiting and unsteady gait. On physical examination the patient looked caquectic, chronically ill but alert. He had orthostatic hypotension. Skin hyperpigmentation was absent. Laboratory assays showed hyponatraemia (127 mEq/l) and a sligthly high potassium (5.6 mEq/l), normoglycemia and anemia. The patient initially responded to intravenous hydrocortisone in large doses with remission of symptoms. But orthostatic hypotension and ionogram alterations persisted so fludrocortisone was added with good results. Screening for malignancy was made with a hole body computed tomography scan (CT) that showed bilateral adrenal masses with more than 10 HU. Further assesment by adrenal MNR scan showed hypointense nodular images in T1 and T2 in both adrenal glands. With a nodule of 4 cm on the right gland and another of 4.5 cm on the left one. They appeared hyperintense in Out Phase, and had a post-gadolinium heterogeneous reinforcement. The ACTH test showed a complete failure of response (Basal Cortisol 0.3 ug/dl post-ACTH Cortisol 30 min: 0.4 ug/dl. Urine metanephrines and catecholamines were normal excluding phaeochromocytoma. Urgent needle biopsy of the left adrenal gland was performed wich revealed diffuse large B-cell lymphoma. Bone marrow biopsy was negative for lymphomatous involvement. After the diagnosis was made the patient deteriorated rapidly and passed away as a result of his condition.
Conclusion
Primary adrenal lymphoma is extremely rare. When it occurs, diffuse large B-cell lymphoma is the most common subtype involved. This case highlights the importance of considering diffuse large B-cell lymphoma (PAL) as an unusual cause of adrenal insufficiency. Specially in older patients who present with adrenal insufficiency associated with bilateral adrenal masses.

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P7

A rare association of Adrenocortical carcinoma with haematological and breast malignancy in a young female

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A 20-year-old female admitted under haematology team for acute myeloid leukaemia. During her admission, she had a whole body CT scan and was found to have a left breast lesion (proven on biopsy to have invasive ductal carcinoma) and a right adrenal mass measuring 6.5 × 7.5 cm with radiological features suggestive of an adrenocortical cancer. Biochemical workup showed raised adrenal androgens: DHA Sulphate 14.9 umol/l (4.0–11.0), 17-OH Progesterone 7.6 nmol/l (0.6–6.0), androsteinedione 59.4 nmol/l (0.9–7.5), testosterone 39.1 nmol/l (<1.8), plasma metanephrines and 24hour urinary cortisol were within the normal range. This patient had three synchronous malignancies diagnosed around same time at 20 years of age. Further detailed family history revealed that the patient had strong family history of deaths in younger age from malignancies including younger brother died at the age of 9 from sarcoma, mother at the age of 35 with breast cancer and the maternal aunt aged 40 from an unknown cancer. Doing Literature search, we found that this strong family history of malignancies could be suggestive of Li-Fraumeni Syndrome (LFS) which is an inherited condition with a predisposition to the development of malignancies secondary to a mutation in the tumour suppressor gene TP53. This mutation make individuals susceptible to develop multiple malignancies like bone sarcoma, breast cancer, brain tumour, adrenocortical carcinoma and acute leukaemia. Li-Fraumeni Syndrome (LFS) is a rare condition in which affected Individuals have a lifetime cancer risk that approaches 100% by age 70 years. In her case, genetic testing confirmed diagnosis of Li-Freemen Syndrome (LFS).Patient had chemotherapy for her breast cancer alongside her treatment for AML. She underwent Right sided adrenalectomy and histology confirmed adrenocortical carcinoma with high mitotic index.Few days after Surgery patient was re-admitted with severe neutropenic sepsis and multi organ failure and despite critical care interventions including organ support, unfortunately she died.

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P8

Metabolic and cardiovascular profile of 143 adrenal incidentalomas

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Objective
To study the differences in the metabolic profile of patients with non-functioning adrenal adenomas (NFA) and autonomous cortisol secretion (ACS).
Methods
143 patients diagnosed of adrenal incidentaloma (AI) between 2010 and 2018 were retrospectively analyzed. AI was defined as an adrenal mass $\geq$1 cm, accidentally discovered by radiologic examination. ACS was confirmed by serum cortisol post-dexamethasone suppression test (Nugent) $\geq$3 µg/dl and no typical features of Cushing's Syndrome (CS). NFA were considered when the whole hormonal evaluation was normal (Nugent test $<$3 µg/dl, aldosterone/renin ratio (when appropriate) and urinary metanephrines). The statistical analysis was performed with STATA 15.0 and ACS and NFA patients were included (n=132).
Results
The mean age was 63.2(10.74) years and 55.9% were women. 78.3% patients had NFA, 11.9% ACS, 1.4% CS and 8.4% other diagnoses. In the univariate analysis, we found no statistically significant differences between ACS and NFA in the prevalence of hypertension (70.6 vs 47.8%, P=0.08), diabetes (35.3 vs 26.1%, P=0.4), dyslipidemia (47.1 vs 48.7%, P=0.9), cardiovascular (17.7 vs 8.8%, P=0.3) and cerebrovascular disease (11.8 vs 3.5%, P=0.1). The prevalence of obesity was significantly lower in ACS than in NFA (17.7 vs 37.7%, P=0.01), however no statistically significant differences were found in the BMI (28.0 vs 30.0 kg/m^2, P=0.4). Neither significant differences were found in the mean of systolic or diastolic blood pressure (128.4 vs 131.5 mmHg (P=0.48) and 76.6 vs 78.8 mmHg, (P=0.47), respectively); fasting plasma glucose (FPG) (109.4 vs 107.8 mg/dl, P=0.83), total cholesterol (188.5 vs 188.2 mg/dl, P=0.98); LDL (108.5 vs 115.1 mg/dl, P=0.52), HDL (52.5 vs 53.1 mg/dl, P=0.93) and triglycerides (133.2 vs 125.9 mg/dl, P=0.68). No significant correlation was found between Nugent test and cardiovascular risk factors ($p>0.05$ in the Pearson correlation). In the linear regression model, Nugent test was a good predictor of the maximum adenoma diameter (R-squared=0.13, P=0.01) and urinary free cortisol (R-squared=0.23, P=0.00) but it was inadequate to predict ACTH, basal cortisol, DHEAS, FPG, cholesterol, LDL, HDL or triglycerides ($P>0.05$). There was no progression to CS in any case and only 3 NFA developed ACS during the study period (mean=27.7 months). In both groups, the metabolic profile remained stable throughout the follow-up.
Conclusions
Our data suggest a higher prevalence of hypertension, diabetes mellitus, cardiovascular and cerebrovascular disease in patients with ACS compared to NFA. However, there were no statistically significantly differences probably due to small sample size. We did not find the Nugent test to be a reliable predictor of the metabolic profile in AI patients.

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P9

HNRNP Q suppresses polyglutamine huntingtin aggregationby post-transcriptional regulation of Vaccinia-related kinase 2

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The misfolded proteins with abnormal polyglutamine (polyQ) expansion cause neurodegenerative disorders including Huntington's disease (HD). Recently, Vaccinia-related kinase 2 (VRK2) were found to accumulate polyQ aggregates by controlling TCP-1 ring complex (TRiC)/Chaperonin-containing TCP-1 (CCT), which has an essential role in preventing against the aggregation and cytotoxicity of polyQ proteins. Interestingly, VRK2 expression is known to be much higher in actively proliferating cells, but is maintained at a low level in the brain via unknown mechanism. Here we found that neuronal cell-specific basal level of VRK2 is regulated by post-transcriptional regulation rather than the regulation in transcription itself. Moreover, heterogeneous nuclear ribonucleoprotein Q (hnRNP Q) specifically binds to 3'UTR of *VRK2* mRNA in neuronal cells and reduces its mRNA stability. In relation to that we found a dramatic decrease in CCT4 protein level due to a reduction in hnRNP Q, followed by an increase in polyQ aggregation. Taken together, these studies could provide new insights into how neuronal hnRNP Q regulates *VRK2* mRNA stability and contributes to HD prevention, and open new prognostic marker of HD.

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P10

Study of body composition and phase angle in relation to nutritional parameters in patients with neuroendocrine tumors

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Introduction
Neuroendocrine tumors are an heterogeneous group of neoplasms with increasing incidence and high survival. The therapies, could be have a negative impact on nutrition and pronogsis of these patients.
Objetives
To analyze analytical and anthropometric parameters in relation to disease stage and survival.
Material and methods
An observational, retrospective and cross-sectional study that includes patients with neuroendocrine tumors. Data are collected at first nutrition appointment in Virgen de la Victoria Clinical Hospital, since 2015 to 2018.
Results
We analyzed data from 42 patients of 59.9$\pm$17.6 years of age, 47.6% males; with diagnosis of intestinal neuroendocrine tumor 35.8%, pancreatic 33%, carcinoid 11.9%, gastrinoma 14.3%, other locations 4.8%; Ki67 proliferation index medium 8.9$\pm$11.7, stages 1 and 2 95% and non-functioning (73.2%). 36.6% of the patients underwere subjected with pancreatic resection, 29.3% had bowel resection, 2.4% had another type and 31.7% had not surgery, and 28.6% had SSA; SSA + everolimus, QT or imatinib 16.8% and only QT 11.9%. Without treatment 33.3%. No evidence of disease was found in 19%, localized 19% and disseminated 61.9% with a follow-up time of 4.48$\pm$4 years. They presented diabetes mellitus previously 23.8%, 14.3% with oral antidiabetics; after diagnosis, increase a 14.3%, treated with ADOs 23.8%, insulin 9.5% and both 4.8%. 43% present steatorrhea, treatment with pancreatin 52.4%, adequate intake 62%; enteral supplements 35.8%, supplements of vitamin D 33.3% and multivitamins 33.3%. Anthropometric parameters: weight 67.4$\pm$12.2 kg (decrease of 4.8 Kg compared to usual), BMI 25.1$\pm$4.2, MM 48$\pm$11 Kg; MG 17.9$\pm$7.8 Kg (27$\pm$8.8%); AT 35.8$\pm$7.2 Kg; IMP 505$\pm$109, MB 1373$\pm$212 Kcal, AF 5.7$\pm$1.2. And analytical: Glucose 102.5$\pm$25.8 mg/dl, HbA1c 6.09$\pm$1.1, CT 174$\pm$51 mg/dl, TG 115$\pm$54 mg/dl, Albumin 3.8$\pm$0.5 mg/dl, prealbumin 26,2$\pm$7.5 mg/dl, vitamin D 26.6$\pm$12.2 mg/dl, magnesium 2.2$\pm$0.2 mg/dl. In the follow-up there were 4 deaths (9.5%).
Conclusions
Our patients have an acceptable nutritional status, some of them with supplementation. It would be advisable to perform an early screening for an adequate approach.

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P11

A case series of two patients with intrapericardial paragangliomas

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Two patients have presented to a regional Australian Hospital with intrapericardial paragangliomas in the last decade. In 2011, a 28-year-old Indigenous male presented with a hypertensive crisis. He had a two-year history of symptoms during physical exertion, including abdominal pain, nausea, and vomiting. He had also experienced paroxysmal light-headedness and sweats, and had been previously diagnosed with hypertension. Urinary and serum catecholamine testing revealed markedly elevated noradrenaline. Subsequent imaging showed a synchronous functioning paraganglioma in the right atrium and retrocaval region. He had a surgical resection of both lesions, with normalisation of catecholamines post-operatively. The SDHB gene mutation was identified, however the ongoing follow-up of this patient has since been limited. The second case, a 38-year-old female, presented in 2018 with a 12-month history of paroxysmal severe headaches, flushing, tachycardia and eight kilograms of weight loss. Workup revealed significantly elevated urine and plasma fractionated metanephrines, including noradrenaline, dopamine, vanillylmandelic acid, normetanephrine, and 3 methoxytyramine. Gallium-68 DOTATE PET revealed an intensely DOTATATE avid left atrial/atrial-septum lesion consistent with paraganglioma. Further imaging included a cardiac MRI and echocardiogram. She underwent pre-operative assessment with a coronary

angiogram, which showed 3 coronary artery tributaries feeding the tumour. She was pre-operatively treated with phenoxybenzamine, followed by metoprolol. She had a surgical resection which revealed a highly vascular 70 mm tumour in the inter-atrial groove. Histopathology was consistent with paraganglioma and her genetic studies showed SDHC mutation.

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P12

Combined autophagy and mTOR inhibition reduces cells proliferation and induces apoptosis in a lung carcinoid in-vitro model

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Introduction
Treatment options for patients with metastatic lung carcinoids (LC) are limited. Everolimus (RAD001), an mTOR inhibitor (mTORi) which suppresses tumor cells growth & proliferation, appears to be efficient in these patients; however, it promotes autophagy, thereby paradoxically supporting tumor cell survival and development of drug-resistance. We have previously demonstrated in a BON1 pancreatic NEN model that adding chloroquine (CQ, an autophagy inhibitor) to mTORi inhibited cell proliferation and induced apoptosis compared to mTORi alone.
Aim(s)
To investigate the effect of CQ $\pm$ mTORi on LC cell viability, proliferation and apoptosis.
Materials and methods
The LC cell line NCI-H727 was treated with CQ, RAD001 and Torin1, alone or in combination. Cell viability and proliferation were examined by XTT and Ki67 staining. Flow cytometry and Western blot were used to assess drug effects on cell cycle, apoptosis, PI3K/Akt/mTOR and autophagy pathways. The effect of differential timing of drug administration was examined by using a cytotoxicity kit.
Results
CQ alone reduced LC cell viability by $\sim$ 30%; the addition of CQ to RAD001 or Torin1 significantly reduced cell viability by 60% and 98%, respectively. Torin1 or RAD001 combined with CQ induced a higher degree of apoptosis and accumulation of LC3-II (a marker of autophagy). Our results imply that the inhibition of cell proliferation may result from CQ effects on cytosol and lysosomes nutrient content causing an indirect inhibition of mTOR.
Conclusion
In the present LC model, CQ alone and mainly in addition to a mTORi, promotes apoptosis and suppresses cell proliferation, potentiating the effect of mTORi. Further experiments are needed to understand the role of CQ in the treatment arsenal of patients with metastatic LC.

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P13

Pheochromocytoma – 3 sides of the same story

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Background
Pheochromocytomas are rare tumors, with prevalence less than 0.2% of hypertensive patients, in general population being unknown. With increasing access to imaging and hormonal workup, more pheochromocytomas are diagnosed. This may have changed the occurrence of the classic presentation with hypertension and the classic triad.
Methods
We present 3 cases of pheochromocytoma diagnosed in our departments over the last 2 years, with 3 different phenotypes: the classic form, a resistant form of secondary hypertension and a normotensive patient.
Case reports
Case 1- classic triad: A 62 years old man was referred with classic symptoms: headache, palpitations, diaphoresis, severe hypertension, with paroxysmal rises. Hormonal workup confirmed the diagnosis: elevated metanephrines and normetanephrines level, dyslipidemia, hyperglycemia. The imagistic evaluation revealed right adrenal tumor. The histopathological and immunohistochemical exam suggested a malignant pheochromocytoma. After suprarenalectomy, we obtain a proper control of the arterial tension, with no paroxysm, normal hormonal profile. *Case 2- resistant secondary hypertension:* The second case is a 30 years old man, that complained of resistant hypertension, without a specific pattern and no other signs. He had a significant family history of cardio-vascular diseases, both his parents died in their 30's. Hormonal profile shown pheochromocytoma: elevated normetaphrines level with normal metanephrines, normal aldosteron/renin ratio, normal Dexamethasone suppression of Cortisol; normal calcemia and PTH level. Imagistic evaluation identified right adrenal tumor. The patient was treated with doxazosin and perindopril/indapamid/amlodipin association. Despite high normal calcitonin level, he refused all other investigation, therefore no data about a genetic disorder is available. *Case 3- normotensive:* A 57 years old woman, with history of thyroidectomy for benign nodular goiter, was evaluated for an inferior deep cervical mass; she presented mild tachycardia, anxiety and insomnia. Hormonal workup: normal metanephrines level and elevated plasma and urinary normetanephrines level, high cromogranine A and serotonine level; normal Calcitonin and PTH level, without any other sign of a genetic disorder. CT/MRI scans describes 3 masses: an inferior deep cervical tumor, a paravertebral thoracic lesion and left adrenal mass. After treatment with doxazosin well tolerated, the surgical cure with histopathological and immunohistochemical exam revealed a benign neck schwannoma and adrenal pheochromocytoma; the patient is still in investigation for genetic disorders, given association of schwannoma with pheochromocytoma.
Conclusion
Though hypertension is common, hypo to normotensive presentation is possible. The spectrum of the presentation of pheochromocytoma continues to expand. In some cases, genetic disorders should be considered.

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P14

Analysis of the 22-years experience of surgical treatment of adrenal tumor in single specialized endocrinological center

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Objectives
To analyze the data of the 22-year-old clinical experience surgical treatment of the adrenal tumor patients in the single specialized endocrinological center.
Materials and methods
There were analyzed the diseases stories of the perioperative period in 1256 patients with adrenal gland tumors who underwent adrenalectomy for the period 1995–2017 in specialized endocrinological center. Average data are given in the format $M \pm \sigma$.
Results
Having analyzed the surgical access, we have been noted that 255 (20.3%) out of total 1256 were performed with open, laparotomic or lumbol-aparotomic access (LTA) operations and 1001 (79.7%) operations were performed using the laparoscopic access (LSA). Among of the total 256 pheochromocytoma patients 81 (31.8%) surgical interventions were performed by using LTA and rest 174 (68.2%) of the operations were performed using the LSA. In terms of gender, men were 334 (26.6%), women – 922 (73.4%), and among patients with the adrenal gland pheochromocytoma – 80 (31.4%) men, 175 (68.6%) women. The average age of the adult patients operated on adrenal glands were 47.7 ± 14.6 years. The average blood loss with LTA was 357.5 ± 192.7 ml, with LSA - 42.2 ± 31.6 ml (significant difference ($P = 0.012$) according to the Wilcoxon test). Total intravenous anesthesia was applied in 93.3% patients with LTA, and in 73.0% of the LSA patients. The inhalative sevoflurane anesthesia was used in 6.7% of LTA patients and in 27.0% of LSA cases (significant difference ($P = 0.024$) according to the Pearson's chi-square test). The intervention duration was 130.3 ± 46.9 min. and 63.1 ± 19.2 min. with LTA and LSA respectively (significant difference, $P = 0.013$). The duration of inpatient stay in the LSA patients was 7.3 ± 4.9 days, in the LTA patients was 12.3 ± 6.9 days (significant difference, $P = 0.028$). The using of narcotic analgesics in the LTA patients were on average 4.2 ± 2.7 days, in the LSA patients was 1.2 ± 0.9 days (significant difference, $P = 0.012$). The average dose of morphine was 94.5 ± 41.3 mg for LTA interventions, and 24.5 ± 11.3 mg for LSA (significant difference, $P = 0.021$).
Conclusion
Thus, the introduction of laparoscopic methods of surgical intervention for adrenal tumors contributes to a more rapid recovery of patients, a reduction in the hospital stay, accompanied by less blood loss, less expressive pain syndrome.

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P15

Immunohistochemical characteristics of adrenal tumors in patients with primary aldosteronism

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Introduction
CYP11B2 is a key enzyme of primary aldosteronism, and several factors are involved in the regulation of CYP11B2 expression and the overproduction of aldosterone. Somatic mutations in aldosterone-driver genes are strongly associated with CYP11B2 expression and have been only detected in the CYP11B2-positive tumor area, indicating that aldosterone producing adenoma (APA) intratumoral heterogeneity corresponds to non-uniform CYP11B2 expression in neoplastic cells. In addition, CYP11B2 can contribute to the clinical diagnosis of primary aldosteronism. CYP11B2 has the potential to synthesize hybrid steroids, which is a unique and characteristic behavior of APA that is distinctive from bilateral hyperaldosteronism (BHA). However, the pathophysiology of primary aldosteronism in both APA and non-neoplastic subtypes remains controversial.
Objective
To assess the functional heterogeneity of adrenal tumors in primary aldosteronism
Material and methods
Retrospective evaluation adrenal tumors from patients with primary aldosteronism ($n=20$). According to CT unilateral macrohyperplasia was detected in 19 patients (95% of total), all of them were confirmed to have unilateral hyperproduction of aldosterone according to AVS. Selected tumors were stained with anty-CYP11B2 antibody.We evaluated the CYP11B2 expression in the adenoma and in the adjacent adrenal cortex.
Results
Immunohistochemistry studies of the resected adrenals from 20 patients with PA operated due to unilateral production of aldosterone using CYP11B2 staining showed that 10 of those with an adenoma on CT scanning showed CYP11B2 staining in the adenoma. Furthermore, 5 cases of an unilateral adenoma, showed CYP11B2 staining in the adjacent adrenal cortex and an absence of staining for CYP11B2 in the adenoma. 5 cases showed CYP11B2 expression is heterogeneously immunolocalized throughout the tumor area.
Conclusions
Thus, the functional heterogeneity of adrenal tumors in primary aldosteronism has been proven. It is necessary to compare the data of immunohistochemical studies on the expression of CYP11B2 with the indicators of the level of 18-hydroxycortisol, 18-oxocortisol.

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P16

Cortex protecting surgery in MEN 2A

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Cortex protecting surgery for bilateral pheochromocytoma protects the patient from adrenal insufficiency. Risk of relapse is low. 35 years old woman had paroxysmal seizures and hypertension crises for the last year which became more frequent in the last 10 days. She had thyroidectomy and under the use of levothyroxine the patient. Because of a nodule on ultrasonography and paternal history of MEN 2A which led to a check of calcitonin level that resulted 8 times higher than the upper limit, at the age of 23 she had had a thyroid surgery. Patology: 0.4 and 0.9 mm medullary thyroid carcinoma. Her father had a surgery for MEN 2A years ago. Abdominal MRI: Right adrenal gland had a mass of pheochromocytoma at the size of 42×41 mm, and the left one had a mass at the size of 331×32 mm. Urine metanephrin: 3093 (N: $<$298 ug/24 hours), normetanephrin: 6837 (N: $<$354 ug/ml), PTH:244 (N:15–65 pg/ml), Neck ultrasonography showed no enlarged parathyroid gland. RET protooncogen: Exon 11 and Codon 634 mutation. Surgery was scheduled for bilateral cortex protecting adrenalectomy and 3.5 parathyroidectomy. Pathology report: Parathyroid hyperplasia and pheochromocytoma. Postopetative follow up revealed normal calcium levels, cortisol: 11 mcg/dl, no hypertension. Because of the normal serum cortisol levels without any replacement, we recommend cortex protecting adrenalectomy for patients with bilateral pheochromocytoma on the condition of an experienced surgeon.

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P17

Unilateral non-haemorrhagic adrenal infarction (NHAI) as a cause of abdominal pain during pregnancy

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Adrenal infarction is usually associated with bilateral adrenal hemorrhage in the setting of antiphospholipid syndrome or hemodynamic variation. A few cases of unilateral non-hemorrhagic adrenal infarction (NHAI) have been described in the literature. Here, we report a case of unilateral non-haemorrhagic adrenal infarction occurring during pregnancy and a literature review of this clinical entity. A 30-year-old woman presented at 32 weeks of gestation with sudden-onset right abdominal pain and contractions. Unilateral adrenal infarction was diagnosed following computed tomography (CT). It showed an enlarged right adrenal, without uptake after injection. Contractions persisted despite medical care and she delivered a healthy girl, weighting around 2500 g. Abdominal pain decreased right after delivery. No treatment was administered as the patient was healthy. At 3 month, CT scan imaging showed an atrophy of the right adrenal and a normal left adrenal. The patient's adrenal hormonal function was normal. Accurate diagnosis of NHAI may be difficult as its clinical presentation is not specific. It can only be performed with adrenal imaging. Magnetic resonance imaging (MRI) shows diffuse enlargement of one or both adrenals as well as increased signal intensity on T2-weighted images. Anticoagulation therapy may be discussed. Patients should be evaluated between 3 and 6 months after the event to assess adrenal's size and function. In summary, NHAI during pregnancy is probably underdiagnosed and obstetricians should be aware of this diagnosis.

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P18

Evaluating the applicability of urinary miR-483-5p as a non-invasive marker in adrenocortical cancer patients

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Introduction
Minimally invasive blood-borne circulating microRNAs might be used for the preoperative differentiation of adrenocortical carcinoma (ACC) and adrenocortical adenoma (ACA). Circulating *hsa-miR-483-5p* is so far the best microRNA biomarker of ACC. To the best of our knowledge, there have been no studies concerning the potential applicability of urinary *has-miR-483-5p* as a non-invasive biomarker of ACC and its correlation with plasma *hsa-miR-483-5p.*
Aim
Our aim was to investigate the expression of urinary *hsa-miR-483-5p* and its correlation with its plasma counterpart.
Methods
Plasma and urinary samples from 23 ACC and 23 ACA patients were analysed using real-time RT-qPCR. To evaluate the diagnostic applicability of *hsa-miR-483-5p*, ROC-analysis was performed.
Results
Significant overexpression of *hsa-miR-483-5p* was observed in carcinoma patients' plasma samples compared to adenoma patients' ($P<0.0001$, sensitivity: 87%, specificity: 78.3%). In urinary samples, however, no significant difference could be detected between ACC and ACA patients.
Conclusions
Plasma *hsa-miR-483-5p* has been confirmed as significantly overexpressed in adrenocortical cancer patients and thus might be exploited as a minimally

invasive preoperative marker of malignancy. The applicability of urinary *hsa-miR-483-5p* for the diagnosis of adrenocortical malignancy could not be confirmed.

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P19

Allgrove syndrome (Triple A syndrome): A case report

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Introduction
Allgrove syndrome is a rare autosomal recessive disorder characterized by a Lacrima, achalasia, adrenal Insufficiency and Neurologic disorders. Mutation in (AAAS) gene on chromosome 12q13, has been implicated.
Case report
Eighteen-year-old male referred to the Endocrinology clinic for evaluation of suspected adrenal insufficiency. The patient reported generalized weakness, fatigue, anorexia recurrent fainting attacks, and progressive hyperpigmentation of the skin for 6 months. Regarding his past history. His mother noticed absence of tears since early childhood for which he was diagnosed as alacrimia and given tear substitutes. At the age of 12 he presented with progressive dysphagia more for liquids than solids. Clinical findings included; Weight: 38.5 kg, height: 163 cm, BMI: 14.5 kg/M^2. Pluse: 80/min, blood pressure was 80/60 with no postural variation. Dark pigmentation generalized more in back, side of chest and face. Neurological examination revealed wasting of thenar and hypothenar muscles, bilateral partial claw hand, he has generalized wasting but normal tone, power and reflexes, with preserved superficial and deep sensation, nasal twang of voice. pubic hair Tanner stage 4, peins (8 cm), and testis (5×3×2 cm). Baseline investigations revealed normal complete blood counts, serum creatinine and normal electrolytes (serum Na,137 mmol/L; serum K, 4.14 mmol/L). TSH: 3.7 μIU/ml (normal: 0. 33–5.5), free T4; 1.2 ng/dl (0.8–1.9), Free T3: 2.3 pg/ml. Basal serum cortisol (8:00 AM) was very low (0.5 μg/dL) normal range (10–20 μg/dL). Plasma ACTH levels were markedly elevated (1,250 pg/mL; normal range, 9 to 52 pg/mL). CT abdomen and pelvis were normal with no definite adrenal mass. Diagnosis of primary adrenal insufficiency was established. Barium swallow showed dilated thoracic oesophagus above the lower oesophageal. sphincter and bird beak appearance. Esophageal manometry showed; lower esophageal resting pressure was 27 mmHg,incomplete relaxation with swallows of 56% (N: 85–100%). The average amplitude of the distal esophageal body was low of 16 mmHg (N: 40–120 mmHg) confirming the diagnosis of achalasia cardia. Nerve conduction tests revealed radiculoneuropathy. On the basis of primary adrenal insufficiency (with normal mineralocorticoid balance), alacrimia, achalasia cardia, and peripheral neuropathy a diagnosis of Allgrove syndrome was established.
Conclusion
Allgrove syndrome is a multisystem disease and the cardinal manifestations may appear at any time from infancy to adulthood. Patients are likely prone to complications like Addisonian crisis, recurrent aspiration and failure to thrive.

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P20

A case series of metastatic pheochromocytomas and paragangliomas: patients characteristics, therapeutic approach and follow-up

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Background
Metastatic pheochromocytomas (PCs) and paragangliomas (PGLs) are rare neuroendocrine neoplasms with a $<1{:}10^6$ incidence, defined by the presence of metastatic disease besides recurrent or locally invasive disease.
Aim
Retrospective analysis of clinical, biochemical/hormonal, imaging, genetic and histopathological features of patients with malignant PCs/PGLs diagnosed over 15 years.
Results
Thirteen patients (aged 49.5 ± 15.5 years old) with either metastatic PCs ($n=6$) or PGLs ($n=6$) were collected; one had both PCs and PGLs. The mean follow-up period was 6.38 years (range: 1–14 years). Almost half of the patients presented with synchronous metastases mostly in lymph nodes (cervical and abdominal); the remaining developed metastases after a mean follow-up of 4 years (range 2–10 years). Seventy per cent of the patients had functional neoplasms; 6 (46%) had concomitant normetanephrine and metanephrine secretion, one only dopamine and 2 only normetanephrine secretion. Out of 6 patients tested genetically, one had SDHB mutation and another SDHD. The mean Ki-67% proliferative index of the primary and metastatic sites were 11 ± 3.8% and 44 ± 7% respectively. Eight patients (62%) underwent surgical resection of the primary tumour or multiple surgical interventions. Two developed stable disease (SD) without further treatment whereas the remaining progressed (PD) and received additional therapeutic modalities. Four patients had treatment with radiopeptides (PRRTs) (2 with 17Lu-DOTATE and 2 with 131I-MIBG) either as monotherapy or after surgery; two exhibited SD. Four patients received chemotherapy, either as monotherapy or after surgery but all developed PD. Two patients had localised radiotherapy, the first as monotherapy and the second after chemotherapy and they both progressed. Two patients (15%), deceased during the follow-up period: the first one year after the detection of metastases and the second 8 months after initial diagnosis.
Conclusions
Metastatic PGLs and PCs are rare tumours that can achieve prolonged survival. In our small series, it seems that PRRTs could be a promising treatment for advanced and/or non operable PCs/PGLs. However, allthese patients require multiple therapeutic modalities either local or systemic best dealt in a multidisciplinary setting.

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P21

Retroperitoneal paraganglioma: clinical case

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Background
Paraganglioma is a rare neuroendocrine tumor from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis. About 15–20% of chromaffin-cell tumors are paragangliomas. In most cases paragangliomas produce catecholamines in large concentrations and the lack of treatment can lead to cardiovascular and cerebral catastrophes. That is why early diagnosis of this tumor is so important and, consequently, knowledge of its diagnostic criterion, too.
Clinical case
A 59-year-old man was presented to a cardiologist for rapid increasing of blood pressure (BP) (>220/120 mmHg), which was accompanied by severe headache and epigastric pain in September 2017. From anamnesis it is known: the disease began suddenly and had paroxysmal flow. The first attack lasted for about 3 minutes and finished itself. Then such attacks occured with different frequency (from 1 per month to several times per week) and were connected with physical activity. The cardiologist suspected diagnosis of pheochromocytoma. The result of urinary fractionated metanephrines measurement showed its levels higher than normal rage but did not confirm suspected diagnosis reliably. Then patient referred to a surgeon in May 2018. On the basis of patient's complaints on epigastric pain during the attacks and the neck inflection of the gallbladder revealed by ultrasonography, it was decided to carry out cholecystectomy. A week after the operation the patient referred to the endocrinologist because of the continuing attacks. The diagnosis of pheochromocytoma was suspected again, the urinary fractionated metanephrines measurement was repeated, which revealed elevated normetanephrine level of 1008 μg/day (normal rage:<700 μg/day). A CT of retroperitoneal space revealed a spherical mass sized about 17×16×18 mm in paraaortal region under left renal vein. The retroperitoneal tumor was removed laparoscopically in August 2018. Pathological examination of the removed mass showed a paraganglioma with uncertain potential of biological behaviour. BP was normal and remained within range without the need of any antihypertensive medication until discharge from hospital. The patient is asymptomatic and normotensive during his follow-up visits.
Conclusion
This clinical case shows how a tumor with bright and specific symptoms can be revealed only in several years and after referring to several specialists. Also, this case highlights the importance of knowledge of diagnostic process of different diseases. In the present case the paraganglioma would have been revealed earlier if only the CT of retroperitoneal space had been done just after getting the results of free metanephrines, which were higher than normal.

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P22

The frequency of confirmed primary hyperaldosteronism in patients with high aldosteron renin ratio

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Introduction
The aldosterone-to-renin ratio (A/R) is the most frequently used screening test for primary hyperaldosteronism (PH) and a confirmation test is recommended when it is high. We aimed to determine the frequency of PH in patients with high A/R and investigated possible clinical features that might help to prevent unnecesary confirmation tests.
Method
Patients who underwent saline infusion test because of high A/R (>3.8) were retrospectively reviewed. PH was diagnosed in patients with plasma aldosteron >10 ng/dl after 4 hours of saline infusion. Patients with postinfusion aldosteron level between 5–10 ng/dl and with <5 ng/dl were defined as indeterminate and not to have PH, respectively. Patients with and without PH were compared.
Results
There were 38 patients (27 female and 11 male) with a mean age of 55.18 ± 10.13. Mean serum potassium (K) was 4.01 ± 0.69 mmol/l and aldosteron was 30.24 ± 14.61 ng/dl. Median renin and A/R were 2.015 ng/l and 12.913, respectively. After saline infusion test, the diagnosis of PH was confirmed in 17 (43.6%) and excluded in 11 (28.2%) patients. Indeterminate results were obtained in 10 (25.6%) patients. There were 9 female and 8 male patients with PH, while all 11 patients without PH were female ($P=0.007$). 16 (94.1%) patients with PH and 7 (63.6%) without PH were hypertensive ($P=0.040$). The age, presentation, adrenal imaging findings, sodium and renin were similar in patients with and without PH. Mean serum K were 3.57 ± 0.65 mmol/l and 4.31 ± 051 mmol/l in patients with and without PH, respectively ($P=0.003$). Mean aldosteron and median A/R were higher in patients with PH, however the differences were not statistically significant [For aldosteron; 36.67 ± 15.38 ng/dl vs 25.14 ± 13.02 ng/dl, $P=0.050$, for A/R 16.27 (4.90–264.50) and 7.36 (3.97–53.84), $P=0.051$]. Median aldosteron after saline infusion was 19.40 ng/dl (10.26–64.35) in patients with PH and 3.70 ng/dl (1.50–4.83) in patients without PH ($P<0.001$).
Conclusion
Confirmation of PH in less than half of patients with high A/R is suggestive for high false positivity of this screening method. It may be rational to repeat measurements before confirmation tests in women, patients without HT and without hypokalemia. However, male sex, presence of HT and hypokalemia seem to be stronger clinical findings that requires confirmation tests in patients with high A/R.

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P23

Evaluation of angiotensin II in primary aldosteronism and other forms of hypertension – a preliminary study

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Background
The renin-angiotensin-aldosterone system (RAS) constitutes a key hormonal system in the physiological and pathological regulation of blood pressure. In effort to understand complex and multifunctional aspects of this system, current biochemical approaches target to characterize and define its various components with angiotensin II being in the mainstream.
Objective
The aim of this study was to evaluate concentrations of angiotensin II in hypertensive patients undergoing laboratory screening for primary aldosteronism.
Methodology
Plasma aldosterone, angiotensin II and direct renin concentrations from 49 patients (including 11 with primary hyperaldosteronism, 22%) were analyzed. Patients were taking most of their antihypertensive drugs, excluding mineralocorticoid receptor blockers. Angiotensin II was measured by two distinct, thus available in our conditions, methods: immunoassay (ELISA without previous chromatographic separation) and LC-MS/MS.
Results
Median ELISA Angiotensin II concentrations in primary aldosteronism patients were lower than in the control group: 689 pg/ml (IQR: 444.49–897.3) vs 873.18 pg/ml (IQR: 689.99–1267.63). However, the difference was not statistically significant. Surprisingly, if measured by LC-MS/MS, Angiotensin II showed the opposite trend. Median LC-MS/MS Ang II was 475.34 pg/ml (IQR: 253.77–520.79) in primary aldosteronism patients compared to median 123.66 pg/ml (IQR: 72.15–251.87) in the control group ($P=0.0248$). If calculated as ratios with aldosterone, only ELISA angiotensin II concentrations showed statistical significance. Areas under the receiver operation characteristic curve (AUROC) for aldosterone-to-angiotensin II ratio (AA2R) and aldosterone-to-renin ratio (ARR) were 0.79 and 0.92 accordingly, despite ongoing antihypertensive therapy.
Conclusions
The accurate assessment of angiotensin peptides is the next step to ascertain the status of the RAS, particularly in pathological conditions or under the influence of interfering therapeutic agents. However, such evaluation is hampered by many factors. They contribute to the marked variability in angiotensin values evident in the literature and raise concerns on the identity of angiotensin II detected in the circulation. Therefore, the question if the extent to that altered peptide content truly reflects or contributes to a particular phenotype, still requires more studies and, most of all, ubiquitous technical progress.

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Management of adjuvant mitotane therapy for adrenocortical carcinoma: a survey in Italy

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Background and objective
Mitotane is widely used as post-operative adjuvant treatment of adrenocortical carcinoma. However, the management of therapy is largely empirical. Mitotane monitoring is recommended but we do not know what impact target concentrations do have on patient outcome. The aim of the study is to evaluate its use in expert Italian centers, analyzing data of Lysosafe Online® database.
Methods
Retrospective analysis of patients reported on the Lysosafe Online® database, treated with mitotane for ≥ 6 months and with >3 measurements of plasma mitotane levels during follow-up. Data are expressed as median and interquartile range.
Results
We identified 110 patients (F/M = 67/43, aged 47, 35–58 years), treated with adjuvant mitotane for 47 (28–62) months with a maintainment dose of 2.0 (1.5–2.5) g/day. Adjuvant treatment was initiated after 1 (1–2) months from first surgery in 92.7% and discontinued permanently in 53.6% of cases, of which 61.0% for end of treatment and 8.5% for toxicity. Achievement of target mitotane levels required 8 (5–19) months. At multivariate analysis, Ki67 index (HR 2.71, 95% CI, 1.06–6.90; $P=0.048$) and time to the first target level (HR 1.35, 95% CI, 1.02–1.80; $P=0.046$) were predictive factors of recurrence. In a separate model considering only the first 3 years of treatment, peak mitotane concentration was associated with lower risk of recurrence (HR 0.56, 95% CI, 0.38–0.85; $P=0.006$).

Conclusions
In Italy, a low-dose regimen of adjuvant mitotane therapy is used that has the likely advantage of being rather well tolerated for long time with the drawback of a slow rise of mitotane levels to target. The study shows that monitoring of mitotane levels may have an impact on patient outcome.

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Management of mitotane for advanced adrenocortical carcinoma: a survey in Italy

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Background and objective
Mitotane is the main option of treatment for advanced adrenocortical carcinoma (ACC). However, limited evidence is available regarding practical management of mitotane treatment and its eventual combination with chemotherapy or radiotherapy. The aim of the study is to do a survey on the use of mitotane for advanced ACC in expert Italian centers, analyzing data of the LYSOSAFE database.
Methods
Retrospective analysis of patients with advanced ACC treated with mitotane for $\geq$3 months and with at least 2 measurements of plasma mitotane levels during follow-up reported in the LYSOSAFE database. Data are expressed as median and interquartile ranges.
Results
We identified 90 patients (F/M = 61/29, age 50, 36–59 years). One group of 29 patients have been previously treated with adjuvant mitotane, while 61 patients started *de novo* palliative mitotane. Median duration of palliative treatment was 28 months (14–47) with a median dose of 2.5 g/day (2.0–3.0). Achievement of mitotane levels $>$14 mg/l required 7 months (3–11) from the start of therapy, considering that only 2 patients had values in range during adjuvant therapy. The palliative treatment was discontinued in 64 patients, of which 50 for death and 9 for ACC progression, without any discontinuation for toxicity. A group of 21 patients received only mitotane, while 69 patients were treated with a combination of mitotane and other treatments (22 patients underwent 1 chemotherapy treatment, 21 patients 2 chemotherapy treatments and 26 patients $>$3 radiotherapy and/or chemotherapy treatments). The most common drug used in combination with mitotane was cisplatin (61/69 patients). Twenty-one patients had no mitotane level $>$14 mg/l, while the remaining 69 had mitotane in range in 35% (25–50%) of the measurements, and 18 patients had more than 50% of mitotane levels in range. At the end of the follow-up (39, 24–65 months), 59/90 patients were dead.
Conclusions
In Italy, mitotane therapy of advanced ACC is usually done in combination with chemotherapy. However, toxicity of the treatment remains acceptable, and most patients are able to achieve the therapeutic range, although with significant fluctuations of mitotane levels during follow-up. Mitotane is often continued as background treatment in addition to different chemotherapy regimens for quite a long period of time.

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How do sex and BMI affect glucocorticoid treatment in adrenal insufficiency?

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Background and objective
Optimization of glucocorticoid (GC) replacement therapy in adrenal insufficiency (AI) is crucial to avoid consequences of under- or overtreatment. Dosing of GC replacement is mainly based on clinical grounds; however, the impact of patient's characteristics on daily GC requirement is poorly evaluated. The aim of the study is to assess the influence of sex (M/F) and BMI on dosing GC in patients with AI of different etiology.
Patients and methods
We retrospectively analysed 203 patients (104 primary AI [pAI], and 99 secondary AI [sAI]) followed-up for $>$12 months over the last 2 decades treated with hydrocortisone (HC), HC modified release (HCMR) or cortisone acetate (CA). We evaluated the total daily dose (TDD) and per-Kg-daily dose (KDD) of GC either at baseline or at the last visit. We considered comorbidities (arterial hypertension, diabetes mellitus and dyslipidemia) at each time point.
Results
At baseline, we did not observe any difference in clinical characteristics and comorbidities between F and M patients with pAI (65 F, 39 M). KDD was higher in F than in M (F, 0.47 ± 0.19 vs M, 0.38 ± 0.47 mg/kg per day, $P = 0.016$). At last visit, BMI was stable in F, but KDD and TDD were significant lower than at baseline (0.47 ± 0.19 vs 0.38 ± 0.14 mg/kg per day, $P = 0.014$ and 25.77 ± 8.02 vs 23.24 ± 6.33 mg/day, $P = 0.048$, respectively). In M with pAI, BMI, KDD and TDD were not different between baseline and last visit. Therefore, KDD and TDD were not significant different between genders at last visit. In patients with sAI (53 F, 46 M) both at baseline and at last visit, KDD was not significant different between genders. Conversely, TDD at last visit was significantly lower in F than in M (F 18.40 ± 6.95 vs M 23.37 ± 8.14 mg/day, $P = 0.001$). Comorbidities were comparable between groups. At baseline, the use of hydrocortisone was preferred in pAI, while the use of CA was more frequent in sAI. At last visit, the rate of patients in HCMR was higher in pAI than in sAI. BMI was higher in sAI than in pAI, as well as TDD and KDD.
Conclusions
Our real life study demonstrates that in pAI GC replacement is likely overdosed in F when treatment is initiated. Optimization of replacement and a more extensive use of HCMR lead to a marked GC dose reduction in F patients with pAI during follow-up. In sAI patients, lower GC starting doses are used with minimal dose adjustment during follow-up.

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Abstract Unavailable.

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Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency

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Introduction
Congenital adrenal hyperplasia (CAH) due to 11 beta-hydroxylase deficiency (11βOHD) is a rare autosomal recessive genetic disorder. It results defects in adrenal cortisol and aldosterone synthesis. Early diagnosis and initiation of treatment in

male patients are essential in order to prevent serious complications. We report a male patient with CAH who developed complications because of late diagnosis
Case Report
44-year-old male patient who admitted to emergency department with hypokalemia. Azoospermia was identified with the complaints of infertility two years ago. At andrology depatment; the laboratory tests were consistent with hypergonadotropic hypogonadism, chromosome analysis revealed a 46XY karyotype and scrotal ultrasonography showed bilateral testicular atrophy. The patient had a history of gynecomastia operation six years ago. Medical history revealed a growth retardiation observed at the age of 11 years. He did not have ambiguous external genitalia. He had a history of bilateral orchitis when he was 13 years old. The patient was consulted in the endocrinology department for bilateral adrenal masses, hypokalemia and hypertension. In the physical examination, body height was 162 cm and weight was 80 kg. His blood pressure was 160/80 mm/Hg. The other systems were examined and found normal. Laboratory assessments showed elevated levels of adrenocorticotropic hormone (ACTH) (76.2 pg/ml), androstenedion (2.17 ng/ml) and 11-deoxycortisol (13.82 ng/ml). After correction of hypokalemia; plasma renin and aldosterone concentrations were under normal limits. After ACTH stimulation test, 17-hydroxyprogesterone (17-OHP), 11-deoxycortisol and cortisol levels were 11 ng/ml, 289 ng/ml and 17 µg/dl at 60th minute, respectively. The hypokalemic hypertension, elevated 17-OHP, 11-deoxycortisol, androstenedione and low renin, aldosterone levels were all suggestive for an 11βOHD diagnosis. Abdomen magnetic resonance imaging scan showed bilateral adrenal masses with the sizes of the masses were 14.5×7 mm on the right adrenal and 32×28 mm on the left adrenal. Bilateral adrenal masses were thought to be related with CAH. Impaired gonadal function is common in adult men with CAH. This is indicated by the presence of testicular adrenal rest tissue and/or hypogonadotropic or hypergonadotropic hypogonadism. Our patient has hypergonadotropic hypogonadism and bilateral testicular atrophy without mass. This unpredictable feature is thought to be due to the history of bilateral orchitis.
Conclusion
CAH due to 11βOHD is a rare disorder with significant challenges in diagnosis and management. Wide spectrum of clinical presentation depending on the underlying enzymatic deficiency can cause late diagnosis. Both fertility and adrenal glands can be protected with an early diagnosis and an early glucocorticoid treatment.

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Pheocromocytoma, newly diagnosed during pregnancy in a subject with neurofibromatosis type 1: A case report and review of literature

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Introduction
Pheocromocytoma, is a rare cause of hypertension diagnosed during pregnancy, with a prevalence 0.002%, due to its non-specific presentation and difficulty to distinguish its hypertension from other clinical conditions during pregnancy. Early diagnosis and appropriate treatment have a great impact on maternal and fetal mortality. Pheocromocytoma is sporadic in the majority of cases, but up to 25% may be syndrome-associated.
Case report
We report a clinical case of a woman 29 years old, with neurofibromatosis type 1, presented during the third trimester (31 weeks) of her first pregnancy with severe hypertension, at maternity hospital.
Medical history
She was diagnosed since child with neurofibromatosis type 1. Without other medical problems during her life. Negative familiar history. She referred episodes of severe hypertension till 280/160 mmHg, initiated during the second trimester (13 weeks), characterized by headache, palpitation, tachycardia, tachypnea, sweeting, pallor that lasted some minutes. The situation was normalized without treatment. Out these crises, the blood pression was normal (120/80 mmHg). At the beginning, these episodes were not frequent (1 per month), but after 31 weeks of pregnancy, they became more frequent (1 per week). It was started treatment with α/β blockers (Methyldope 250 mg 4×2 pills, aspirine 100 mg per day) but after 33 weeks they became very frequent, 1 episode per day at different time of the day, without any specific trigger. It was suspected for pheocromocytoma. Catecholamines and metanephrines were measured in 24-hour urine that resulted high: 566 µg/24h (N<565) and 600 µg/24h (N 30–180 for >17-year-old) respectively. Magnetic resonance of abdomen resulted with a solid regular mass in left adrenal gland with dimensions 58×40 mm. It was started doxazosine 2 mg/day, and atenolol 100 mg 2×1/2. After that, she was stabilized. At 38 weeks, she underwent section cesarean under a multidisciplinary team assistance and everything went well. Four months after delivery, she continues to be stabilized under treatment with doxazosine and atenolol, waiting for surgery (left adrenalectomy) in a second time, hoping a definitive resolution of pheocromocytoma.
Conclusion
Given the low frequency of hypertension due to pheocromocytoma diagnosed during pregnancy, and the important role of early diagnosis and adequate treatment, on maternal and fetal mortality, physicians should beware of possible pheocromocytoma (especially in a subject with neurofibromatosis type 1) as cause of hypertension during pregnancy. A multidisciplinary team assistance is important to provide the better pregnancy outcomes.

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P30

Becoming of patients with primary aldosteronism according to their treatment

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Introduction
Unilateral forms or primary aldosteronism (PA) can be treated by adrenalectomy of by mineralocorticoid receptor antagonists, whereas bilateral forms are always treated by mineralocorticoid receptor antagonists. Most studies find similar results for the control of blood pressure and kalemia, but also to reverse organ damages, however recent studies are discordant and show a benefit of adrenalectomy regarding cardiovascular events and blood pressure (BP). Regarding these discrepancies, we wanted to evaluate the outcomes of PA treatments in clinical practice.
Methods
148 patients diagnosed for PA in our center with the realization of an adrenal venous sampling between January 2009 and December 2012 and evaluated after five years were included. Patients with no active follow-up in our center were contacted for a medical consultation or a telephonic standardized interview.
Results
Surgical and medical treatments provided similarly BP (OR=0,308 [0,277–1,335]) and kalemia control, for 70% of followed patients. Hypokalemia was persistent in 15.9% of patients in the medically treated group versus none among the patients who underwent surgery. We observed 7% of cardiovascular events without differences according to the treatment ($P=0.246$). Renal function was slightly better after surgery. Surgical treatment allowed 39% of cure rate and a significant decrease of the daily defined dose (DDD) of 2.5.
Conclusion
80 months after the diagnosis, medical and surgical treatment of PA are similar for the control of blood pressure. No difference in the occurrence of cardiovascular events appears according to the treatment. The benefice of surgery is especially represented by the reduction of antihypertensive drugs, the cure of hypokalemia and the cure rate of 39%.

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Predictors of bilateral and unilateral primary aldosteronism: a retrospective observational study

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Primary aldosteronism is a frequent cause of secondary hypertension, with early diagnosis being important for appropriate treatment and minimizing the risk of

organ damage due to excessive aldosterone. Treatment, however, varies for unilateral and bilateral primary aldosteronism, with oral aldosterone antagonist being the treatment of choice for the bilateral form and adrenalectomy, for the unilateral form. As surgical treatment for unilateral primary aldosteronism is effective, early and accurate differentiation of the unilateral and bilateral forms is important. However, there has not been established an alternative diagnostic method except adrenal vein sampling to distinguish them. In this study, we undertook a retrospective comparison of the clinical and serum markers between patients with bilateral and unilateral primary aldosteronism, diagnosed by adrenal vein sampling, to identify factors strongly associated with the unilateral form. We also evaluated the outcomes of surgical treatment in unilateral cases to confirm the usefulness of adrenalectomy. The prospective study group was formed of patients with suspected PA, based on findings of juvenile hypertension, hypokalemia and resistance to antihypertensive treatment. Of these, 249 completed the Captopril challenge, saline infusion and the furosemide upright tests for PA diagnosis, with a positive diagnosis in 239 patients. 96 out of 239 patients underwent adrenal vein sampling for localization of primary aldosteronism diagnosis at our hospital between 2010 and 2018. On univariate analyses, systolic blood pressure, plasma aldosterone concentration, and the aldosterone-to-renin ratio were significantly higher in the unilateral than in the bilateral group, whereas the serum potassium level was lower. On multivariate analysis, Captopril challenge test results and serum potassium level were retained as independent predictors of unilateral primary aldosteronism. Adrenalectomy was effective in lowering systolic blood pressure, plasma aldosterone concentration, and serum potassium levels, as well as decreasing the number of therapeutic drugs used. Therefore, unilateral primary aldosteronism is differentiated from bilateral aldosteronism by a higher plasma aldosterone concentration and aldosterone-to-renin ratio, indicative of excessive aldosterone being secreted, with serum potassium and Captopril challenge test results being reliable diagnostic predictors as it resulted good sensitivity and specificity.

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18-oxocortisol synthesis in aldosterone-producing adrenocortical adenoma and significance of KCNJ5 mutation status

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Peripheral 18-oxocortisol level could contribute to the detection of aldosterone-producing adenoma in patients with primary aldosteronism. However, peripheral 18-oxocortisol varies among such patients, which is a big drawback concerning its clinical application. We studied 48 cases of aldosterone-producing adenoma, 35 harboring *KCNJ5* mutation, to clarify the significance of clinical and pathological parameters regarding peripheral 18-oxocortisol. Peripheral 18-oxocortisol concentration ranged widely from 0.50 to 183.13 ng/dL and correlated positively with intra-tumoral areas stained positively for steroidogenic enzymes ($P<0.0001$). The peripheral 18-oxocortisol level also correlated significantly with that of circulating aldosterone ($P<0.0001$) but not with that of cortisol, a precursor of 18-oxocortisol. However, a significant correlation was detected between peripheral 18-oxocortisol and intra-tumoral glucocorticoids ($P<0.05$). In addition, peripheral 18-oxocortisol correlated positively with the number of hybrid cells double positive for CYP11B1 and CYP11B2 ($P<0.0001$). Comparing between the cases with and those without *KCNJ5* mutation, the *KCNJ5*-mutated group demonstrated a significantly higher concentration of peripheral 18-oxocortisol (28.4 ± 5.6 ng/dL vs 3.0 ± 0.9 ng/dL, $P<0.0001$) and a larger intra-tumoral environment including the hybrid cells ($P<0.001$), possibly representing a deviation from normal aldosterone biosynthesis. Following multivariate analysis, *KCNJ5* mutation status turned out to be the most influential factor involved in 18-oxocortisol synthesis in aldosterone-producing adenoma ($P<0.0001$). Results of our present study firstly revealed that enhanced 18-oxocortisol synthesis in aldosterone-producing adenoma could come from a functional deviation of aldosterone biosynthesis from the normal zona glomerulosa and the utility of peripheral 18-oxocortisol measurement could be influenced by the prevalence of *KCNJ5* mutation in an aldosterone-producing adenoma.

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Complete remission of a highly aggressive, metastasized, SDHB-related paraganglioma after chemotherapy with CVD and peptide-receptor radiotherapy

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Case
A 40-year-old woman presented in 04/2015 with pain in the upper abdomen and a history of paroxysmal tachycardia. Plasma normetanephrines were highly elevated. Imaging revealed a large retroperitoneal tumor ($15\times12\times8$ cm), which could be completely resected after pre-treatment with urapidil. Histology confirmed diagnosis of a paraganglioma. Genetic diagnostics detected a previously unknown mutation in intron 2 of the SDHB-gene (c.200+5G>C). Six month after initial surgery, plasma normetanephrines increased and imaging showed a single liver metastasis, which was successfully resected. A further five month later, increasing normetanephrine levels and MR-imaging indicated pulmonary, osseous and lymphatic metastatic spread. According to the recommendation of our multidisciplinary tumor board, palliative chemotherapy with monthly administrations of cyclophosphamide, vincristine and dacarbazine (CVD) was initiated in 05/2016, complemented by two peptide-receptor radiotherapies (PRRT) with ^{177}Lu-DOTATATE in 09/2016 (6.03GBq) and 03/2017 (6.8GBq). Follow up in 11/2016 and 02/2017 revealed a significant reduction of metastases. Normetanephrine levels normalized and remained stable. Due to considerable bone marrow toxicity, both therapies had to be stopped after ten cycles of CVD in spring 2017. Quarterly staging images during follow up showed further regression of metastases, which were no longer detectable in MRI since 09/2018.
Conclusions
Malignant paragangliomas are rare and evidence for treatment of patients with metastases is very limited. Studies available show a rather moderate response to chemotherapies as well as radiotherapeutics. We report the encouraging case of a complete, ongoing remission of an initially rapid progressive malignant paraganglioma under multimodal treatment with CVD and PRRT. Considerable side effect was a, yet reversable, bone marrow toxicity.

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Aldosterone measurement in the Diagnosis of primary aldosteronism – comparison between two automated immunoassays and two liquid chromatography tandem mass-spectrometry methods

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Poor agreement between different analytical methods measuring aldosterone concentrations impedes applicability of uniform cut-offs in the diagnostic work-up of primary aldosteronism (PA). We compared 4 analytical methods (2 immunoassays and 2 LC-MS/MS) in plasma samples before and after saline infusion test (SIT). 80 hypertensive patients underwent the standardized diagnostic work-up within the German Conn's registry. Patients (PA $n=39$/non-PA $n=41$) were classified by a experienced endocrinologists panel based on suppression of aldosterone as measured by our routine immunoassay (LIAISON, Diasorin, LSN) to concentrations <50 pg/mL, imaging, adrenal vein sampling findings, immunohistochemistry and treatment response. Aliquots from all blood samples were used to also measure aldosterone by the IDS iSYS immunoassay (iSYS) and 2 different LC-MS/MS methods (Munich LC-MS, Agilent 1290/Sciex 6500+, utilizing a Chromsystems commercial kit, and Leipzig LC-MS, an in-house method published before). Aldosterone concentrations measured by the 3 alternative methods moderately correlated to those

obtained by LSN (Pearson's r from 0.917 to 0.959), but agreement was limited (slope vs. LSN from 0.6486 to 0.9635, intercept from −24.3 to −10.0). Correlation was best between Leipzig LC-MS and iSYS. Mean and median aldosterone concentrations of all samples ($n=160$) were significantly higher with LSN as compared to all other assays. Bland-Altman plots showed significant mean bias (−81.15% to 14.78%) with higher scatter at concentrations <100 pg/mL. Compared to the expert panel classification, LSN post SIT aldosterone was falsely high (>50 pg/mL) in 7 cases (17%), but there were no false negatives. Because all other methods reported lower absolute aldosterone concentrations, applying the same cut-off would have resulted in a high number of false negatives (iSYS 38.5%, Leipzig LC-MS 28.2%, Munich LC-MS 56.4%). Accordingly, applying the cut-off of 50 pg/mL to ROC analysis AUC was 0.967 for LSN, but lower for iSYS (0.838), Munich LC-MS (0.883) and Leipzig LC-MS (0.916). Using the expert panel classification as 'gold standard', the best cut-offs for aldosterone during SIT are 61 pg/mL (LSN), 37 pg/mL (iSYS), 34 pg/mL (Leipzig LC-MS) and 20 pg/mL (Munich LC-MS). Aldosterone concentrations measured by different analytical methods differ significantly, particularly at lower concentrations, crucial for interpretation of SIT. Discrepancies occur between different immunoassays, between immunoassays and LC-MS methods, but also between different LC-MS methods. Our data emphasize the need for method-specific aldosterone cut-offs, even when LC-MS methods are used. Compared to the cut-off of 50 pg/mL traditionally used with LSN, other methods evaluated require significantly lower cut-offs to achieve the same sensitivity in detecting PA.

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P35

Embolization of the adrenal artery to control severe adrenal hemorrhage

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Background
The adrenal hemorrhage is rare and potentially lethal. Its diagnosis is difficult because atypical. We report the case of a patient beautifully treated by embolization of the adrenal artery.
Case report
A 68-year-old female patient admitted for abdominal pain, with as background, a diabetes, atrial fibrillation under anticoagulation with recent relay Previscan Innohep and a right adrenal incidentaloma (for 9 years, 43 mm of centerline and density spontaneous < 10 UH, never explored). Explorations concluded unilateral active bleeding on right adrenal adenoma. Evolution was made towards a deglobulisation motivating the transfusion of two globular units and the realization of an embolization of the right adrenal artery, in less than 10 minutes (see images) to postpone surgery. Given the non-embolic nature of the atrial fibrillation, anticoagulants were arrested and 3 weeks later, the scanner objective regression of the hematoma. Hormonal exploration of adenoma was normal and the patient, waiting for its resection.
Discussion-conclusion
This case reports an unusual and efficient treatment of adrenal hemorrhage. On 24 patients with adrenal hemorrhage after adrenal catheterization, no gesture was made[1]. Another series reported surgery in 40%, but not selective embolization[2]. A few gestures of embolization have been described in the context of bleeding on the adrenal artery aneurysms[3]. An adequate technical platform and a confirmed radiologist is vital. We do not know if this gesture can improve the subsequent functional prognosis of the adrenal and would therefore be preferable to an adrenalectomy.
References
1. Monticone S, Satoh F, Dietz AS, Goupil R, Lang K, Pizzolo F, Gordon RD, Morimoto R, Reincke M, Stowasser M, Mulatero P. Clinical Management and Outcomes of Adrenal Hemorrhage Following Adrenal Vein Sampling in Primary Aldosteronism. Hypertension. 2016 Jan;67(1):146–52.
2. Karwacka IM, Obołończyk Ł, Sworczak K. Adrenal hemorrhage: A single center experience and literature review. Adv Clin Exp Med. 2018 Mar 27.
3. Patel A, Downing R, Vijay S. Spontaneous rupture of the adrenal artery successfully treated using the endovascular approach: a report of 2 cases. Vasc Endovascular Surg. 2013 Feb;47(2):124–7.

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P36

Vitamin D deficiency is a predictor marker of tumor aggressiveness in sporadic and MEN1-related well-differentiated, low-grade GEP-NET

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Background
Vitamin D has several 'noncalcemic' implications, including effects on cell signaling and differentiation. Patients with gastroenteropancreatic (GEP) neuroendocrine tumors (NET) have an increased risk of vitamin D deficiency, due to the tumor itself, systemic therapies and abdominal surgery. However, data regarding vitamin D status are limited. Aim of this study was to evaluate 25-hydroxy-vitamin-D (25(OH)D) levels in GEP-NET patients and correlated them with markers of tumor aggressiveness.
Methods
A retrospective cross-sectional study including 101 patients affected by well-differentiated, low-grade (G)1 and G2 GEP-NET (65 sporadic and 36 with multiple endocrine neoplasia type 1 (MEN1)) and 123 healthy controls, belonging from the same geographic area and matched for age, gender and BMI, was performed. Concentration of 25(OH)D, calcium, albumin, phosphorus and PTH were measured at baseline. Regarding MEN1 patients, only those with normocalcemic primary hyperparathyroidism were included. In GEP-NET, the association of 25(OH)D with tumor grading, stage, progression-free survival (PFS) and disease-specific survival (DSS) were analyzed.
Results
No difference in 25(OH)D levels was observed between patients with sporadic and MEN1-related tumors ($P=0.29$). Considering those patients as one group, concentration of 25(OH)D was significantly lower compared to controls (mean levels 18.3±8.5 *vs* 24.2±7.7 ng/mL, $P<0.001$). Particularly, 58.4% of GEP-NET *vs* 29.2% controls had vitamin D deficiency (≤20 ng/mL), comprising 17.8% *vs* 1.6% with severe deficiency (<10 ng/mL;$P<0.0001$). Patients with G2 tumors and metastasis at diagnosis had significantly lower 25(OH)D levels than those with G1 (mean levels 15.6±7.7 *vs* 20.1±8.6 ng/mL, $P=0.02$) or localized tumor (mean levels 13.1±5.3 *vs* 19.8±8.7 ng/mL, $P=0.001$). A cut-off of 25(OH)D<15.7 ng/mL was associated with increased risk of G2 ($P=0.01$, sensitivity 66.7%, specificity 68%) and metastasis at diagnosis ($P<0.0001$, sensitivity 83.3%, specificity 69%) by ROC analysis. Patients with vitamin D deficiency had shorter PFS compared to those with insufficiency (median PFS 204 *vs* 377 months, $P=0.02$, HR=2.64, 95%CI 1.13–1.26) and sufficiency (median PFS undefined, $P=0.002$, HR=5.66, 95%CI 1.90–16.9). No correlation was observed between vitamin D status and other investigated parameters, including DSS.
Conclusion
We confirmed that vitamin D deficiency is highly prevalent among sporadic and MEN1-related GEP-NET patients and it is associated with G2 and metastasized tumors. Thus, vitamin D deficiency might represent a marker of tumor aggressiveness that might help us to identify those patients with higher risk of disease progression.

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P37

Role of KCNJ5 mutations in mediating cell growth in aldosterone-producing adenomas

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Background
Primary aldosteronism is commonly caused by an aldosterone-producing adenoma (APA). Somatic mutations in the *KCNJ5* gene (encoding an inwardly rectifying potassium channel) are found in around 40% of APAs, *KCNJ5*

germline mutations cause familial hyperaldosteronism type III. The role of *KCNJ5* mutations in excessive aldosterone production is established but their role in cell growth is unclear.
Objective
To study the effects of *KCNJ5* mutations on cell viability and apoptosis under controlled conditions of gene expression and to assess the expression level of KCNJ5 in APAs.
Methods
Human adrenocortical (HAC15) cell lines stably expressing either a KCNJ5 mutant (G151R, L168R, G151E or T158A) or wild type KCNJ5 and a control cell line transfected with empty vector were established using a cumate-inducible PiggyBac vector system. Cell viability and cell death by apoptosis were quantified using specific assays following induction with cumate. A highly specific monoclonal antibody for KCNJ5 was developed and used in immunohistochemistry and immunofluoresence to demonstrate the distribution and expression level of KCNJ5 in normal adrenals, APAs and corresponding adjacent cortex.
Findings
Under the conditions tested, expression of KCNJ5 G151R, L168R and G151E mutants in HAC15 cells induced apoptosis, KCNJ5 T158A had no effect on cell death. After 12 hours, low level expression of mutated KCNJ5 caused a significant increase in cell proliferation compared with control cells. KCNJ5 displayed low level expression in APAs carrying a KCNJ5 mutation but high expression in APAs with wild type KCNJ5 or with somatic mutations in other genes.
Interpretation
Expression of mutated KCNJ5 at a low level induces cell proliferation in adrenocortical cells. In APAs with *KCNJ5* mutations, cell growth is sustained when expression of mutated KCNJ5 is low.
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P38

Influence of Tumor Microenviroment in response modulation to treatment in human BP-NENs

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Introduction
Broncho-Pulmonary Neoplasms (BP-NENs) are rare neoplasms arising from neuroendocrine cells of the respiratory epithelium. Since previous studies in our lab have demonstrated the efficacy ofEverolimus, approved for BP-NENs treatment, and Dinaciclib, a Cyclins and CdKs inhibitor, on monolayer system we have investigated if a more complex tumour system could generate a change in drugs effects and cell resistance. Therefore, through the use of 3D culture model, we have cultured BP-NENs tumour cells alone or together with a lung fibroblasts cell line in order to verify the possible role of Tumour Microenvironment in BP-NENs development and drug resistance.
Material and Methods
NCI-H720 and NCI-H727 cell lines were used as BP-NENs model while MRC5 cell line was used as lung fibroblast model. Two lipophilic tracers were used to stain tumour cells and fibroblasts. Everolimus and Dinaciclib were used at 100 nM. Ultra-low attachment 96-well plates with clear round bottomwere used to obtain Spheroids while metabolic activity was assed using MTT assay.
Results
For both cell lines, when tumour cells were co-cultured with MRC5, spheroids appeared more solid and compact. Our results also showed how the spheroids were different: NCI-H727 spheroids were denser in comparison with NCI-H720 and, in addition, when synthetic extracellular matrix was added the latter failed to invade. Tracers analysis also revealed spheroids cellular distribution underlying a tumour cells core with peripheral collocation of fibroblasts. MTT analysis on tumours cells spheroids showed a 20% significant metabolic activity reduction (vs. vehicle DMSO spheroids) for spheroids treated with Dinaciclib while Everolimus treatment didn't affect basal cell metabolic activity in both cell lines. On the other hand, once in co-culture with MRC5 cells, the cell metabolic reduction observed with Dinaciclib treatment was lost.
Conclusions
Our preliminary results indicate that TME could be important in cell aggregation and spheroids formation and might have a role in drug resistance.
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P39

A novel CYP11B1 mutation presenting as a classical congenital adrenal hyperplasia due to 11beta-hydroxylase deficiency

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Background
Congenital adrenal hyperplasia (CAH) is a rare autosomal recessive disorder, of which 21-hydroxylase deficiency (21OHD) is the most frequent form. 11 beta-hydroxylase deficiency (11bOHD) is the second most common type of CAH. This pathology results from inactivating mutations in *CYP11B1* gene.
Case presentation
We describe a case of a 48-year-old woman with 11bOHD, presented with hypokalemia hypertension, early adrenarche and mild virilization at age of 11 years. She was referred to our department at age of 46, after presenting an adrenal crisis, while suffering a pneumonia process, which was resolved with high dose corticoids. She had received over-replacement with glucocorticoids (hydrocortisone 40 mg/day) since she was 11 and developed long-term complications such as osteopenia and poorly controlled hypertension in spite of use of 4 drugs. Physical examination showed cushingoid appearance, with excessive hair growth, short adult stature (145 cm) and central obesity (BMI 38 kg/m^2). She had neither obvious abnormalities in external genitalia at birth nor menstrual disorders. She presented mild left ventricular hypertrophy and hypertensive nephropathy as end-organ damage secondary to hypertension. The biochemical results of the diagnosis during childhood were not available and genetic study was not previously performed. Laboratory examination, under glucocorticoid treatment, revealed low ACTH levels, low androgen levels, normal serum aldosterone and rennin activity and high deoxycorticosterone (DOC) levels. A molecular analysis by sequencing *CYP11B1* gene exome identified a homozygous splicing mutation, c.596-2A>G, not previously reported. This modification in the splice site consensus sequence affects the acceptor critical site in the intron 3- exon 4 boundary. The mutation will most likely lead to a loss of enzymatic activity. Therefore, we confirmed the diagnosis of CAH due to 11bOHD. Following the diagnosis, the patient was advised to reduce the dosage of hydrocortisone to 20 mg day (10 mg in the morning, 5 mg in midday and 5 mg in the afternoon). After dose adjustment of glucocorticoid, blood pressure improved, she lost weight and clinical parameters ameliorated. We did not prescribe treatment with spironolactone because she had high concentration of potassium and her hirsutism disappeared only with glucocorticoid treatment.
Conclusions
We have identified a novel mutation of *CYP11B1* causing CAH. Recognition of novel mutations is clinically significant and would contribute to the knowledge of the phenotype-genotype relationship of CAH in the future.
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P40

Available 3D cultures methods: study on a Pancreatic Neuroendocrine Neoplasm cell line

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Background
Pancreatic Neuroendocrine Neoplasms (pNENs) are malignancies arising from the endocrine pancreas. Past *in vitro* studies have led to a better comprehension and characterization of this malignancy under several points of view. However, effective medical therapies are still not available, therefore, it is essential to continue studying this malignancy in order to identify a successful approach. Due to tumour complexity, techniques such as 3D cultures, able to generate a more realistic model, have been important to study the topic more accurately. On the other hand, several approaches are available to generate 3D cultures and it is still difficult to understand which one should be used to obtain the best results. This study aims to compare three different 3D culture systems in order to possibly identify the most suitable option in studying pNEN.
Methods
The BON1 cell line has been used as a pNEN model and spheroids were treated with Sunitinib 2,5 uM, 5 uM, 7 uM and 10 uM. The first method employed a 48-well plate with a cell-repellent surface and, in order to obtain spheroids formation, the plates were shaken overnight. Subsequently, spheroids were treated and theirsize was measured using Image J software.The second technique employed a 96-well hanging drop plate and spheroids were generated by self-assembly of tumour colonies.Spheroids were moved into another 96-well plate for treatment and MTT analysis was performed to assess metabolic activity. The third method involved the use of ultra-low attachment 96-well plates with clear round bottom: cells were centrifuged in order to generate spheroids and treated by addition of fresh medium and compound to each well. Also in this case MTT analysis was performed.
Results
Spheroids size measurements didn't highlighted a decrease in spheroids diameter after treatments with Sunitinib at different concentrations while MTT analysis on spheroids cultured with the second method indicated a decrease in metabolic activity after treatment with Sunitinib 2,5 uM, 5 uM, 7 uM of a 10% (treated cells vs. vehicle cells treated with DMSO). MTT results for spheroids cultured with the third approach have shown a decrease of metabolic activity of a 20% (treated cells vs. vehicle cells treated with DMSO) after treatment with Sunitinib 2,5 uM, 5 uM, 7 uM. Results were more homogeneous for cells seeded with the third method in comparison to the second one.
Conclusions
According to our results the third method appears to represent the easiest and most reliable technique to culture spheroids and obtain reproducible results.

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P41

Prevalence and prognosis of bone metastases in pancreatic and small intestinal neuroendocrine tumours

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Background
Neuroendocrine tumours (NET) can affect various tissues and organs, have different clinical presentation and prognosis, depending on the primary tumour site, grading, differentiation and functional status. Reported prevalence of bone metastases (BM) from NETs has been increasing with improved imaging modalities, reaching >40% in some reports. The BM diagnosis is associated with reduced overall survival; however, this was not confirmed by all studies.
Methods
We performed a retrospective single centre analysis of patients with pancreatic (pNET) and small intestinal (siNET) primaries ($n=377$) and identified 40 patients diagnosed with BM (19 with pNET, 21 with siNET). The scans were assessed by an independent radiologist blinded to the primary site diagnosis and to the history. IBM SPSS-24 was used to compare overall survival. The survival was calculated based on 'alive' status as per 1st December 2017. Statistical significance was accepted at $P<0.05$.
Results
The prevalence of BM was 10% for pNET and 11.2% for siNET; BM were present at the time of diagnosis in 23 patients (57.5%), including 68.4% pNET patients who developed BM at some point in their disease course, as opposed to 47.6% siNET, $P=0.249$. Nine patients had lytic, 24 sclerotic and 3 mixed bone lesions. Data regarding fractures was available in 33 patients, 4 of them had fractures identified, however only 2 had fractures related to the BM, in both of them tumours originating from pancreas. Almost half of pNET patients who developed BM had grade 3 tumours, as opposed to only about 10% of siNET. We observed a significantly higher prevalence of lytic lesions in pNET as compared to siNET. Interestingly, 2/3 of pNET with lytic BM were grade 3 tumours vs grade 1 for siNET. Overall survival (OS) was better for siNET in our analysed cohort of patients, having a longer survival since the time of diagnosis of NET ($P=0.034$); the difference in survival post diagnosis of BM was not statistically significant. The median OS for the whole cohort of pNET and siNET since the time of detection of BM ranged from 12 months in G3 pNET to 58 months in G2 siNET. The sclerotic BM were associated with more favourable prognosis; however, the difference did not reach the statistical significance.
Conclusions
A substantial proportion of NET patients with BM have skeletal lesions at the time of initial diagnosis of NET. BM from pNET are associated with higher grade primaries, lytic lesions and shorter OS.

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P42

Endocrine hypertension?

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An 18-years-old woman without medical history was referred for study of hypertension and an adrenal incidentaloma. The family history was significant for essential well-controlled hypertension in her father; diagnosed at 39 years-old. The patient complained of headache, asthenia, edema in lower limbs, high blood pressure values (200/150 mmHg) for one year (well controlled with losartan 100 mg/12 h, amlodipine 10 mg/24 h and doxazosin 4 mg/24 h) and marked facial acne previous months; without hirsutism. She had regular menstrual cycles. Physical examination: weight 82.4 kg, BMI 28 kg/m^2, BP 131/89 mmHg, no acanthosis nigricans and no clinical stigmata of hypercortisolism. Patient provided abdominal CT without contrast with a hypodense nodular 0.8 cm thickening in left adrenal gland, normal renal Doppler ultrasound and echocardiogram with moderate left ventricle eccentric hypertrophy. We requested laboratory tests: glycemia 92 mg/dl, creatinine 0.75 mg/dl, glomerular filtration rate >90 ml/min/1.73 m^2, sodium 140 mEq/l, potassium 3.56 mEq/l, TSH 0.88 µUI/ml, FT4 1.1 ng/dl, cortisol 23 mcg/dl, ACTH 11 pg/ml, aldosterone 5.1 ng/dL, PRA 14.9 ng/ml/h, ratio aldosterone/PRA 0.34 (<30), urinary free cortisol 258 µg/24h (<180), dopamine 573 µg/24h (<500), adrenaline 4.4 µg/24h (<35), noradrenaline 140 µg/24h (<100), normetanefrin 508 µg/24h (<500), metanephrines 186 µg/24h (<300) and Nugent test 14 mcg/dl. Due to discordance with initial study, we requested a new study interrupting antihypertensive treatment and administering verapamil 240 mg/24h and doxazosin 8 mg/24h, with result: potassium 2.8 mEq/l (<3.5), ACTH 20 pg/ml, cortisol 29 mcg/dl, PRA 20 ng/ml/h, aldosterone 24 ng/dl, aldosterone/PRA 1 (<30), Liddle test 0.6 mcg/dl and catecholamines and metanephrines in urine in range. Suspecting secondary hyperaldosteronism (reninoma) we requested an abdomen CT with contrast showing a solid, well-defined rounded focal 22 mm. cortical lesion in right kidney lower pole, and subtle 8 mm thickening in left adrenal gland. It is derived to Urology for laparoscopic right partial nephrectomy. Histological examination: well-delimited, not encapsulated tumor, without atypia, necrosis, mitosis, vascular invasion or adjacent renal parenchyma invasion. Immunohistochemistry: CD34 and vimentin intensely positive, with no evidence of immunoexpression for actin, CD117 or CK7, compatible with a juxtaglomerular cell tumor (immunoexpression of CD117/actin are pending in a reference center to confirm the lesion). After surgery, the patient remains normotensive without treatment and with normality on the renin-aldosterone axis (PRA 1.2 ng/ml/h, aldosterone 7.6 ng/dl).

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P43

Ninety-four serum steroids measured by gas chromatography tandem mass spectrometry (GC-MS/MS) in patients with Cushing's syndrome

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Introduction
Gas chromatography tandem mass spectrometry (GC-MS/MS) quantitatively detects many steroids at one time in a single serum sample. Cushing's syndrome (CS) caused by adrenal adenoma is often associated with decreased DHEAS, whereas low levels of aldosterone in ACTH dependent CS and also low levels of 18-oxocortisol were observed in ectopic CS. We aimed to evaluate steroid differences in various types of CS.
Methods
In serum from patients with CS (51 with Cushing's disease, 6 with ectopic ACTH-dependent CS, 16 with adrenal adenoma, 7 bilateral adrenal hyperplasia (BMAH) with overt CS, 23 controls) using novel gas chromatography-tandem mass spectrometry (GC-MS/MS) method we measured 94 steroids to evaluate differences between groups.
Results
In Cushing's disease and ectopic ACTH producing tumors we observed elevated levels of androgens and their metabolites when compared with healthy controls. Mineralocorticoid precursors were elevated in ectopic ACTH syndrome. The levels of androgens were decreased in adrenal adenomas and BMAH. ROC analysis showed 100% sensitivity and 93.6% specificity of 11β-hydroxyepiandrosterone sulfate for discrimination of Cushing's disease from ectopic ACTH secretion (where it was more elevated). We did not find any significant ($P < 0.05$) difference in steroids that would discriminate BMAH from unilateral adenomas causing Cushing's syndrome.
Conclusion
Steroid profiling in CS patients shows significant differences between CS types that could ease the achievement of appropriate diagnosis. Further prospective studies are needed for the confirmation of these results.

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Comparative study between autoimmune metaplastic atrophic gastritis (AMAG) and type 1 gastric neuroendocrine tumors (G-NETs) in Hospital Clínico San Carlos (HCSC), Madrid

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Introduction
Type 1 Gastric neuroendocrine tumors account for 70 to 80 percent of all gastric neuroendocrine tumors (G-NETs) and they are found more commonly in older adults, particularly women. They are associated with autoimmune metaplastic atrophic gastritis (AMAG) with or without pernicious anemia. Endoscopically, they are usually smaller than 1 cm and often multiple. These tumors usually present a non-aggressive evolution. Our goal is to approach the presence of risk factors to develop G-NET in patients with AMAG.
Material and methods
Descriptive and observational study of 16 patients diagnosed with AMAG (controls) and 31 patients diagnosed additionally with type 1 G-NET (cases). The 47 patients were retrieved from the Endocrinology department of HCSC in the last 15 years. Variables between both groups were compared using the statistical program SPSS 23.0.
Results
Mean age was 64.75 (SD 12.03) in controls and 63.47 (SD 11.35) in cases. 75% of controls and 62% of cases were female. The diagnosis of AMAG in controls was due to vitamin B12 deficiency in 68.8%. In cases the diagnosis of G-NET was due to follow-up AMAG in 40.6%. We did not find differences between the personal and family history in both groups. 86.7% of controls and 71.8% of cases were non-smokers without reaching statistical significance. The presence of H. pylori was found in 18.8% of controls and in 3.1% of cases ($P = 0.101$). The median of vitamin B12 in controls was 186 pg/ml (IQR 141.5–398.5) and 288 pg/ml (IQR 204–386) in cases ($P < 0.05$). There were no statistically significant differences in the levels of hemoglobin, ferritin or serum iron although the median values were lower in controls. Regarding autoimmunity, anti-parietal cell antibodies could protect the development of G-NET OR: 0.192 (0.038–0.956). We found a higher prevalence of intrinsic factor antibodies in controls (41.2% vs 21.7) that was not statistically significant ($P = 0.185$).
Conclusions
In our sample, the presence of anti-parietal cell antibodies might be a protective factor against G-NET development. However other studies are needed to support these results in other populations. Vitamin B12 levels were significantly higher in cases than in controls. Further research confirming these data might help to establish the usefulness of Vitamin B12 levels in early diagnosis of G-NET in patients with AMAG. Larger studies are necessary to assess whether the presence of intrinsic factor antibodies and H.Pylori infection are indeed associated with a lower risk of developing G-NETs in patients with AMAG.

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P45

Pheochromocytoma and disorders of carbohydrate metabolism

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Introduction
Pheochromocytoma is a rare tumor secreting catecholamines, which are part of the hormones of carbohydrate counter-regulation. The aim of our work is to evaluate the glycemic balance in patients in pre- and post-operative pheochromocytoma.
Material and methods
A retrospective study of 18 cases of pheochromocytoma over a period of 5 years. A pre- and post-operative metabolic assessment was performed as well as an evaluation of the other clinical parameters.
Results
The mean age of the patients was 47 years (Sex F/H ratio: 2.6). Diabetes is found in 50% of patients and had the following characteristics: the average evolution of 5.7 years, with a strong type II diabetic heredity in 67.1% of cases and an average body mass index of 26.4 kg/m^2. One-third of patients had HBA1C greater than 8%. No diabetic patient had a ketoacidosis decompensation, and 55.5% of our diabetic patients were under INSULNE + oral anti-diabetic on admission. In postoperative: only 22% of our patients were on oral anti-diabetic + Insulin, blood glucose level normalized in 22% of cases under no treatment, improved in 33% of cases under the same treatment and average HBA1C decreased from 7.57% in pre-op to 6.65% in post-op.
Discussion
The glucoregulation disorder of pheochromocytoma is quite common in our series as in some literature results. The radical surgery of pheochromocytoma has a remarkable impact on the glycemic balance.

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P46

Heart and vessels after a pheochromocytoma: which outcomes?

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Introduction
Pheochromocytoma is a rare tumor. It can be revealed or complicated by cardiovascular manifestations. The aim of our work is to study the cardiovascular manifestations of pheochromocytoma and the evolution of hypertension after surgery.
Patients and methods
A retrospective study of 18 cases of pheochromocytoma followed at the endocrinology and metabolic diseases department of Mohammed VI university hospital of Oujda during a period of 5 years. Clinical data, electrocardiogram and trans-thoracic ultrasound were recorded for each patient.
Results
The mean age of the patients was 47 years. Discovery conditions were dominated by the Menard triad in 7 cases and incidentaloma exploration in 6 cases. The dosage of urinary methoxylated derivatives was greater than 3 times the normal value in 94.4% of cases. Half of the patients were hypertensive, 8 of whom were diabetic. On electrocardiogram: Left ventricular hypertrophy was noted in 4 cases, tachycardia in 2 cases, bradycardia in 1 case, and repolarization disorders in 2 cases. Trans-thoracic ultrasound was normal in 5 cases, and showed a left ventricular hypertrophy in 4 cases, an aneurysmal dilatation of the ascending aorta in one case and a pericardial detachment in 1 case. The evolution after the

surgical cure was marked by the normalization of the blood pressure values under no treatment in 44% of the cases, and improvement with a reduction in the number of antihypertensives drugs in 22% of cases.
Conclusion
Pheochromocytomas are high-risk cardiovascular tumors that can be life-threatening. Surgical treatment normalized blood pressure in 44% of cases.
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P47

First presentation of Addison's disease as hyperkalaemia: a rare case report

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Introduction
Addisson's disease is a rare endocrine disorder; that continues to be a diagnostic challenge in the 21st century; mainly due to the slow and non specific progression of symptoms. We report the case of a 45-year-old woman who was admitted with acute adrenal insufficiency discovered in the context of a severe hyperkalemia.
Case report
A 45-year-old woman was admitted in our institution with a history of extreme weakness and vomiting. On physical examination we noticed a significant dehydration and a blood pressure of 60/40 mmHg. Initial blood tests revealed hyponatremia 124 mmol/l and severe persistant hyperkalemia higher than 10 meq/l with estimated glomerular rate 42.42 ml/min. Her ECG showed tall tented T waves in all leads besides wide QRS complexes. Furthermore, 0800 h serum cortisol was low. The patient was started on intravenous hydrocortisone and fluids according to local treatment protocol for acute adrenal insufficiency. At the same time, she underwent urgent haemofiltration along with conventional medical management of hyperkalemia resulting in subsequent improvement. Elevation of ACTH with low cortisol taken at 0800 h at discharge confirmed the diagnosis of primary adrenal insufficiency. After the resolution of the electrolyte abnormalities and the improvement of hemodynamic statement; she was discharged on oral hydrocortisone and fludrocortisone tablets.The patient was followed up in the endocrinology department of Oujda's Mohammed VI university hospital, for further investigations and a well conducted disease's education.
Conclusion
This report describes a non-specific presentation of Addison's disease. Therefore, a high index of suspicion is warranted in patients with a life-threatening hyperkalemia and may requires haemofiltration in spite of a prompt management of acute adrenal insufficiency based on preliminary clinical diagnosis.
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P48

Pharmacokinetic Interaction Study of the Effects of Multiple-dose Gastric Acid Reducers Omeprazole (OMP) and Famotidine (FAM on the Pharmacokinetics (PK) of Single-dose Telotristat Etiprate (TE) in Healthy Subjects

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Background
TE is indicated for the treatment of carcinoid syndrome diarrhea in patients with metastatic neuroendocrine tumors.
Objective
To evaluate the effects of a proton pump inhibitor (OMP) and H2 antagonist (FAM) on the PK of TE and its active metabolite LP-778902 via an open-label study of OMP (40 mg orally QD $\times$ 4 days) or FAM (40 mg orally BID $\times$ 4 days) with a single 250 mg oral dose of TE. Eligible subjects: healthy, nonsmoking, aged $\geq$18-$\leq$65 years/BMI $\geq$18.0-$\leq$32.0 kg/m^2. Parallel cohorts of 16 subjects each received 250 mg TE on Day 1 followed by a 72-hour washout. On Day 4–6 subjects received either OMP ($n=16$) or FAM alone ($n=16$). On Day 7 subjects received 250 mg TE and OMP or FAM. Fasting and meals were controlled. PK blood samples were collected on Day 1 and 7. Safety assessments were conducted at Screening and throughout the study.
Analysis
PK parameters included maximum observed concentration (C_{max}), time of maximum concentration (T_{max}), area under the plasma concentration-time curve extrapolated to infinity (AUC_{inf}), and AUC from first dose until the last quantifiable concentration (AUC_t). A lack of DDI was declared if the 90% confidence intervals (CIs) for the ratios of geometric least square means fell within the accepted range of 0.8 – 1.25 for AUC_t, AUC_{inf}, and C_{max}.
Results
For TE alone, mean AUC_t, AUC_{inf}, and C_{max} were 3.4, 2.8, 1.7 and 2.2, 2.1, and 1.2 times higher when TE was co-administered with OMP or FAM, respectively. Median T_{max} for TE was delayed by 1.3 hours and 0.5 hours, respectively. Boundaries of the 90% CIs were not within the 0.8–1.25 interval, indicating a DDI with OMP and FAM on TE exposure. However, no-significant difference in exposure (AUC_t, AUC_{inf}) to LP-778902 was observed and there was a $<$7% decrease in C_{max}, following coadministration of TE with either OMP or FAM. There were no clinically significant findings in any safety assessments. One subject who received FAM experienced mild pruritis that was considered unlikely related to either study drug and resolved by the end of the study.
Conclusion
Single oral doses of 250 mg TE administered alone or with either OMP or FAM were safe and well tolerated. Coadministration with either OMP or FAM alters the exposure of TE but has no marked effect on exposure to the active, more potent metabolite, LP-778902, and therefore, is unlikely to be clinically significant.
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P49

Endocrine hypertension: before and after treatment of the endocrinopathy

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High blood pressure of endocrine origin remains a rare cause of hypertension. The interest of the research of endocrine hypertension lies in the severity of certain forms and its potentially curable and reversible nature, hence the interest of oriented screening. The aim of our work was to study the profile of endocrine hypertension among a population suffering from secondary diabetes. This is a retrospective descriptive study of 55 patients followed in endocrinology department of the M8 ward, Charles Nicole Hospital, Tunis between 1985 and 2015. Dysthyroidism was excluded. The average age of our population was 44.85$\pm$12.74 years with a female predominance of 72.2%. It included Cushing's syndrome in 40.7%, acromegaly in 22.2%, pheochromocytoma in 16.7% and primary hyperaldosteronism in 20.4% of cases. Mean systolic and diastolic arterial pressures were 166.3$\pm$23.2 mmHg and 97.00$\pm$15.2 mmHg, respectively. Hypertension was severe in 31.5% and resistant in 13% of cases. It was controlled by tritherapy in 22.2%, dual therapy in 24.1% and monotherapy in 27.8% of cases. We did not find a correlation between the severity of hypertension and the baseline hormonal level. After remission of the underlying endocrinopathy, blood pressure was statistically improved in all cases. Antihypertensive treatment was even discontinued in 61.1% of patients with Cushing's syndrome, 66.7% of acromegalic patients, 44.4% of patients with pheochromocytoma and 9.1% of patients with primary hyperaldosteronism. Endocrine hypertension is a severe but often curable form of high blood pressure. Associated with diabetes, it increases cardiovascular risk during endocrinopathies. It is therefore imperative to detect and balance it while waiting for the treatment of the underlying endocrinopathy.
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P50

A seminoma with entrapped nerve ganglion masquerading as a paraganglioma

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Background
The differential diagnosis of retroperitoneal tumors includes lymphoid, germ cell and neurogenic tumors such as paraganglioma. Paragangliomas are rare neuroendocrine tumors of the autonomic nervous system, which may secrete catecholamines and their metabolites. Clinical features include sustained or

paroxysmal hypertension, headaches, sweating and palpitations. Here we present an unusual case of a retroperitoneal tumor entrapping a sympathetic nerve ganglion and mimicking paraganglioma.
Case study
A fifty-seven-year-old man with a history of controlled hypertension presented with paroxysms of tachycardia, flushing, high blood pressure and headache. Ambulatory blood pressure monitoring showed uncontrolled labile hypertension with a normal nocturnal dip. Abdominal CT demonstrated a 6.1 cm mass in the right retroperitoneum with adjacent lymphadenopathy. Paraganglioma was suspected and urinary 24-hour collection was performed, demonstrating mildly elevated normetanephrines (575 μg/24 h, norm 5-290) and VMA (8.3 mg/24 h, norm 0.5–6.6). 68-Gallium DOTATATE PET/CT showed weak uptake in the retroperitoneal mass and no other mass lesions. Following preparation with alpha-adrenergic blockers, surgical excision was performed with diagnostic and curative intent. Post-operatively, hypertension and paroxysmal symptoms resolved completely. The histopathology report described seminoma with an entrapped large ganglion within the tumor.
Conclusion
We describe a retroperitoneal seminoma with an entrapped ganglion causing hypertension and paroxysmal symptoms, with laboratory and imaging features compatible with paraganglioma. Awareness of the rare possibility of mechanical pressure on a ganglion, within the differential diagnosis of retroperitoneal mass and sympathetic symptoms may aid in clinical decision making in atypical cases.

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P51

Magnetic resonance imaging in the initial diagnosis of pancreatic insulinoma: primary data analysis

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Introduction
Insulinoma visualization is the most difficult stage of diagnosis of this disease. Currently, in most cases the contrast-enhanced multislice computer tomography of abdomen and retroperitoneal space (CE-MSCT) is the method of choice in topical diagnosis of insulinoma. This method is associated with radiation exposure and administration of contrast agents, so it is invasive. Thus, an alternative highly informative and safe method for initial topical diagnosis of insulinoma is necessary. In particular, the magnetic resonance imaging without contrast enhancement (MRI without CE) is a promising imaging method.
Materials and methods
In 24 patients aged 20–72 years with hypoglycemic syndrome the MRI without CE and CE-MSCT were performed.
Results
According to MRI, pancreatic neuroendocrine tumor was detected in 96% of patients ($n=23$). CE-MSCT revealed the pancreatic tumor in 100% of patients ($n=24$), among them the tumor in the head of pancreas in patient with negative result of MRI. According to CE-MSCT, there were 23 neuroendocrine and one solid pseudopapillary tumor. In all patients ($n=24$) the surgery was performed. Intraoperative revision confirmed the localization of pancreatic tumor in 100% of patients with positive result of MRI, and in patient with negative result of MRI the tumor in the tail of pancreas was revealed. Data of intraoperative revision were confirmed by the pathomorphological investigation in all patients. The immunomorphological features of insulin-producing tumor were revealed in 23 patients (96%) and in one patient the solid pseudopapillary tumor was diagnosed, in accordance with data of MSCT. Thus, the sensitivity of MRI without CE and CE-MSCT in detection of pancreatic tumors (reference is the localization according to intraoperative revision) is identical (96%), 95% confidence interval (79%; 100%). The sensitivity of methods in identifying the origin of tissue (reference is the result of histological investigation) is also not statistically different – 96% (79%; 100%) and 100% (86%; 100%) respectively.
Conclusion
MRI without CE and CE-MSCT are equivalent highly sensitive methods of topical diagnosis of insulin-producing neuroendocrine pancreatic tumors, but MRI without CE has additional advantages: the lack of ionizing radiation and necessity for contrast agents administration. Thus, for diagnosis of insulinoma it is advisable to use the MRI without CE as the first-line imaging modality, and the CE-MSCT should be used in difficult cases as additional method.
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P52

Exome analysis of pituitary adenoma tissue derived cell cultures

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Introduction
Pituitary adenomas (PA) are tumours of the anterior pituitary. Despite the benign nature these neoplasms cause increased mortality and morbidity. Clinically relevant PAs affect around 0.1% of population during their lifetime. Currently, there is no human PA cell culture models. Tissue cultures derived from PA surgery materials depending on harvesting conditions can form free floating aggregates called pituispheres (PS) or adherent mesenchymal stromal cells (MSC). We studied genetic relationship between patients’ germline DNA, tumour tissue somatic DNA, DNA of PS and MSC obtained from culture of primary surgery material to investigate usability of these culture cells as human PA model.
Methods
Five PA patients were enrolled to national biobank – Genome Database of Latvian Population from Pauls Stradins Clinical University Hospital where transsphenoidal surgery of PA was performed for all patients. Germline DNA was isolated from white blood cells using phenol-chloroform method, tumour somatic DNS was isolated using AllPrep DNA/RNA Mini Kit (Qiagen, Netherlands). To obtain PS primary PA tissue material was harvested using EGF, FGF, and B-27 supplement methodology, but adherent MSCs were developed using DMEM/serum supplemented culturing. PS and MSC were used as DNA source in whole genome amplification (WGA) to obtain sufficient DNA for library preparation. Exomes (Illumina TruSeq_Rapid_Exome_TargetedRegions_v1.2) of germline, tumour somatic, PS and MSC were sequenced using Illumina NextSeq with 75bp paired end reads. Sequencing data were analyzed with Illumina Basespace Enrichment App (v3.0.0) aligning to human HG19 reference genome using Isaac Genome Alignment Software, variants called with Starling algorithm and variants annotated with Illumina Annotation Engine. Filtered variants were reviewed using IGV 2.3.14.
Results
Germline and somatic DNA sequencing captured median 98.4% of the target regions (range 96.4–99.0%). WGA region capture was lower with median 95.6% (range 79.6–99.2%). Variation analysis revealed low amount of somatic mutations (median 4, range 0–5) in the PAs. Somatic mutations of the primary tumour can be detected in the respective PS, but not in the respective MSC. Genetic alterations of MSCs corresponded to mutations in PA patients’ germline DNA.
Conclusions
For the first time we show that genome of PS represents genome of PA while MSC derived from the same primary surgery material does not contain PA characterizing mutations in their genome therefore most likely representing normal cells of pituitary or surrounding tissues. This indicates that PS can be used as a model to study PAs.

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P53

A rare association of neuroendocrine tumor with adenocarcinoma of ampulla of vater: difficulties for diagnosis and effects of multi therapeutic approach

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Introduction
The neuroendocrine tumor of the ampulla of Vater represent a very rare disease, corresponding up to 2% of the periampullary malignancies and less than 1% of gastrointestinal NET. Less than 130 patients have been reported until 2013. The biological and clinical behavior is very unpredictable especially if it’s associated with another tumor, like adenocarcinoma. We present a case of a fifty-one-years-old woman who complained of weight loss, jaundice, abdominal pain and anemia. MR-cholangiography revealed an ampullary ulcerated tumor with duodenal invasion, Forrest IIA and biopsy and endoscopic hemostasis was practiced. Also

multiple liver tumors were described, the larger one in segment III, about 6 cm. The patient underwent a Whipple procedure and hepatectomy in segments II-III for bulky necrotic metastases. The immunohistochemical study of the neoplasia showed the expression of chromogranin A, synaptophysin, CD56 and also cytokeratin7, CEAm, CA19-9, beta-catenine with a proliferation index Ki67-12%. The TNM classification was pT3N1M1a- stage IV and by WHO was NET well differentiated G2 with adenocarcinoma associated (<10%), non-MANEC. The evolutive CT revealed incomplete thrombosis of right hepatic artery and the Octreoscan showed multiple bone metastases. The patient started chemotherapy with Capecitabine, Lanreotide and Zoledronic acid for bone metastases. Because of the elevated serum markers (chromogranin A, neuron specific enolase, carcinoembryonic antigen), postsurgical complications (acute superior digestive hemorrhage) and disseminated disease (liver, bones) the patient was recommended undergo radioisotope therapy cycle with Lutetium 171/Yttrium 90 in Europe, therapy not currently available in Romania. The particularity of this case of ampullary neuroendocrine tumor associated with adenocarcinoma make more insidious the progress and worsen prognosis of the disease, by being difficult to predict the effects of multisystemic therapy- chemotherapy, somatostatin analogs and newly, peptide receptor-targeted radiotherapy.
Conclusions
Although neuroendocrine tumors of the ampulla of Vater represents a rare disease, it has been increasingly reported in the last years. Radical surgery should be the standard approach. The presence of distant metastases is the most important prognostic factor in determining survival.

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P54

Continuous glucose monitoring during the prolonged fast test for the diagnosis of hypoglycemic diseases: primary data analysis

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Introduction
To diagnose the hypoglycemic diseases (HD), firstly, proving the hypoglycemia presence is necessary. For this purpose, the prolonged fast test, which can reach 72 h, is performed. In case of late completion this test has a potential risk of hypoglycemic coma. Repeated glycemia control by glucometer brings discomfort to patients and increases the labor costs of medical workers. In this regard, it was relevant to conduct a study on the comparison of continuous glucose monitoring by portative system (CGMS) in interstitial fluid and regular glucose monitoring by glucometer in capillary blood.
Methods
We performed the fast test in 38 patients aged 18–72 years with suspicion of HD. In the ranges of glycemia 2.6–3.0 and 2.2–2.5 according to glucometer data and at the time of finishing the test we fixed the glycemia according to CGMS data and took the venous blood. We estimated the CGMS accuracy in relation to venous glycemia and glucometer data: in normoglycemia (venous glycemia more than 3 mmol/l), in hypoglycemia (venous glycemia 3 mmol/l and less). The comparative estimation of financial cost and labor costs (CGMS calibration and glycemia determination by glucometer) was performed. We compared the test duration: actual and hypothetical (provided that completion criteria were determined in accordance with CGMS data - glycemia less than 2.8 mmol/l).
Results
Mean deviation of CGMS indicators compared to laboratory values in normoglycemia is +0.57, in hypoglycemia is +0.9; compared to glucometer: in normoglycemia is +0.14, in hypoglycemia is +0.59. Mean actual test duration in patients with confirmed HD ($n=25$) is 35.3 h, mean hypothetical test duration is 19.3 h. Mean frequency of CGMS calibration is 2.2 per day, mean frequency of glycemia determination by glucometer is 7.2 per day. Taking into account the cost of in-patient stay in a hospital, sensors for CGMS, test strips for glucometer, the expenses of measuring glucose by CGMS and by glucometer do not differ significantly.
Conclusion
The CGMS accuracy is higher in high glycemia and comparable to a glucometer. Using CGMS has the same financial cost like glucometer using. The CGMS timely warns about glycemia decreasing. CGMS reduces the labor costs and, in certain conditions, decreases the test duration. Doctors can orientate on CGMS indicators given the fact of their overstatement. We need to accumulate data for the final conclusion and recommendations for using CGMS in diagnosis of HD.
Funding
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P55

Clinical case of a repeated life-threatening upper gastrointestinal bleeding due to previously unknown primary hyperparathyroidism

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Background
Peptic ulcer bleeding due to primary hyperparathyroidism is extremely rare and only a few cases have been reported in the literature.
Material and methods
Man with repeated upper gastrointestinal bleeding, with a history of kidney stones and previously unknown primary hyperparathyroidism.
Case
Man M., 46 y.o., with a history of 4 episodes of gastrointestinal bleeding and a ten-year history of multiple kidney stones. In 2014 resection of the stomach with Roux anastomosis was conducted to arrest the hemorrhages. High level of calcium was first diagnosed. However, he had been consistently treated for ulcer and kidney stones without any further work-up. In 2018 in the therapeutic department with ulcer rebleeding: PTH – 48.7 pmol/l (1.7–6.4), calcium – 3.06 mmol/l (2.2–2.65), phosphorus – 0.8 mmol/l (0.81–1.45). Primary hyperparathyroidism was confirmed. On a neck and abdomen CT scan with contrast: two parathyroid adenomas (larger mass size 7×12×15 mm), adenoma of the right adrenal gland (18×15×21 mm) and polycystic kidney disease. Urine metanephrine – 709 μg/24 hours (20–345) and normetanephrine – 507.3 μg/24 hours (30–440), GFR level –46 ml/min/1.73 m^2. MRI performed and pituitary adenoma (10×8×9 mm) was found. After laboratory evaluation prolactinoma was diagnosed (PRL – 5925 mE/l (72–229). Gastrinoma was also supposed because of repeated GI-bleeding. An immunohistochemistry analysis of stomach sample from 2014 revealed neuroendocrine pancreatic tumor Ki67-25% (PPoma). Genetic examination was performed: result in processing. Parathyroidectomy and adrenalectomy were performed. Postoperatively, calcium and PTH levels were normalized. The ulcer healed – 3 months after parathyroidectomy.
Conclusion
The serum calcium level and PTH level must be considered routine tests in patients with a peptic ulcer bleeding, especially when it is accompanied by a history of kidney stones and repeated gastrointestinal bleeding.
Keywords: primary hyperparathyroidism, neuroendocrine, multiple endocrine neoplasia.

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P56

A difficult diagnosis: pheochromocytoma or methamphetamine abuse?

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Introduction
Pheochromocytomas represent rare but potential lethal tumors arising from the adrenal medulla. Early recognition and diagnosis represent a challenge due to the non-specific character of signs and symptoms. The classic presentation includes headache, sweating, palpitations and other signs and symptoms of apparent catecholamine excess occurring in paroxysms. Sympathomimetics may result in a similar presentation, potentially complicating the diagnosis.
Clinical case
We report the case of a 35-year old male with a 17-year history of drug addiction. For a long time, he complained of daily short spells of severe headache, nausea, vomiting, profuse sweating, palpitations, pallor, anxiety, tremor and constipation that were present even though the patient claimed to have given up his amphetamine addiction 18 months before referral to our clinic. During that 18-month period the patient was prescribed escitalopram, which was reported to amplify the intensity of symptoms. The patient was without a history of hypertension or other comorbidities but reported lumbar pain and digestive complaints. Due to the latter complaints, his general practitioner performed an ultrasound, which revealed a large mass in the region of the right adrenal. A 5 cm adrenal mass was confirmed by magnetic resonance imaging and the patient was referred to the Departments of Urology for adrenalectomy and Endocrinology to exclude hormonal activity. Twenty-four-hour blood pressure monitoring revealed episodic hypertension, tachycardia, and no nocturnal dipping, while biochemical

testing revealed a plasma metanephrine of 2111 pg/ml (N < 84 pg/ml) and normetanephrine of 701 pg/ml (N < 125 pg/ml). This was interpreted as unlikely to reflect amphetamine abuse. The tumor was confirmed after surgical resection by pathology. All signs and symptoms were resolved after adrenalectomy.
Discussion
In this patient, the almost complete constellation of typical signs and symptoms of a catecholamine-producing tumor was possibly ignored for some time due to the long history of amphetamine abuse. The presence of the tumor was only discovered incidentally due to abdominal complaints. It is unlikely that the persistent signs and symptoms were due to continued use of methamphetamine since all signs and symptoms completely resolved after removal of the tumor.

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P57

Association of the BclI glucocorticoid receptor polymorphism with body composition and metabolic parameters in female patients with adrenal incidentalomas

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Interindividual variations in tissue sensitivity to glucocorticoids (GC) have been partly attributed to polymorphisms in the glucocorticoid receptor (GR) gene. The aim of this study was to investigate whether *Bcl*I variant of the GR gene may contribute to metabolic abnormalities frequently present in patients with adrenal incidentaloma (AI). Biochemical tests and hormonal evaluation were performed in 106 consecutive women with AI. Non-diabetic patients underwent an oral glucose tolerance test with 75g glucose. Insulin resistance was assessed by homeostasis model assessment (HOMA-IR) index. The hypothalamic-pituitary-adrenal axis (HPA) activity was evaluated using the dexamethasone suppression *tests* (DST). Body composition was measured with dual-energy X-ray absorptiometry. DNA was obtained from peripheral blood leucocytes. The polymorphism was detected using PCR, RFLP and DNA sequencing. Carriers of the C allele of *Bcl*I had significantly less suppression of cortisol levels after 0.5 mg dexametasone (126.4 ± 111.4 *vs* 80.9 ± 75.7 nmol/l, $P = 0.026$). Post low-dose DST cortisol levels negatively correlated with appendicular skeletal muscle mass (AMSS) ($r = -0.023$, $P = 0.004$). 24-h urinary free cortisol level inversely correlated with total lean body mass (TLBM) ($r = -0.196$, $P = 0.007$) and lag fat mass ($r = -0.430$, $P = 0.016$). Fasting glucose (4.5 ± 0.6 *vs* 4.8 ± 0.8, $P = 0.046$) and the 2-h post-challenge glucose levels (5.4 ± 1.5 *vs* 6.7 ± 2.6, $P = 0.010$) were lower in carriers than non-carriers, as well as prevalence of type 2 diabetes mellitus (T2DM) (9.1% *vs* 26%, $P = 0.034$) and impaired glucose tolerance (IGT) (2.6% *vs* 17.5%, $P = 0.031$). We observed no differences in mean age (57 ± 9.6 *vs* 56.5 ± 11.8, $P = 0.823$), BMI (29.3 ± 6.0 *vs* 28.0 ± 6.5, $P = 0.316$), abdominal fat mass, dyslipidemia, HOMA-IR and hypertension. *BclI* polymorphism negatively correlated with T2DM ($r = -0.219$, $P = 0.034$), IGT ($r = -0.245$, $P = 0.031$), TLBM ($r = -0.232$, $P = 0.037$), ASMM ($r = -0.319$, $P = 0.004$), and positively correlated with percentage of leg fat ($r = 0.221$, $P = 0.047$). Our results indicate intra-individual tissue-specific sensitivity to GC. *BclI* polymorphism has been associated with relative GC resistance of the HPA axis and peripheral fat tissue, and GC hypersensitivity at the muscle level. Insulin sensitivity and glucose homeostasis could be possibly modulated by muscle and leg fat masses. This polymorphism has a protective role and reduces the risk of diabetes in women with AI, particularly in a state of subtle cortisol excess.

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P58

A case of Von Hippel-Lindau disease with bilateral pheochromocytoma and ectopic hypersecretion of intact parathyroid hormone

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Introduction
Von Hippel-Lindau (VHL) disease is an autosomal dominant inherited syndrome predisposing to a variety of highly vascularised tumors in different organs. Although bilateral pheochromocytoma was reported in patient with VHL disease, the coexistence of primary hyperparathyroidism is not a common condition. Herein we report a case of a primary hyperparathyroidism secondary to an ectopic secretion of intact parathyroid hormone (PTH) in a patient with VHL disease and bilateral pheochromocytomas.
Observation
A 17-year-old woman was referred to our department for exploration of a newly diagnosed diabetes mellitus with severe arterial hypertension. Her past medical history was unremarkable. As symptoms, she had headaches, palpitations and hot flashes. On examination, she had a body mass index of 21 kg/m^2, a blood pressure of 200/100 mmHg, a regular pulse of 120 bpm and multiple café-au-lait spots. Thyroid exam was normal. Blood tests disclosed hypercalcemia (111 mg/l, normal range: 85–105) with increased intact PTH level (182 pg/ml, normal range: 10–65) consisting with the diagnosis of primary hyperparathyroidism. 24-hour urinary nor*metanephrine* level was elevated (3150 µg/24h, normal range: 30–440) pointing to a catecholamine-secreting tumor. Thyroid functions, 25 OH vitamin D and calcitonin tests were normal. The abdominal computed tomography showed two adrenal masses; the first in the right measuring 35 * 55 * 70 mm with a spontaneous density of 130 UH enhanced in the arterial time heterogeneously showing areas of necrosis with an absolute washout of 40%, the second in the left measuring 24 * 27 mm and is well limited. MIBG scintigraphy exhibited a high accumulation of tracer in both adrenal tumors. Cervical ultrasound and (99mTc)-sestamibi scintigraphy were normal. Genetic testing revealed a mutation of the VHL gene. After medical preparation, patient underwent a bilateral adrenalectomy and the pathological examination confirmed bilateral adrenal pheochromocytoma. The postoperative evolution was marked by the spontaneous normalization of calcium and PTH levels.
Discussion and conclusion
Coexisting pheochromocytoma and primary hyperparathyroidism usually occurs as a part of multiple endocrine neoplasia and was rarely reported in VHL disease. In our case, the elevation of intact PTH and its spontaneous normalization after surgical treatment of pheochromocytoma confirm its ectopic secretion. Therefore, we consider that controlling calcium and PTH levels postoperatively remains useful if the topographic assessment of primary hyperparathyroidism associated with pheochromocytoma was negative.

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P59

Adrenal pheocromocytoma during childhood – a case report

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Pheochromocytoma is a rare tumor made up of chromaffin cells from the adrenal medulla that secrete catecholamines. It can occur at any age, with a peak incidence between the fourth and fifth decade of life, and only 10% of cases occur in children. The majority of cases are sporadic and approximately 10% are malignant. The existence of familial syndrome, multiple or extra adrenal tumors is more common at younger ages. The clinic is very variable, and hypertension (HTA) is the most frequent manifestation (90% of cases). We present a case report of a 15-year-old girl with no relevant personal history taken to the Emergency Department with complaints of intense headaches with progressive aggravation accompanied by visual disturbances. At physical evaluation, she was hypertensive and the ophthalmologic observation revealed severe hypertensive retinopathy. There was no family history of hypertension, or use of oral contraception. Laboratory tests showed elevation of urinary metanephrines (1302.2 ug/24h N: 64–302), urinary normetanephrines (4178.1 ug /24 h, N: 162–527), serum cromogranin A (47.7 mmol/l N < 3) and parathyroid hormone (PTH) (111.5 pg/ml, N: 15–65); normal calcium and calcitonin; and vitamin D deficiency. Abdominal CT revealed a 6.5 × 5.3 × 6 cm mass in the left adrenal gland, with nodular morphology and regular contours. MIBG scintigraphy was compatible with a tumor of cells derived from the neural crest at the left adrenal gland without other images of uptake. The patient underwent a left laparoscopic supradrenalectomy, and the histology confirmed the diagnosis of pheochromocytoma. Genetic study was negative for mutations of the RET, SDHB, SDHD and VHL genes. In the last evaluation, the patient was asymptomatic, normotensive and without biochemical or imagiologic evidence of the disease. Although unusual, it is intended with this case to recall the importance of considering the diagnosis of pheochromocytoma in the investigation of hypertension in the child/adolescent. It is a treatable cause of hypertension and potentially lethal if not diagnosed in a timely manner. Family syndromes should always be excluded in this age group.

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P60

Adrenal morphology in a large cohort of adult subjects with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Introduction
The adrenal morphology in congenital adrenal hyperplasia (CAH) is poorly described in the literature, so that adrenal radiological evaluation is not recommended in patients with CAH. The aim of this study was to evaluate the adrenal morphology in a large cohort of adult patients with CAH due to 21-hydroxylase deficiency and its correlation with the subtype of CAH (non-classical-NCAH, simple virilizing-SV, or salt wasting-SW), the hormonal status and the treatment regimen, respectively.
Methods
We conducted a retrospective study on a population of 96 adult CAH patients in care at our Endocrinology Unit since 2002; 54 patients had the NCAH, 12 the SV and 30 the SW form. At the first visit all patients performed an abdominal Computed Tomography (CT) prior to and after administration of the contrast medium. Clinical parameters, hormonal status and the cumulative dose of glucocorticoid therapy in pediatric agewere analyzed.
Results
Based on CT scan, 51 patients (53%) resulted with normal (NM group) and 45 (47%) with abnormal adrenal morphology (AM group), of which 40 subjects (89%) had micronodular hyperplasia (microH subgroup), whereas 5 (11%) had macronodular hyperplasia (macroH subgroup). ACTH and 17OH-progesterone measured at the time of the CT scan and the cumulative dose of hydrocortisone taken by the time of the diagnosis differed between NM and AM groups. In particular, ACTH levels were 31.8 ± 5.7 pg/ml in NM group and 70.4 ± 11.5 pg/ml in AM group (P value <0.01); 17OH-progesterone levels were 1344 ± 396 ng/dl in NM group and 3342 ± 746 ng/dl in AM group (P value <0.05); and the cumulative dose of hydrocortisone was 104.6 ± 6.6 g in NM group and 68.5 ± 8.1 g in AM group (P value <0.05). When analyzed according to the subgroups, ACTH levels were 65.1 ± 10.6 pg/ml in microH subgroup and 112.6 ± 62.7 pg/ml in macroH subgroup (P value <0.01); 17OH-progesterone levels were 3038 ± 647 ng/dl in microH subgroup and 5773 ± 4559 ng/dl in macroH subgroup (P value <0.01); and the cumulative dose of hydrocortisone was 58.7 ± 7.4 g in microH subgroup and 141.4 ± 29.4 g in macroH subgroup (P value <0.05).
Conclusions
The insufficient treatment of CAH seems to be associated with adrenal hyperplasia and its progression towards adrenal micro and macronodules. Clinicians should be aware that an evaluation of adrenal morphology is recommended in these adult patients, regardless of the subtype of CAH.

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Calcium and Bone 1

P61

Vitamin D status and linear growth in a sample of Egyptian adolescents

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Vitamin D deficiency is a worldwide health problem. The lack of appreciation of the importance of sensible sun exposure for providing children and adults with their vitamin D requirement has led to a worldwide vitamin D deficiency pandemic,vitamin D deficiency can have a negative influence on bone development, causing not only rickets, but also interfering with attainment of genetically programmed height.
Aim of the study
To assess vitamin D status among healthy egyptian adolescents and its relation to height percentile.
Methods
Our study was conducted on 180 healthy adolescent males and females aged 10–19 years, Subjects with chronic systemic diseases and those with height <2 S.D. below the mean of their age were excluded from our study, detailed history including sun exposure, dietary pattern, socioeconomic status, physical and anthropometric evaluation, Laboratory investigations including: Hb concentration, serum creatinine, Serum albumin, corrected serum total calcium, serum phosphorus, serum 25 hydroxy-vitamin D level by Elisa.
Results
The prevalence of vitamin D deficiency was 142 out of 180 (78.9%), 88 out of 180 (48.89%) had moderate deficiency (10–20 ng/ml, this was significantly higher among females, mean serum 25 (OH) D3 level was 22.45 ± 9.114, therewas a positive significant correlation between vitamin D level and stature for age percentile ($r=0.174$) ($P=0.019$).
Conclusion
Subclinical vitamin D insufficiency and deficiency are common problems in apparently healthy Egyptian adolescents with negative impact on height percentile.

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P62

The effectiveness of colecalciferol and selective vitamin D receptor agonists treatment on secondary hyperparathyroidism in chronic kidney diseases patients

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Background
Secondary hyperparathyroidism (SHPT) is an early complication of chronic kidney disease (CKD). Maintaining the level of 25(OH)D and parathyroid hormone concentrations in the target range reduce its associated complications (fractures and cardiovascular calcification).
Aims
To examine the effectiveness of vitamin D supplementation and selective vitamin D receptor agonists treatment on SHPT in CKD.
Materials and methods
Prospective observational study to evaluate the efficacy and safety of vitamin D therapy SHPT in 54 in patients with CKD. The first phase (24 weeks) – treatment of suboptimal 25-hydroxycalciferol (25(OH)D) levels. The second (16 weeks) – treatment colecalciferol-resistant SHPT by combination of cholecalciferol with paricalcitol. Blood samples were taken to assess parathyroid hormone (PTH), 25(OH)D, creatinine, calcium, phosphorus levels and calcium excretion.
Results
After 8 weeks of cholecalciferol treatment all patients achieved 25(OH)D levels above 20 ng/ml, however 78% of patients still had SHPT. After 16 weeks, the decrease of PTH was achieved in all patients, but significantly only in patients with CKD 2 (19.2%, $P<0.01$) and 3 (31%, $P<0.05$), compared with CKD 4 (17%, $P>0.05$). After 24 weeks of therapy, PTH normalized in all patients with CKD 2, in 15 (79%) with CKD 3 and in 9 (50%) patients with CKD 4. Cholecalciferol treatment resulted in a substantial increase in 25(OH)D levels with minimal or no impact on calcium, phosphorus levels and kidney function. After 24 weeks we initiated combination therapy (cholecalciferol and paricalcitol) for patients with colecalciferol-resistant SHPT ($n=13$). PTH levels decreased from 149.1 ± 13.4 to 118.2 ± 14.1 pg/ml at 8 weeks, and to 93.1 ± 9.7 pg/ml ($P<0.05$) at 16 weeks of treatment. No significant differences in serum calcium, phosphorus or urinary calcium levels. Normalization of PTH was achieved in all patients with CKD 3 and in 8 patients with stage 4. One patient with CKD 4 needed an increase in paricalcitol dose.
Conclusions
Cholecalciferol can be used in correcting vitamin D deficiency in patients with all stages of CKD, however, its effectiveness in reducing PTH in stage 4 is limited. Selective analogs, such as paricalcitol, were well-tolerated and effectively decreased PTH levels.

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P63

Osteoporosis in developing-nations: need for centralized-data-collection & treatment-guidance centers to study epidemiology

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Issues
This is non-interventional, Demographic, observational study in asian population. Osteoporosis common in Developing-nations. Not-a-single Center exist designated for diagnosis/treatment. No proper epidemiological, mortality/

morbidity data available. In asian population Osteoporosis is diagnosed at advanced stage hence poor-prognosis. Worsened by High incidence of malnourished. Increased awareness/improved diagnosis needed to identify cases.
Aim
To study osteoporosis treatment issues by survey among 40 endocrine practitioners.
Methodology
$n=40$, survey questionnaire distributed among these 40 endocrine practitioners. 27 from private clinics and 13 from government hospitals. From July 2016 to April 2017 all responses evaluated and suggestions compiled.
Current therapy problems
High incidence of crude-tobacco-smoking in Asian countries increases osteoporosis-rate. Therapy restricted to supportive care, as diet-modification. Treatment drugs needs to be provided at subsidized cost to rural/tribal areas to decrease Osteoporosis related fractures mortality. Lack of diagnosis, Rx-expertise in rural/tribal india makes poor Rx-Outcome. We need national-Osteoporosis-registry, educate doctors about diagnosis/treatment to improve QOL. Treatment-cost non-affordable to majority sufferers.
Conclusion
Alternative Therapies as antioxidants gaining reputation in endocrine disorders. we patient advocates from NGO's working in rural/tribal areas of developing-nations can collaborate with Osteoporosis-care-centers from USA-Europe for training/upgrading staff. we participants need collaboration with ESE in research-projects in resource-poor-nations. We asian-representatives need exposure to research methodologies used by European-experts in endocrinolohy. Our institute working since 2007 on health-education & Osteoporosis prevention intends to raise these issues at congress venue.

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P64

Prevalence and the main risk factors for vitamin D deficiency in pregnant women living in a locality of Algiers

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Introduction
Vitamin D deficiency seems to be common in pregnant women and would be associated with an increased risk of maternal and fetal poor outcomes.
Aim of the study
Determine the prevalence and the main risk factors for vitamin D deficiency in pregnant women living in a locality of Algiers.
Material and method
It is a cross-sectional prospective and descriptive study. 310 pregnant women of west Algiers were followed during their pregnancy, by Plasma 25-hydroxyvitamin D (25-OHD) sampling between 24 and 28 weeks of amenorrhea and a second one between 37 and 40 weeks. An univariate and a logistic regression test was assessed to identify potential factors for vitamin D deficiency, and an univariate analysis to assess impact of this deficiency on the course of the pregnancy and on the newborn.
Results
We have followed 310 pregnant women with a mean age of 30.36 ± 5.38 years. Mean BMI is 26.67 ± 4.49 kg/m^2. Mean plasmatic level of Vitamin D in the second trimester of pregnancy is 7.80 ± 5.06 ng/ml 4–33.6 ng/ml. 96.1% of pregnant women had levels of vitamin D under 20 ng/ml; 88.7% levels of vitamin D under 12 ng/ml, and a severe deficiency under 5 ng/ml in 27.1% of the women. The same results are found at the end of the pregnancy with a mean level of vitamin D of 7.39 ± 5.11 ng/ml 4–42,4 ng/ml. 96.2% of the pregnant women have a vitamin D level inferior to 20 ng/ml, 89.3% inferior to 12 ng/ml, and a severe deficiency in 33.8% of the cohort. The daily dietary intake of vitamin D is estimated at 260.00 ± 254.80 UI/j, clearly lower than the recommended dose. Vitamin D deficiency risks factors founded in the logistic regression analyse are seasons of low sunshine, ORa 3,116, IC à 95% 1,524–6,371, $P=0{,}002$, the wear of covering clothes ORa 13,131(IC à 95%: 4,084–42,217), $P<10^{-3}$, and non vitamin D supplementation during pregnancy ORa 5,841(IC à 95% 2,890–13,105) $P<10^{-3}$. We did not find any statistic link between vitamin D deficiency and obstetric complications: pre-eclampsia, gestational diabetes, premature delivery and Caesarean Delivery. Neither the link with low birth weight and neonatal hypocalcaemia.
Conclusion
It is the First study evaluating the status of vitamin D in pregnant women carried out in Algeria. High prevalence of vitamin D deficiency indicates the need for urgent implementation of national recommendations.

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P65

Effects of dexamethasone for calcium channels and mucin-related genes regulation on A549 cell line

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Calcium is important for physiological functioning in many tissues and is essential in mucus secretion. Previously reported, Mucin secretion is regulated predominantly by cytosolic calcium-dependent pathways. Cytosolic of calcium are regulated by calcium channels such as TRPV6, NCX1, and PMCA1. A549 cell line was treated with 10^{-8} M dexamethasone (DEX) and 10^{-6} M RU486. Subsequently, the expression of TRPV6, NCX1, and PMCA1 in A549 cell line were examined. There was no significant differences in PMCA1 expressions in DEX-treated groups, but TRPV6 was increased in DEX-treated groups and was recovered by DEX + RU486 treatment. NCX1 was decreased in DEX-treated groups and was recovered by RU486 treatment. In addition, mucin secretion, related genes MUC4 and MUC5AC, was also decreased by DEX treatment. Control of calcium channel gene expression may affect the control of mucus secretion in the lung cancer. These results could be used for understanding the basis of treatment mucin secretion related disease such as cancer.

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P66

Regulatory effect of dexamethasone on tracheal calcium processing proteins and mucosal secretion

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Introduction
Dexamethasone inhibits mucin secretion considering the primary option for treating acute asthma exacerbation. However, the mechanism underlying dexamethasone-induced decreased in mucosecretion is unclear. Recent studies have reported that dexamethasone exerts an inhibitory effect on mucosecretion in the lung by modulating the expression of calcium-processing genes. However, the expression of the calcium-processing genes in trachea are not examined yet. Thus, the present study is the first to report glucocorticoid-induced regulation of calcium processing genes such as transient receptor potential vanilloid-4 (*Trpv4*), transient receptor potential vanilloid-6 (*Trpv6*), calbindin-D_{9k} (*CaBP-9k*), and plasma membrane Ca^{2+}-ATPase (*Pmca1*) in the mouse trachea.
Materials and methods
In this study, mice were subcutaneously injected with dexamethasone for 5 days, or injected with estradiol or progesterone for 3 days. The tracheal tissues were collected by dividing the trachea into cervical and thoracic sections based on its anatomical structure. Real-time PCR was performed to investigate mRNA expression of calcium-processing genes. Immunohistochemistry and immuno-fluorescence were performed to localize the calcium-processing proteins. Tracheal mucosubstances were detected by performing Alcian blue-periodic acid-Schiff staining.
Results
The localization of TRPV4, TRPV6, CaBP-9k, and PMCA1 proteins was detected in the tracheal epithelium, submucosal glands, cartilages and muscles. Dexamethasone treatment downregulated the mRNA expression of the four calcium-processing genes and mucin 1, mucin 4, mucin 5ac, and mucin 5b genes. Dexamethasone decrease in the secretion of mucosubstances in the trachea.
Conclusions
The findings of the present study suggest that glucocorticoids regulate the tracheal expression of calcium-processing genes and tracheal mucosecretion.

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P67

The effect of steroid hormone on the expression of the calcium-processing proteins in the immature rat brain

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The cytosolic calcium concentration is regulated by calcium-processing proteins such as transient receptor potential cation channel subfamily V member 5 (TRPV5), TRPV6, sodium-calcium exchanger 1 (NCX1) and plasma membrane Ca^{2+} ATPase 1 (PMCA1). Those calcium-processing proteins are important for physiological functions in the brain. The effects of steroid hormones on

calcium-processing protein expressions in the brains are undescribed. Thus, the effects of steroid hormones on the distribution, localization, and expressions of calcium-processing proteins in the brain were analyzed. Immature female rats were injected for 5 days with estrogen (E2), progesterone (P4), dexamethasone (DEX), and their antagonists (ICI 182,780 and RU486). The localization and expression of calcium-processing proteins in rat brain were observed by immunofluorescence and western blot analyses, respectively. We found that TRPV5 and TRPV6 proteins were highly expressed in the cerebral cortex (CT), hypothalamus (HY), and brain stem (BS) compared to that in the olfactory bulb (OB) and cerebellum (CB). Also, the NCX1 protein was highly expressed in CT and BS compared to that in OB, HY, and CB, and PMCA1 protein was highly expressed in CT compared to that in other brain regions. Furthermore, expression levels of TRPV5, TRPV6, NCX1, and PMCA1 proteins were regulated by E2, P4, and/or DEX in the CT and HY. In summary, calcium-processing proteins are widely expressed in the immature rat brain, and expressions of calcium-processing proteins in CT and HY are regulated by E2, P4, and/or DEX and can be recovered by antagonist treatment. These results indicate that steroid hormone regulation of TRPV5, TRPV6, NCX1, and PMCA1 proteins may serve as a critical regulator of cytosolic calcium absorption and release in the brain.

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Distribution of and steroid hormone effects on calbindin-D9k in the immature rat brain

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Calbindin-D_{9k} (CaBP-9k), one of the major calcium-binding and calcium-buffering proteins, is important in the physiological functioning of organs. The neuroanatomical localization of CaBP-9k in the rodent brain has not been reported; thus, this study investigated the neuroanatomical distribution of CaBP-9k and the regulation of CaBP-9k expression on steroid hormones in the immature rat brain. To confirm the influence of steroid hormones on CaBP-9k expression, immature female rats were injected for 5 days with estrogen (E2), progesterone (P4), dexamethasone (DEX), and their antagonists (ICI 182, 780 and RU486). The localization and expression of the CaBP-9k protein in brain regions were identified by immunofluorescence and western blot assays, respectively. We observed that CaBP-9k expression was especially strong in hypothalamus, cerebellum, and brain stem. In addition, CaBP-9k was colocalized with mature-, GABAergic, dopaminergic, and oxytocinergic neurons. We also observed that the CaBP-9k protein level was significantly increased by P4 and reversed by antagonist RU486 treatment in immature rat brain. In summary, CaBP-9k positive cells have a wide distribution in the immature rat brain, and CaBP-9k expression is regulated by P4. We suggest that CaBP-9k regulated by steroid hormone may serve as an important regulator of cytosolic calcium concentration in the brain.

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Pledoary for using Trabecular Bone Score as a method for osteoporosis diagnosis, not only for the risk

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Introduction
Trabecular bone score (TBS) was introduced in FRAX, to evaluate more precisely the risk for fracture. However, FRAX is a method for editing a risk, not for making a diagnosis. WHO established conventionally, based on the level of standard deviation (SD), named T score, for Bone Mineral Density (BMD) that $< -2,5$ SD is compatible with the diagnosis of osteoporosis.
Aim
Our aim was to analyze if it is possible to used T score (SD) for TBS in the diagnosis of vertebral osteoporosis, in the same manner, i.e. conventionally, as it is used BMD. Two arguments could sustain our goal: 1. since the predictive ability to show the fractures of TBS is independent of FRAX clinical risk factors and femoral neck BMD; and 2. the calculated probabilities for fracture have been shown to be more accurate when classical FRAX was computed with TBS.
Method
1. DEXA machine - GE-Lunar Prodigy Pro #500074. TBS soft - TBS iNsight®, version 3.0.2.0. 2. There were registered 4 TBS/BMD T scores: a. the highest T scores; b. the lowest TBS T score; c. BMD T scores corresponding to 'a' and, respectively, 'b'. 3. T test was performed for analyzing the difference between scores. 4. Conventionally - 2,5, and -1 T scores were used for an interference graphic between TBS and BMD.
Results
A. Patients: no. 536 women: 508 men: 28 (5.22%), mean age: 65.94 years. B. T score averages: Lowest TBS: -3.48. Corresponding BMD: -1.61. Highest TBS: -1.43. Corresponding DMO: -1.32. C. T tests: for highest TBS/BMD scores: $P \ll 0.001$. For lowest TBS/BMD scores: $P = 0.19$. D. Interference graphic: a. TBS > -1: BMD $> -1 = 24/4.5\%$; BMD -1 - $-2.5 = 6/1.1\%$, BMD $< -2.5 = 4/0.7\%$. b. TBS -1 - -2.5: BMD $> -1 = 41/7.6\%$; BMD -1 - $-2.5 = 51/9.5\%$, BMD $< -2.5 = 21/3.9\%$. c. TBS < -2.5: BMD $> -1 = 69/12.9\%$ (lack of diagnostic); BMD -1 - $-2.5 = 187/34.9\%$ (lack of diagnostic), BMD $< -2.5 = 133/24.8\%$.
Conclusions
1. The lowest TBS T score was more altered than the lowest BMD T score, $P \ll 0.001$, suggesting that the vertebral microarchitecture modify before losing bone. 2. This should be the moment when considering the starting treatment. 3. When interfering TBS T score with BMD T score, it seems that 47.8% (12.9 + 34.9) of patients lack the osteoporosis diagnostic. 4. Therefore, TBS should be used as a tool for osteoporosis diagnostic not only for calculating risks.

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Relationship between leptin level, body mass index and parathyroid hormone in chronic hemodialysis patients

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Bone metabolism disorders in hemodialysed patients (HD) involve several humoral factors, of which PTH plays the central role. Leptin is a protein hormon secreted by the adipocytes and related to malnutrition, anemia and bone metabolism disorders in chronic kidney disease patients. The aim of the study was to was to evaluate serum leptin levels and bone metabolism in chronic HD patients depending on body mass index (BMI). This cross section study included 93 HD patients distributed based on BMI in: underweight ($n = 7$), normal weight ($n = 38$), overweight ($n = 38$) and obesity ($n = 10$). Underweight patients had significantly significantly lower leptin level (2.02 ± 1.7 vs 8.62 ± 10.66 vs 32.99 ± 34.52 vs 78.02 ± 51.61, $P < 0.001$), higher PTH level (686.42 ± 1100.43 vs 271.60 ± 321.47 vs 242.0 ± 271.54 vs 254.20 ± 280.68 $P < 0.001$) and higher alkalne phosphatase (156.27 ± 27.13 vs 81.92 ± 44.69 vs 84.50 ± 28.16 vs 66.70 ± 19.27, $P < 0.001$). There were no significant differance in calcium and phosphate level between groups. A significant direct correlation was observed in all groups between leptin level and BMI ($P < 0.001$) and indirect correlation between leptin and PTH level in underweight and obesity group ($P < 0.05$). Hypoleptinemia in chronic HD patients was associated with high PTH and undernutrition.

Keywords: leptin, body mass index, parathyroid hormone, hemodialysis
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P71

Challenging clinical case of primary hyperparathyroidism caused by atypical adenoma

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Introduction
Primary hyperparathyroidism (PHPT) is a frequent endocrinopathy caused mostly by parathyroid adenoma. Classic manifestations, less prevalent nowadays, may have a misleading aspect. Here we describe the case of a patient presenting nephrolithiasis, multiple brown tumors revealing PHPT.

Observation
A 37-years-old female was diagnosed with nephrolithiasis treated by shockwave lithotripsy without success. CT scan showed coralliform lithiasis in addition to multiple lytic lesion in the pelvis and the fourth lumbar spine suggestive of metastasis. Bone biopsy was done revealing a brown tumors aspect. High blood level of calcium (3.46 mmol/l) and PTH (836 pg/ml) confirmed the diagnosis of PHPT associated with low 25-Hydroxy-vitamin D concentration (11.9 ng/ml). She had constipation, bone pain, asthenia and weight loss. The neck examination showed a lateral neck tumefaction corresponding to a 3 cm nodule. The ultrasonography and MIBI scan confirmed an upper left parathyroid adenoma which was resected after a medical preparation. The anatomopathological examination found an atypical adenoma due to mitosis and necrosis. After surgery, the patient developed hypocalcemia requiring alfacalcidiol and calcium supplementation. PTH level, dropped initially after surgery to 57 pg/ml, kept increasing to 187–264 pg/ml although the normal postoperative MIBI scan and the absence of hungry bone syndrome. A molecular analysis of CDC73 gene was done since the diagnosis of parathyroid carcinoma is highly suspected.
Conclusion
Palpable parathyroid tumor, high serum calcium and PTH levels must attract attention to suspect the diagnosis of parathyroid carcinoma which remains difficult to differentiate it from atypical adenoma.

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Severe hypocalcemia: when the skin expresses itself

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Introduction
Impetigo herpetiformis is a rare dermatological disorder, mimicking generalized pustular psoriasis. It is characterized by a generalized erythema-pustular eruption accompanied by fever. Its etiopathogenesis is poorly coded but triggers have been identified such as hypocalcemia in more than half of cases and pregnancy. We report a case of severe hypocalcemia secondary to hypoparathyroidism revealed by impetigo herpetiformis.
Case report
Forty-six-year-old patient with lobo-ishmectomy at 12 years of age with iatrogenic hypoparathyroidism undergoing replacement therapy, had been presenting for 15 days erythematous cupboards which had recently confused, with a notion of stopping the ergocalciferol for 2 months. The admission examination found a febrile patient at 38.5°C with erythroderma covering more than 80% of the skin surface, strewn with afollicular pustules. The mucous membranes were spared. The neurological examination was without abnormalities. Biology revealed severe hypocalcemia at 57 mg/l, hyperphosphoremia, with PTH at 2 µg/ml (VN> 24). The ECG showed a long corrected QT space. The histological aspect was that of impetigo herpetiformis. The patient was treated with calcium infusion and 3 g/day of oral calcium and 2 microgram of ergocalciferol per day. The evolution was marked by the regression of the pustules of more than 90% of the lesions with appearance of desquamation plaques wide at the 4th day, with a complete disappearance of the lesions at the 8th day, concomitant with the correction of the calcemia.
Discussion
Impetigo Herpetiformis is a rare skin disorder. The factors implicated are mainly hypocalcemia and pregnancy, then cortisone withdrawal, topical corticosteroids with high activity under occlusive dressing, bethalactamines, lithium, stress and alcohol intoxication. Cadherins are essential for cell adhesion and these molecules are calcium-dependent. Vitamin D plays an important role in the differentiation and proliferation of skin cells.
Conclusion
All observations of amicrobial pustulosis illustrate the definite relationship between the rash and the calcium-PTH-vitamin D axis, presumably by hypocalcemia.

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P73

Ultrasound detection of parathyroid hyperplasia in patients with chronic kidney disease treated by dialysis

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Aim
The aim of this prospective study is to assess if there is any correlation between parathyroid hyperplasia detected by ultrasound and variables connected with secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) stage 5, treated by dialysis and to determine the PTH level, above which the hyperplasia of parathyroid glands could be visualized.
Methods
Thirty-one patients (14 men and 17 women) with CKD stage 5, treated by haemodialysis for more than 6 months in The University Hospital ‘St. Marina’ in Varna, Bulgaria participated in the study. There are divided in two groups according to the presence of parathyroid hyperplasia visible by high- resolution ultrasound: group 1- patients without parathyroid hyperplasia and group 2- patients with visible hyperplasia. We analysed variables such as duration of dialysis and CKD, levels of parathyroid hormone (PTH), calcium, phosphorus, calcium x phosphorus, alkaline phosphatase. In group 2 we also assessed the number of enlarged parathyroid glands, their total volume, the volume of the most enlarged parathyroid gland and the cut-off value for PTH above which the hyperplasia is visualized by ultrasound.
Results
Using a high-resolution ultrasound we detected parathyroid hyperplasia in 24 patients (77.4%). In group 2 the average PTH level is significantly higher compared to group 1 (P 0.00) with higher levels of phosphorus, calcium x phosphorus, alkaline phosphatase, duration of the CKD and time on dialysis therapy. Significant difference in alkaline phosphatase levels between the two groups is also observed (P 0.004). There is moderate significant correlation between the total volume of enlarged parathyroid glands and levels of phosphorus (r 0,443) and calcium x phosphorus (r 0.466). According to our results the level of PTH above which the hyperplasia becomes visible is 617.5 pg/ml.
Conclusions
SHPT is a relatively common abnormality seen among patients suffering from chronic kidney disease. Its early detection is very important for starting an appropriate therapy, preventing bone and cardiovascular complications.
Keywords: secondary hyperparathyroidism, chronic kidney disease, hyperplasia, ultrasound, parathyroid hormone

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Multiple fragility fractures in young female patients caused by FGF23-induced hypophoshatemic osteomalacia

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Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome of abnormal phosphate metabolism caused by a small mesenchymal tumor that secrete fibroblast growth factor 23 (FGF23). A 29-year-old female has suffered from two low-traumatic hip fractures, multiple fractures at the pelvic and sacrum, and diffuse bone pain for more than 3 years. Her mobility was limited in the last year (used crutches) because she had severe muscle weakness. Laboratory examination at the time of admission showed serum phosphate – 0.4 mmol/l (0.87–1.45), alkaline phosphatase 490 U/l (50–150), tubular reabsorption of phosphate (TRP) 45% (85–95%). Somatostatin receptor scintigraphy with 99 mTc-HYNIC-TOC revealed subcutaneous tumor in the left femur. CT scan confirmed the location of a tumor in the proximal left femur, 10×11×29 mm in size. The patient had complete recovery in phosphate levels the next day after surgical treatment, which remained within the reference range after 6 months of follow-up. The clinical improvement was evident after 3 months of observation when the patient fully restored the normal ability to walk without crutches. Histopathology confirmed mesenchymal tumor. A 34-year-old female suffered from bone pain, muscle weakness and decrease in height by 20 cm more than 8 years. At the age of 31, the patient developed two low-traumatic hip fractures and multiple vertebral fractures. The routine investigation at the time of admission revealed: serum phosphate 0.54 mmol/l (0.87–1.45), alkaline phosphatase 656 U/l (50–150), TRP 57.5% (85–95%). Somatostatin receptor scintigraphy with 99 mTc-HYNIC-TOC showed lesion in the subcutaneous tissue of left hip. CT scan confirmed the location of the tumor, 30 mm in diameter. Surgical treatment was effective for phosphate normalization and clinical improvement of the patient. Conclusion: tumor-induced osteomalatia should be suspected in young patients with fragility fractures. Serum phosphate and tubular reabsorption

phosphate measurements along with somatostatin receptor scintigraphy with 99mTc-HYNIC-TOC are sufficient for TIO diagnostics with a good prognosis after successful treatment.

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P75

Clinical significance of parathyroid incidentalomas during thyroidectomy: a South Indian experience

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Background
Often parathyroid indicentalomas (PI) in the form macroscopically enlarged single or multiple parathyroid glands are encountered during surgical thyroidectomy. The reported incidence in literature is variable (0.4–4.5%), but we feel its underreported compared to its frequency, as only less than 500 cases were reported thus far. Another enigma about PI is their clinical significance and natural history. In this context, we analysed our own experience and tried to derive lessons on its clinical relevance.
Methods
This is a retrospective study conducted in Endocrine Surgery department of tertiary care Hospital. All surgical thyroidectomies were performed by single primary endocrine surgeon. Study spanned over 10 years from 2009 to 2018. In all 2105 cases of thyroidectomies with no preoperative diagnosis of hyperparathyroidism are included in this study. A retrospective analysis was performed to identify patients in whom abnormal parathyroid tissue was removed at surgery.
Results
31/ 2105 patients (1.47%) had a single macroscopically abnormal parathyroid gland removed (29 patients) and two glands (in 2 cases) sent for histopathology. Twenty eight patients were found to have histological evidence of a parathyroid adenoma or hyperplasia. Three patients had normal parathyroid histology. Preoperatively, 26 patients had no abnormal serum calcium detected, 3 patients had raised serum calcium level and in 3 patients serum calcium testing was not done. Postoperatively, 25 patients had normal calcium, six had temporary hypocalcaemia. Two patients had temporary recurrent laryngeal nerve palsy.
Conclusions
1) We opine that the entity of PI is underreported and underinvestigated, 2) Though there is risk of removing a histologically normal gland, we believe that PI found during surgery should be excised as majority of them may be causing subclinical or early or normocalcemic hyperparathyroidism. Moreover, we have found this to be a safe procedure with minimal morbidity to the patient. By removing them at the original operation, the patient is saved complicated redo neck surgery, when clinically apparent primary hyperparthryoidism develops later, 3) The scenario of PI also emphasizes the need and provides a chance for routine clinical and biochemical evaluation for associated hyperparathyroidism in all cases of thyroid disease.

Keywords: Thyroidectomy, Parathyroid adenoma, Hyperplasia, Hypercalcemia, Calcium

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P76

Value of ultrasonography guided fine-needle-aspiration in the diagnosis of an intrathyroidal parathyroid adenoma associated with thyroid pathology

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Introduction
Intrathyroidal parathyroid adenomas (IPA) are a rare cause of primary hyperparathyroidism (PHP) and their differential diagnosis includes other parathyroid and thyroid lesions. Although $<7\%$ of parathyroid adenomas are intrathyroidal, this location represents almost 20% of ectopic cases and their preoperative identification can pose difficulties, often being an intraoperative finding.
Clinical case
A 70-year-old woman diagnosed with breast carcinoma in remission, nephrolithiasis, osteopenia, vitamin D deficiency and hypertension, was evaluated to complete the study of PHP detected in September 2016. In the laboratory tests the following was observed: calcium 12.56 mg/dl, albumin 4 g/dl, PTH 335.2 pg/ml, 25-OH-vitamin D 20 µg/l, phosphorus 2 mg/dl; renal and thyroid function were normal. The cervical CT showed 'indeterminate' hypodense thyroid nodules whose size ranges from 7 to 10 mm and the Tc99 m-sestamibi scintigraphy, a nodule in the left thyroid lobe with little probability of corresponding to a parathyroid adenoma. Therapy with cinacalcet was started but, at a 60/90 mg/day alternation, it did not control calcium and PTH, and more imaging tests were performed. In the 2nd cervical CT, 2 nodules <1 cm were identified in the right thyroid lobe and a nodular lesion of $1.2\times1.4\times2.8$ cm, with a central cystic area measuring 0.4×1.7 cm of tubular morphology and thickened walls in the left thyroid lobe. Thyroid ultrasonography-guided fine-needle-aspiration (US-FNA) showed multiple nodules <1 cm in both thyroid lobes and the nodule described in the left lobe, of $3.12\times1.26\times1.14$ cm, was heterogeneous, lobed, with thick hypoechoic halo and increased peripheral flow, and was sonographically suspicious. The cytology was compatible with parathyroid tissue and negative for malignant cells and PTH in the wash fluid was $>3{,}230$ pg/ml with a wash fluid/serum PTH ratio >18. In August 2018, left hemithyroidectomy was performed and total and ionic calcium were normal 1 day later; PTH was 3.4 pg/ml. Histopathological diagnosis: Intrathyroid parathyroid adenoma associated with nodular hyperplasia.
Discussion
In this patient, the IPA was identified by US-FNA cytology but, according to literature, this test is not always useful in recognizing the parathyroid origin of an intrathyroid nodule and PTH estimation in aspirate had an important role in diagnosis. Especially when there is concomitant thyroid pathology or it is necessary to rule out malignancy, application of both methods facilitates planning minimally invasive parathyroidectomy techniques.

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P77

The effect of parathyroidectomy on the BMD in postmenopausal women with mild primary hyperparathyroidism: the results of comparative retrospective dynamic study

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Objective
To study the effect of parathyroidectomy (PTE) on the BMD in postmenopausal women with primary hyperparathyroidism (PHPT).
Materials and methods
We studied 38 postmenopausal women with mild PHPT without osteoporosis (T-score $\geq -2{,}5$ by DXA). In 20 patients was performed PTE, the comparison group:18 postmenopausal patients with PHPT. The duration of observation was 1 year. Examination: total calcium, Ca^{++}, phosphorus, PTH, DXA.
Results
The average age was 63.1 ± 8.74 years, the duration of menopause was 13.4 ± 3.52 years. The were no differences in the age ($U=126.5$, $P=0.120$), height, m ($U=504.5$, $P=0.478$), weight, kg ($U=3556.0$, $P=0.318$), BMI, kg/m^2 ($U=3578.5$, $P=0.350$), duration of menopause, years ($U=146.5$, $P=0.022$), calcium total, mmol/l ($U=0$, $P=1.000$), PTH ($U=11.5$, $P=0.655$), BMD L1-L4$_{total}$ ($U=158$, $P=0.530$), BMD Hip$_{total}$ ($U=157.0$, $P=0.520$) in the both group. After surgical treatment, a significant decrease in calcium and PTH was detected. Against the background of the normalization of indicators of calcium-phosphorus metabolism, a significant increase in BMD L1-L4$_{total}$ ($T=38.5$, $P=0.041$) and BMD Hip$_{total}$ ($T=51.5$, $P=0.046$) was observed. In the group of patients without PTE, there was a significant decrease in BMD L1-L4$_{total}$ ($T=20.0$, $P=0.013$), BMD Hip$_{total}$ ($T=22.0$, $P=0.017$) against the background of continuing hypercalcemia ($T=59.5$, $P=0.420$) and elevated PTH ($T=64.0$, $P=0.836$) content in the blood serum.
Conclusion
The results of a retrospective study confirm the high efficacy of PTE in the postmenopausal women with mild PHPT to prevent bone loss.

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Obstructive urolithiasis as first sign of primary hyperparathyroidism caused by a large parathyroid hyperplasia

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Introduction
Primary hyperparathyroidism (PHPT) is a well-known risk factor for urolithiasis and nephrocalcinosis, wich are now less commonly reported due to an early detection of hypercalcemia by routine measurement of serum calcium. PHPT is most commonly caused by a single adenoma of the parathyroid gland. The incidence of multiglandular disease (MGD) range from 2.4–34%. In case of large tumor differential diagnosis is necessary to rule out malignancy.
Case report
We report the case of a 36 years old man presenting with multiple obstructive lithiasis in the left ureter with consecutive hydronephrosis. Biochemical evaluation revealed hypercalcemia (serum calcium = 13.84 mg/dl, n.v. = 8.6−10, ionizing calcium = 5.97 mg/dl, n.v. = 3.82−4.82) due to PHPT (PTH = 565.7 pg/ml, n.v. = 15−65, serum phosphate = 1.7 mg/dl, n.v. = 2.5−4.5, alkaline phosphatase = 192 U/l, n.v. = 40−129). In order to reduce calcium level the patient received bisphosphonate and calcitonine and, after ureteral stenting, diuretics and hydration. Ultrasound revealed a 5 cm tumor of the right inferior parathyroid gland, with necrotic areas, confirmed also by SPECT- CT. During surgery, beside the tumor, the hyperplasia of the other 3 parathyroid glands was observed. Right lobectomy with tumor, right superior and 50% of the left inferior parathyroid gland resection was performed. A reduction with more than 50% of PTH level was observed 10 minutes after tumor resection. The histopathological examination confirmed the hyperplasia including in the tumoral gland. The PTH level initially dropped off, but then rapidly raised around 150 pg/ml, maintaining this level more than 6 months, despite normal calcemia and then normalised. No recurrence of nephrolithiasis after surgery. There were insufficient criteria for MEN 1 syndrome.
Conclusions
Serum calcium level should be measured in all patients with urolithiasis. The preoperatory diagnose of MGD can be challenging. Elevated PTH levels can be observed after successful surgery as a transient phenomen.

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Parathyroid adenoma in pregnancy: a case report

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Although primary hyperparathyroidism (PHPT) is seen in young women at 8/million ratio, it is more rare to be seen with pregnancy. If diagnosed and not treated during pregnancy, the mother may have nephrolithiasis, hypercalcemic crisis, hypertension, preeclampsia, pancreatitis, death and intrauterine growth retardation in the fetus, low birth weight, preterm delivery, intrauterine death or postpartum tetany. Forty-year-old woman at the 14th week of gestation was diagnosed with Ca: 11,03 (N:8,6−10 mg/dl), P: 2,38 (N: 2,6−4), 5 mg/dl), 25-OH-D: 13.87 (N: 30−80 ng/ml), Parathormone: 141.9 (N: 15−65 pg/ml), creatinine: 0.37 (N: 0.5−0.9 mg/dl), 24 hour urine was Ca: 610 (N: 100−300 mg/24 h). Ultrasonography revealed a parathyroid adenoma in the right lower pole. The patient was diagnosed as primary hyperparathyroidism. The patient was informed about mortality and morbidity and treatment options for PHPT in pregnancy. The patient was operated at the second trimester (17 weeks of gestation). All parathyroids were explored in the operation and the adenoma was removed in the right lower pole. Intraoperative PTH level was found to be 9.47 pg/ml and the operation was terminated. Pathology: Parathyroid adenoma. Postoperative calcitriol 0.5 mg/day, 1×1000 mg calcium was given. On postoperative first day, Ca: 9.71, 8.91 on the second day and 8.87 mg/dl on the fifth day. In patients with parathyroid adenoma in pregnancy, the high complication and mortality rate for the mother and baby can be significantly reduced by the operation of the adenoma in the second trimester.

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P80

Effects of bariatric surgery on bone health

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Introduction
Bariatric surgery has important metabolic complications such as bone mass loss.
Goal
To assess bone mineral density (BMD) after Roux-en-Y gastric by-pass (RYGB) in patients under standard calcium and vitamin D supplementation.
Method
In patients with morbid obesity submitted to RYGB, we measured BMD with a dual X-ray densitometer. Using World Health Organization (WHO) criteria's, values were compared with young controls and same age and sex population, evaluating osteopenia and osteoporosis.
Results
375 pacients were inclueded, 290 women and 85 men. Positive correlation was observed between BMI and BMD lumbar spine (LS) (Femur (F) 0.104, *P* 0.001 y LS 0.104, *P* 0.001) and inverse correlation was observed between BMI postoperative and preoperative BMD lossed (F 0.223, *P* 0.780; LS 0.189, *P* 0.022). Inverse correlation was observed between BMD and age (F −0.314, *P* 0.000 y LS-0.161, *P* 0.000) as well as with preoperative weight excess (−0.284, *P* 0.000). Group correlations are maintained when separated by sex. In women we observed a diminished BMD in femur from 1.086±0.150 g/cm^2 (T-score 0.558±1.188) to 1.00±.150 g/cm^2 (T-score 0.150±1.206) and in LS from 1.206±0.197 g/cm^2 (T-score 0.171±1.22) to 1.192±0.155 g/cm^2 (*P* 0.001) (T-score 0.094±1.267) (*P* 0.000). In femur 8.6% of them were osteopenia, with no cases of osteoporosis, in LS corresponding to 12.9% of osteopenia. Following the follow-up, BMD diminished progressively mainly in left hip, 14.8% osteopenia and 2.1% osteoporosis were found in left hip; 17.2% osteopenia y 2.8% osteoporosis. In men, we observed a BMD F 1.154±0.148 g/cm^2 (T-score 0.490±1.083) and in LS 1.108±0.160 g/cm^2 (T-score 0.180±1.174). After the follow-up BMD were 1.107±0.160 g/cm^2 and 1.247±0.160 g/cm^2 respectively (*P* 0.000 y 0.030) and T-score F 0.274±1.215 and LS 0.245±1.327 (*P* 0.000). In femur 12% of them were osteopenia, with no cases of osteoporosis, in LS corresponding to 16% osteopenia. Following the follow-up, BMD diminished progressively, 14.1% osteopenia and 1.2% osteoporosis were found in left hip; and 17.6% osteopenia in LS.
Conclusion
Patients from both genders and diverse ages after BPYR presented osteopenia and osteoporosis, despite early supplement prescription of calcium and vitamin D (Table 1).

Table 1

	Women 290	Men 85	*P*
Age (years)	46.50±11.03	44.65±10.50	0.077
Preoperative weigth (Kg)	128.44±21.89	155.48±25.70	0.000
Preoperative BMI (Kg/m^2)	50.97±8.51	52.07±8.77	0.230
Postoperative BMI (Kg/m^2)	35.94±7.24	35.94±7.22	0.995
Excess weight lost (%)	53.86±22.18	55.44±20.82	0.501
Time (months)	83.4±14.24	81.27±11.18	0.541

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P81

A rare case of hypoparathyroidism due to MELAS syndrome

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MELAS syndrome is a progressive neurodegenerative disorder characterized by a combination of mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes and endocrine disorders. The frequency of hypoparathyroidism in MELAS syndrome is less than 0.5%. A 22-year-old female was admitted to our center due to episodes of seizures. At admission her height was 147.5 cm, weight 30.5 kg, BMI 13.8 kg/m^2. She reported whole life weight and growth retardation, hearing loss since childhood but normal menses since 12 years old. The patient resembles her mother. Investigation at the time of admission revealed Chvostek's and Trousseau's symptoms, serum calcium 2.05 mmol/l (2.10–2.55), phosphate 1.54 mmol/l (0,74–1,52), parathyroid hormone 13.9 pg/ml (15–65), calcium in 24 h urine 0.63 mmol/24 h (2.5–8), HbA1c 5.5%, C-peptide 1.26 ng/ml (1.1–4.4), plasma lactate 3.21 mmol/l (0–2.4), TSH 0.278 mU/l (0.25–3.5). A month before she had been hospitalized unconscious with stroke like symptoms to a neurological department, where she was also diagnosed with diabetes. (hyperglycemia 20 mmol/l) and hypocalcemia (Ca^{2+} 0.96 mmol/l (1.03–1.29)). According to the results of CT scan, basal ganglia calcification was found. MELAS syndrome was confirmed by the presence of mutations in mitochondrial DNA: m. 3243A > G tRNA-Leu. All signs and symptoms were controlled on alfacalcidol 0.5 μg, 1000 mg of calcium carbonate, cholecalciferol 2000 IU daily and 6 IU of insulin glargine. Conclusion: hypoparathyroidism or diabetes at a young age due to MELAS syndrome seems to be more easily controlled than in sporadic cases or perhaps even partly reversible.

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A case report of tumor-induced osteomalacia

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Objective
Tumor-induced osteomalacia is a rare paraneoplastic syndrome in which fibroblast growth factor 23 (FGF-23) hyperproduction by tumor causes renal phosphate wasting, severe hypophosphatemia and osteomalacia. Localization of the tumor can be a major diagnostic challenge.
Material and methods
We present a clinical case concerning a 62-year old woman previously diagnosed with hypophosphatemic osteomalacia, with a slight improvement of clinical and laboratory manifestations after initiation of medical treatment.
Results
The patient had 10-year history of pronounced lower back pain, decrease in height by 16 cm during life, multiple atraumatic fractures of the ribs and pelvic bones. 6 years earlier she underwent surgical treatment for the mass lesion of the proximal part of the left femur (histologic examination – osteoma). She was diagnosed with hypophosphatemic osteomalacia 4 years earlier and received treatment with alfacalcidol 3 mcg/day, cholecalciferol 15 000 IU/week, calcium 1000 mg/day. The examination showed low serum P level 0.6 mmol/l (0.74–1.52), elevated PTH 111 pg/ml (15–65), normal levels of total and albumin-adjusted serum Ca, a slight increase in alkaline phosphatase (ALP) 158 IU/l (50–150) and CTx 0.836 ng/ml (0.01–0.69), 25(OH)D 23.4 ng/ml. Low tubular maximum reabsorbtion of phosphate corrected for glomerular filtration rate (TmP/GFR) 0.45 indicated renal phosphate wasting. Considering likely ectopic hyperproduction of FGF-23, we performed whole body scintigraphy with somatostatin analogue, which revealed focal intensive radiotracer uptake in left inguinal region. CT scan of the pelvic area excluded the presence of a primary focus in the area of a previously removed osteoma. After tumor-removal surgery, follow-up blood test on the 3rd day showed normalization of serum P level. Four months after surgical procedure, P level remained within the normal range, TmP/GFR showed no renal phosphate wasting. Ca level also remained within the normal range, while elevation of ALP 209 IU/l (40–150) as well as PTH 99 pg/ml (15–65) was observed, 25(OH)D 20.4 ng/ml. Marked elevation of osteocalcin 153 ng/ml (11–43) and CTx 2.34 ng/ml (0.01–0.69) suggested intense bone remodeling. Therapy with alfacalcidol, cholecalciferol and calcium was continued with increase of calcium dose up to 2000 mg/day.
Conclusion
The diagnosis of tumor-induced osteomalacia is challenging and is commonly delayed for years. Attention to biochemical values (especially serum P level) and thorough use of imaging techniques are the key steps. Only surgical removal of causative tumor can provide complete cure.

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P83

Pregnancy-related osteoporosis: a series of cases

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Objective
Pregnancy-related osteoporosis is a rare disorder with potentially severe complications. There is lack of clinical practice guidelines due to low incidence of this disease and few published cases.
Material and methods
We present eight cases of pregnancy-related osteoporosis in women aged between 28–42 years. Six of them were diagnosed between 1 month and 3 years postpartum and two were diagnosed in the third trimester of pregnancy. Most of them had otherwise healthy pregnancy, only one woman had risk factors promoting osteoporosis before pregnancy (heparin treatment).
Results
Blood tests showed normocalcemia and normophosphatemia in all patients. All patients except one had PTH level within normal range (one patient had secondary hyperparathyroidism due to vitamin D deficiency). Serum osteocalcin level was available in four patients, 3/4 had low levels of osteocalcin. Seven patients had multiple vertebral compression fractures at X-ray with a prominent decrease in BMD (spinal Z-score from −2.2 to −4.4) and one patient suffered bilateral femoral neck fracture. Treatment approaches included therapy with calcium (1000–2000 mg/day) and vitamin D (alfacalcidol 0.5–3 mcg/day or cholecalciferol 10,000–15,000 IU/week) in all patients; five patients had received specific treatment for osteoporosis (bisphosphonates in two patients, calcitonin spray in one patient, denosumab in one patient and sequential therapy with strontium ranelate, denosumab and teriparatide in one patient). Four women underwent surgery: three had vertebroplasty and one had bilateral hip replacement. Follow-up data was available in six patients with median 2 years, 5/6 had radiological improvement in lumbar spine.
Conclusion
Described cases confirm the severity of pregnancy-related osteoporosis and its challenging management. Necessity and regimen of specific treatment are the subject for further research. Women diagnosed with pregnancy-related osteoporosis should be advised to have appropriate calcium and vitamin D intake and counseled regarding the risk of potential detrimental effects on the bone health during breastfeeding and newborn care.

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P84

Bone mineral density, prevalence of fractures, antiosteoporotic drugs effectiveness and Ca/Vit D supplementations intake in elder patients with osteoporosis: a cross-sectional study on Moscow population

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Aim of the study
To investigate osteoporosis features in elder patients in Moscow population.
Materials and Methods
It was a retrospective study, during which we analyzed the data of 192 outpatients (183 women and 9 men) admitted to Gerontology Research and Clinical Centre in 2018. In the focus of our attention was patients' past medical history, such as any antiosteoporotic treatment received, vitamin D and Ca supplementations, any fractures in previous 5 years and T-criteria values assessed by DEXA-scan. The statistical analysis was performed using Prism 8 Version 8.0.1 (145). Statistically significant were differences with $P < 0.05$.

Results
Median age of the patients was 77 [73; 87] years. 20% of the patients had history of taking oral glucocorticoids. The prevalence of fractures in PMH was 82% (157 patients). With more detailed analyzing we found out that the number of patients with three and more fractures was quite high and was 89, so more than a half of the group with fractures. The most frequent localization of fracture was lumbar vertebras (53%), meanwhile radius fractures and other localization fractures were found in 27% and 20% of the cases respectively. The values of T-criteria for hip and spine according to DEXA-scans showed significantly lower T-criteria ($P=0.04$) for lumbar vertebras vs hip: Me -3.1 [-2.6; -3.6]. 50% of the patients did not receive any antiosteoporotic treatment; treated patients received bisphosphonates in most cases (63%, $n=59$), followed then by denosumab (18%, $n=17$) and teriparatide (9%, $n=8$). The adverse effects were much higher in BF group (90% of all cases). Patients receiving only Ca supplementation had approximately the same prevalence of fractures compared to patients with no Ca/Vit D supplementation, meanwhile patients receiving only vitamin D had significantly lower prevalence of fractures [$P=0.045$], and patients receiving Ca + VitD did not differ from only Vit D-group.
Conclusion
Vitamin D and combined supplementation is extremely important in prevention of fractures, meanwhile Ca alone does not have any protective effect. In severe osteoporosis the preference should be given to anabolic treatment for better results.
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P85

Brown tumor of the palate as first manifestation of a primary hyperparathyroidism
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Brown tumors represent a late-stage bone change caused by primary hyperparathyroidism, presenting in only 2–3 percent of the cases. Therefore as primary manifestations there is even a smaller percent. The common sites of brown tumor are the long bones, ribs, clavicle or pelvic girdle. The solitary palate brown tumor as initial presentation of a primary hyperparathyroidism is rare and often accompanied by tumors of other facial bones. We present the case of a 67 year old woman with initial presentation of a large tumor of the right palate, with no extension to the orbits. The first histological diagnosis was of a giant cell tumor, which delayed the diagnosis of the underlying cause for about 6 months, when the patient's relatives requested a second opinion on the initial histological findings, the second analysis revealed the same diagnosis but recommended that a primary or secondary hyperparathyroidism should be excluded as the brown tumor is very similar to the one with giant cells. We received the patient at this moment when we immediately diagnosed a primary hyperparathyroidism and sent the patient to surgery. Unfortunately in this case the long progression of high levels of PTH affected a lot the mineral density of the bones and now the patient is highly osteoporotic. The particularity of the case is the location of the brown tumor and the delayed diagnosis of a first primary hyperparathyroidism.
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P86

Difference in trabecular bone score according to spine-femur bone mineral density discordances in healthy postmenopausal women
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Purpose
The purpose of this study was to evaluate the prevalence and characteristics of individuals with spine–femur bone mineral density (BMD) discordance and to examine whether trabecular bone score (TBS) is associated with major and minor BMD discordance in postmenopausal women.
Methods
This retrospective study included 533 healthy postmenopausal women (median age, 60 years; range, 55–82 years) who visited our hospital for a health check-up and performed dual X-ray absorptiometry for the evaluation of BMD between May 2013 and April 2017. Major discordance is defined when the T-score at one site indicates osteoporosis and at the other site indicates normal BMD. Minor discordance refers to one degree of difference in the diagnosis between two sites. The differences were analyzed using the Kruskal-Wallis test.
Results
Two hundred and forty-six participants (48.2%) exhibited spine-femur BMD discordance. Major discordance was noted in 4.5% ($n=24$) of the study population, and these patients were all diagnosed with osteoporosis in the lumbar spine. Minor discordance was noted in 41.7% ($n=222$) of the study population. In the group with normal BMD of the lumbar spine, the participants in the discordance group showed significantly lower TBS (median, 1.364; interquartile range [IQR], 1.328–1.398) than that in the concordance group (median, 1.406; IQR, 1.358–1.439). The participants with discordance who showed normal (median, 1.357; IQR, 1.326–1.399) or osteopenic (median, 1.352; IQR, 1.313–1.387, $P<0.001$) BMD in the femur had significantly lower TBS compared with that in the concordance group (for normal BMD; median, 1.406; IQR, 1.1.358–1.439; for osteopenic BMD, median, 1.364; IQR, 1.328–1.398, $P<0.001$). The major discordance group exhibited the lowest TBS in both groups with normal (median, 1.331; IQR, 1.275–1.384) and osteopenic (median, 1.307; IQR, 1.245–1.345) femoral BMD. The groups with osteoporotic femur or both osteopenic and osteoporotic lumbar spine did show a significant difference in TBS regardless of the presence of discordance.
Conclusions
The high prevalence of discordance between the spine and the femur in terms of BMD may be associated with degraded microarchitecture, especially in the presence of normal or osteopenic BMD, and suggests the need for further risk assessment and management in such patients.
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P87

Heterogenous clinical presentation of primary hyperparathyroidism in Romania
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Introduction
In the last decades, primary hyperparathyroidism (PHPT) has changed in its clinical presentation, being mostly asymptomatic in western countries; in Romania is still common to see various clinical presentations.
Objective
To characterize a retrospective cohort of PHPT Romanian patients.
Patients and methods
271 patients were included: 88% women, ratio F/M 7.5/1, mean age 60.6 ± 12 yrs (15–83), mean BMI 26.3 ± 4.9 kg/m^2 (15.1–43). The biochemistries were measured by automated standard laboratory methods. Serum intact PTH, 25OH-vitamin D, C-telopeptide (CTX) and osteocalcin (OC) were measured by chemiluminescence immunoassay. Areal bone density was measured at the lumbar spine (LS), femoral neck (FN) and distal radius1/3 site (R). Site-matched spine TBS parameters were extracted from the DXA images using TBS iNsight software.
Results
Biochemistries (mean ± S.D.) (range): calcium 11.3 ± 1.1 mg/dl (10–18 mg/dl), PTH 266.5 ± 373.9 pg/ml (31–2812 pg/ml), 25OHD 15.2 ± 9.8 ng/ml (4–90.28 ng/ml), CTX 1.2 ± 1.6 ng/ml (0.1–15.8 ng/ml), OC 66.1 ± 19 ng/ml (8.9–609 ng/ml). Simptomatic hypercalcemia was noted in 15% and the prevalence of severe vitamin D deficiency (<10 ng/ml) was 34.7%. **Renal involvement** (51.7%)**:** nephrolithiasis 47.6% (7.7% had surgery), more likely in males and younger patients; nephrocalcinosis (ultrasound evidence 4.1%); hypercalciuria (30.2%); reduced renal function (13.3%). **Skeletal involvement:** fractures (26.3%; non-verterbral 17%, vertebral 8.1%, both 1.1%) in significantly older; osteitis fibrosa cystica 2.95%; LS- BMD (224 pts) mean T-score –2.3 S.D., FN-BMD (192 pts) mean T-score –1.8 S.D.; R- BMD (38 pts) mean T-score –2.6 S.D.. The prevalence of osteoporosis by a single site: 45.8% (LS), 20.1% (FN), 63% (R). Mean TBS was in the partially degraded range (1.258 ± 0.115); 32% had degraded microarchitecture (TBS ≤ 1.20), 51% had partially degraded microarchitecture (TBS > 1.20 and < 1.35) and 17% had normal TBS. **Etiology** (61.6% operated, 91 pts with available histology): adenoma (94.5%, 8 double), carcinoma (3.3%), hyperplastic (2.2%), probably selection bias in refferal to surgery. Mean adenoma weight (68 pts) 3.70 ± 7.78 g (range 0.05 – 48.6 g). Familial forms in 12 pts (4.5%): MEN (1,2) (8 pts), HPP-JT (3 pts), isolated (2 pts).
Conclusion
Currently in Romania there is a mixture of clinical presentations of all described phenotypes.
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P88

A case of primary hyperparathyroidism due to a giant parathyroid adenoma extending into the mediastinum

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Introduction
Primary hyperparathyroidism is a common disease. It is generally caused by a solitary parathyroid adenoma. Adenomas weighing more than 3.5 g are classified as giant. These giant parathyroid adenomas constitute a rare clinical entity.
Case report
A 54-year-old woman was referred to our ENT department for management of newly diagnosed hypercalcaemia. She had no significant medical history. She reported mild constipation, muscular weakness, nausea and intermittent abdominal pains since 1 month. There was no palpable mass on cervical examination. Biochemical evaluation revealed severe hypercalcemia (serum calcium: 5.54 mmol/l); the levels of serum parathormone were also elevated (2268 pg/ml). Cervical ultrasonography revealed a hypoechoic mass, measuring 3 cm, with augmented vascular Doppler signal at the periphery, which appeared to correspond to the right inferior parathyroid gland. There was no significant lymphadenopathy. A Tc99 m SestaMIBI scintigraphy showed an uptake compatible with an adenoma of the right inferior parathyroid gland extending into the mediastinum. Computed tomography of the neck and chest confirmed the presence of a lesion in the projection of the right inferior parathyroid gland extending to the anterior mediastinum measuring 5.94 cm $\times$ 2.71 $\times$ 2.05 cm. The severe hypercalcemia was temporarily controlled by hydration, forced diuresis and bisphosphonates. The parathyroid adenoma was successfully removed through a transcervical approach. Histopathological examination confirmed a benign giant parathyroid adenoma. The patient's postoperative course was uneventful. Her serum calcium and PTH levels normalized quickly. She is currently asymptomatic and normocalcaemic.
Conclusions
Diagnosis of a giant solitary parathyroid adenoma is based on clinical presentation, biochemical profile, and imaging studies. The parathyroid carcinoma is the principal differential diagnosis. The treatment is based on surgical excision combined with PTH levels measurement.

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P89

Diagnostic and treatment delay in primary hyperparathyroidism (phpt): a pending issue

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Background
PHPT is the leading cause of hypercalcemia in outpatients. Its clinical presentation varies from asymptomatic forms to renal or bone complications. The only curative treatment is surgical resection, and delayed diagnosis can lead to serious morbidity.
Objective
Identify the presence of PHPT at least one year prior to referral to endocrinology consultation. Secondly, determine whether diagnostic delay leads to increased complications.
Methods
Retrospective observational study. We analysed electronical records from a tertiary referral center in 116 patients with PHPT that underwent surgery between 2015 and 2018. Age, presence of nephrolithiasis, serum calcium, alkaline phosphatase, glomerular filtration rate and parathyroid hormone levels determined at least 12 months prior to referral were evaluated. In patients with [Ca] recorded more than one year earlier, the following four surgical criteria were assessed at the time of that determination: nephrolithiasis, age $<$50 years, [Ca] $>$ 11.4 g/dl and glomerular filtration rate $<$60 ml/min.
Results
Among the 116 operated patients, 81 (69.8%) had a previous measurement of serum calcium at a time interval $\geq$12 months. 65 of these 81 patients (56%) had a serum calcium$>$10.4 g/dl and presented an average delay of 57 months to receive a proper evaluation. Even more, 42 of these 65 patients with hypercalcemia (64.6%) had $\geq$1 inclusion criteria for surgery. The group of patients that met the surgical criteria were younger, had higher calcium serum values, a greater frequency of nephrolithiasis and a shorter Interval to undergo a parathyroidectomy than those patients who did not meet at least one surgical criterion. Conversely, the 35 patients that were not checked up $\geq$1 year before the endocrine evaluation was made, were older and had higher calcium serum values that those patients who had normal calcium values evaluated more than one year previously. No differences were found in the presence of kidney stones, surgical criteria or gender between both groups.
Conclusions
In our series of patients with PHPT, the referral to an endocrinologist is performed late, with an average delay of almost 5 years. A significant proportion of these patients have well documented hypercalcemia at least one year before evaluation and more than half of them met criteria for surgery. Despite increased early detection of the disease and avaibility of effective treatment, PHPT continues to be underdiagnosed and undertreated, with increased morbidity. System-level interventions that include proper management of hypercalcemia could improve outcomes.

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P90

Epidemiology of hypoparathyroidism in Korea

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Background
The National Health Insurance Service of South Korea is considered to be one of the most effective systems in the world with high accessibility to health care for all Koreans including foreign residents in the country as many as 50 M people. The accumulative information on the behaviors and the statistics of healthcare use based on the National Health Insurance Sharing Service Database has become important for medical research as a nationwide surveillance.
Methods
We, thereafter, performed analysis of the changes in the incidence and prevalence of hypoparathyroidism which is the common complication of thyroid surgery with the National Health Insurance Sharing Service Database in South Korea. From 2008 to 2015, we selected the postoperative hypoparathyroidism group who were prescribed with vitamin D over 6 months after the thyroid surgery with diagnosis of thyroid cancer.
Results
The incidence of postoperative hypoparathyroidism increased consistently from 2008 to 2013 and decreased in 2015. The number of cases of thyroid surgery reached its peak in 2012 and decreased after then, showing similar tendency. This trend is observed similarly with the incidence of thyroid cancer showing consistent increase from 2008 to 2012, and decrease in 2015. Percentage of hypoparathyroidism resulting from total thyroidectomy except slight increase in 2014 seems to be consistent, indicating at least surgical skill fluctuation.
Conclusion
Thereafter, the incidence of hypoparathyroidism, which is a common complication of thyroid surgery, has decreased with the effect of significant health care improvement.

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P91

Effectiveness of intramuscular Ergocalciferol treatment in a patient with o steomalaciadueto severe vitamin D deficiencyafterbariatric surgery

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Bariatric surgery is a common treatment for morbidly obese patients requiring weight loss and/or metabolic control. Vitamin D (VitD) deficiency and bone loss may occur post-operatively and supplementation with high oral doses of Vitamin D is required. Alternatively, intramuscular depot ergocalciferol (vitamin D2) which slowly releases VitD and overcomes the gastrointestinal tract, could be administrated in such patients.
Aim
To present a case of severe VitD deficiency–osteomalacia after gastric bypass operation for morbid obesity treated with ergocalciferol intramuscularly.
Case report
A 45-year-old woman (BMI 43 kg/m^2) was referred to the Endocrinology Department with a diagnosis of secondary hyperparathyroidism due to VitD deficiency. Two weeks earlier, she was admitted to the Department of Internal Medicine for pain at the upper third of left hip and pelvis and long-standing muscle weakness over the previous months. The last month she was immobilized in a wheelchair. Fifteen years ago she underwent roux-en-Y gastric by-pass for treatment of morbid obesity. Since then she was treated with multivitamin supplements (iron, VitB12, Calcium, VitD). In the last three months, after a neurological examination anti-epileptics and analgesics were also initiated. Despite this treatment, she complained for hips' pain and muscle weakness, which limited her ambulation. During her hospitalization, iron deficiency anaemia (Ht 23%, Hb 8g/dl Ferritine 3 μg/l) vitD deficiency (25OHD 3.7 ng/ml) and secondary hyperparathyroidism (PTH 334 pg/ml, Ca 8.3 mg/dl, Albumin 3 gr/dl, P 1.7 mg/dl, CaUr24h 30 mgr/24 h, PUr24h 200 mgr/24 h) were revealed. The indices of bone turnover (ALP 173IU/L, P1NP 196 ng/ml, βCTX 2.02 ng/ml) were elevated. Radiological evaluation demonstrated insufficiency fractures on the pubic and left femur and reduced lumbar spine (Tscore −2.8) and hip (Tscore −2.9) BMD. Osteomalacia due to vitD deficiency and calcium malabsorption was diagnosed. Calcium citrate 2000 mg daily and im ergocalciferol 600,000 IU every 20 days to correct vitD deficiency were initiated whereas anti-epileptics and analgesics were discontinued. One month after treatment initiation, musculoskeletal pain and weakness had resolved and the patient was mobilized almost completely. Within two months, hyperparathyroidism (PTH 175 pg/ml, Ca 8.7 mg/dl, *P* 3.5 mg/dl, Albumin 3.3 g/dl, ALP 206 IU/l, P1NP 668 ng/ml, βCTX 4.25 ng/ml) and vitD status (25(OH)D 8.1 ng/ml) had improved.
Conclusion
Regular monitoring and prompt correction of vitD and mineral deficiencies is necessary in patients that underwent bariatric surgery. Intramuscular ergocalciferol administration can improve the clinical and biochemical status and thus is suggested to prevent and/or treat osteomalacia in such patients.

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P92

A rare case of hypercalcemia associated with dysgerminoma with elevation of 1,25(OH)2 Vitamin D

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We hereby report a rare case of hypercalcemia-associated with dysgerminoma with elevation of 1,25(OH)2 Vitamin D. A 27-year-old nulliparous woman presented with hypercalcemia during examination of a right ovarian tumour. As the serum calcium level increased gradually, she started complaining of nausea and anorexia. The laboratory data at first-visit showed that serum calcium, LDH, ALP, 1,25(OH)2 Vitamin D and fractional excretion of calcium were elevated and intact PTH was suppressed. (serum calcium 13.3 mg/dl, albumin 4.4 g/dl, phosphorous 3.7 mg/dl, LDH 1411 U/l, ALP 399 U/l, intact PTH 6 pg/ml, PTHrP <=1.0 pmol/l, 25(OH) Vitamin D 15.2 ng/ml, 1,25(OH)2 Vitamin D 96.9 pg/ml, FECa 3.51%, BUN 16.6 ng/dl, Creatinine 0.93 mg/dl). Symptomatic hypercalcemia was treated by intravenous normal saline and elcatonin yet medical treatment had a marginal effect. On the 21st-day from the first visit, a right salpingo-oophorectomy was performed. The right ovary measured 13 cm× 12.5 cm×3.6 cm. Histopathology of the ovarian mass showed proliferation of large and homogeneous tumour cells with infiltration of small lymphocytes (two cell patterns). Immunohistochemical analysis revealed that tumour cell was PLAP (+, partly), CD117/c-kit(+, weak), D2-40(+), hCG(−), AFP(−). There was no evidence of metastasis, and cytology of the ascetic fluid showed no malignant tumour. Hence this patient was classified in stage pT1apNXpM0 (UICC, 2009) Therefore, she got a follow-up examination every 3-months in the first year without receiving chemotherapy. Postoperatively, serum calcium and 1,25(OH)2 vitamin D returned to normal range within a week. There are numerous causes of hypercalcemia. The case of hypercalcemia associated with dysgerminoma showing elevation of 1,25(OH)2 Vitamin D is still rare, whilst there are several previous reports. We would like to present the case series study of dysgerminoma with hypercalcemia of 15 cases including 14 previous reported ones of database from 1990 to 2018 at the day of the presentation.

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P93

Analysis of non-invasive DXA-derived bone structure parameters in patients with acromegaly with regards to vitamin D levels

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Introduction
Patients suffering from acromegaly, despite normal or even higher bone mineral density (BMD), have prevalent vertebral fractures (VFs). Impaired bone microarchitecture is involved fragility fracture development, but vitamin D status could be involved in this impairment.
Aim of the study
Comparison of bone parameters such as BMD, trabecular bone score (TBS) and 3D-SHAPER parameters in acromegaly patients according to level of 25(OH)D3.
Methods
A cross-sectional study recruited all acromegaly patients who came for visit from 6/2016 – 8/2017. In all subjects a single measurements of pituitary axis hormone levels, bone turnover markers (BTMs), BMD, (total hip [TH] and lumbar spine [LS]), TBS and 3D-SHAPER [volumetric BMD (vBMD), surface BMD (sBMD) and mean cortical thickness (mCth)] were performed. Levels of 25(OH)D3 were measured by measured in a chromatographic assay using a simple isocratic HPLC system with UV detection (Chromsystem®) (interassay variability CV, 0.8−3%). All patients were advised to use 800 IU of cholecalciferol and 1000 mg of Ca supplement daily.
Results
106 patients with acromegaly (mean age 56.6 years, BMI 30.2 kg/m^2) were included. Patients in lowest quartile (Q1vitD; mean 111.1 nnmol/) of 25(OH)D levels had lower LS BMD (0.99 vs. 1.06 g/cm^2; $P=0.02$); lower TBS (1.13 vs. 1.23; $P<0.0001$) and higher TH sBMD (183.2 vs. 172.4 g/cm^2; $P=0.05$) in comparison to patients in highest quartile (Q4vitD; mean 34.5 nnmol/l). There was no difference in TH BMD, FN BMD, mCth, vBMD, CTx and P1NP between Q1vitD vs. Q4vitD.
Conclusions
This study indicates that in patients with acromegaly low levels of vitamin D may contribute to significant impairment in trabecular bone at lumbar spine, as represented by TBS. Higher sBMD at TH could indicate increased amount of cortical bone caused by GH hypersecretion, but cortical porosity could be decreased, as showed by previous studies with bone biopsies. We recommend maintaining vitamin D levels in sufficient range in all patients with acromegaly.

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P94

Osteitis Fibrosa Cystica – A Forgotten Clinical And Radiological Feature Of Primary Hyperparathyroidism

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Introduction
Manifestations of primary hyperparathyroidism (PHPT) such as osteoporosis and stone diseases are common primary diagnostic findings beyond a hypercalcemia. Classical skeletal involvement can be the first sign of PHPT, but not recognized because osteitis fibrosa cystica (bone cysts, brown tumors of the long bones) is rarely seen today in Western Europe.
Case report
A 34-year old women from Afghanistan was presented to our out-patient-clinic with a history of chronic back and joint pain, as well as numbness and parasthesia in both arms and legs. Previously she was referred to orthopedic surgery,

neurosurgery and neurology for further investigations. MRI showed multiple intraosseous cystic lesions in the pelvis and multiple ribs. DXA confirmed osteoporosis (lumbar spine T-score: −4,6; total hip T-score −4,1). Biochemical evaluation revealed hypercalcemia of 2.81 mmol/l (ref. range 2.09–2.54), hyophosphatemia of 2.53 mg/dl (2.6–4.5), 25-OH Vitamin D of 26 ng/ml (20–70) under supplementation and elevated parathyroid hormone of 571 pg/ml (15–65). Blood and urine creatinine were normal. Ultrasound of the neck showed hyperplasia of all four parathyreoid glands. Multiple endocrine neoplasia 1 and malignancy of cystic pelvic lesions were excluded. By parathyreoidectomy two cranial parathyroid adenomas were removed. Caudal no adenoma could be identified during surgery. Immediately after surgery the parathyroid hormone decreased >50%. At the follow-up visits the patient showed a good improvement of her symptoms without developing a hungry-bone-syndrome.

Conclusion

The case shows the rare presence of osteitis fibrosa cystica as a clinical manifestation of a PHPT. It emphazises the importance of an early diagnosis of PHPT with a detailed diagnostic workup, including imaging and biochemical investigations of bone metabolism. When radiographic evidence of a lytic lesion and hypercalcemia are present, PHPT should always be considered in the differential diagnosis.

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P95

Clinical use of Cinacalcet in patients with complex primary hyperparathyroidism

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Background

Primary hyperparathyroidism is one of the most common disorders encountered in endocrine clinics and primarily affects women. The current recommendation for patients with primary hyperparathyroidism is to undergo parathyroidectomy which has a 97% success rate. However, there is a small group of patients where surgery is contraindicated, or patients who have a disease pattern not amenable to surgery or patients who refuse surgery. These patients would require an alternative treatment to manage hypercalcemia. Cinacalcet is an allosteric modulator of calcium sensing receptor and is currently commissioned by NHS England for patients with primary hyperparathyroidism who are not suitable for surgery and patients with secondary hyperparathyroidism with end stage kidney disease on dialysis. It is also indicated in treating hypercalcemia secondary to parathyroid carcinoma. European Medicines Agency and British National Formulary both endorse the use of Cinacalcet in these patients.

Method

We conducted a retrospective audit on the patients with primary hyperparathyroidism who were prescribed Cinacalcet against the NHS England Clinical Commissioning Policy (July 2016).

Results

A total of 17 patients were identified as suitable to be included in the audit. Majority of the patients are female ($n=16/17$) and only one male. The age range is between 54 to 91 years old (mean=78). Pre treatment calcium levels are between 2.59–3.3 mmol/L (mean=2.85 mmol/L) and PTH level between 8.92–57.65 pmol/L (mean=19.06). Vitamin D levels are between 9.99–99.26 nmol/L prior to treatment. Seven patients had low vitamin D levels (<50 nmol/L) and one patient did not have vitamin D levels prior to treatment. Calcium levels diminish after 1 month of treatment and were between 2.26–3.09 mmol/L (mean=2.5 mmol/L). Nine patients were started on Cinacalcet as a primary treatment when curative surgery was not an option, whereas only three patients were started with adjusted calcium levels greater than 2.85 mmol/l and significant cognitive impairment. Two patients were started as a secondary treatment where curative surgery had failed and further surgery was not possible.

Conclusion

We would need to continue to work on our practices to meet the criteria set out by NHS England Clinical Commisioning Policy.

We have identified that vitamin D is not consistently checked and replaced prior to starting Cinacalcet.

Majority of patients were started on Cinacalcet as a primary treatment when curative surgery was not an option.

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P96

A rare case of Graves' disease in a patient with type 1B pseudohypoparathyroidism and associated TSH resistance

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Introduction

Pseudohypoparathyroidism (PHP) is a heterogeneous group of endocrine disorders characterized by target-organ resistance to the action of PTH, manifesting with hypocalcemia, hyperphosphatemia, and increased serum concentrations of PTH. PTH receptor couples with the stimulatory G protein (Gsα), leading to cAMP formation. Most cases of PHP are caused by heterozygous inactivating mutations in the *GNAS* gene, encoding Gs((PHP type 1A) or methylation defects within the imprinted *GNAS* locus (PHP type 1B). Resistance to other hormones signaling through G protein–coupled receptors, particularly TSH, is typical in type 1A PHP and can also occur in type 1B PHP.

Case report

In 2014, a 30-year-old woman sought medical attention because of fatigue. Laboratory tests showed: serum calcium 7.4 mg/dl, serum phosphate 5.2 mg/dl, PTH 916 pg/ml, 25OHD 19.8 ng/ml, TSH 5.78 mU/l and free T4 0.8 ng/dl. After 2 years without follow-up, the patient was referred to our hospital because of similar laboratory test results. Except for thigh muscle pains, she was asymptomatic. Clinical examination ruled out Albright hereditary osteodysthrophy, obesity or cognitive impairment. Laboratory examination included: serum calcium 7.2 mg/dl, albumin 3.9 g/dl, serum phosphate 5 mg/dl, magnesium 1.9 mg/dl, urine calcium 40.3 mg/24 h, urine phosphate 475.8 mg/24 h, PTH 948.3 pg/ml, 25OHD 20.8 ng/ml, $1.25(OH)_2D_3$ 66 pg/ml, TSH 6.2 mU/l, free T4 0.57 ng/dl, TPOAb 2 U/ml. Hands x-ray showed no brachydactyly. Thyroid ultrasonography was normal. The patient's genetic study revealed a methylation defect at *GNAS* exons *XL*, *AS* and *A/B*, and a gain of methylation at *NESP55*. DNA analyses from both parents showed normal methylation pattern at all differentially methylated regions, confirming the diagnosis of sporadic PHP type 1B. The patient was treated with oral calcium supplements, calcitriol and levothyroxine. Ten months later she begun with symptoms of severe hyperthyrodism and goiter. A new biochemical assessment showed normalization of serum calcium and phosphate, PTH 304.2 pg/ml, TSH <0.001 mU/l, free T4 3.77 ng/dl, free T3 17.93 pg/ml, TSI 11.2 mU/ml and TPOAb 10.4 U/ml. Since then, she is being treated with antithyroid drugs.

Conclusions

This case demonstrates that, although TSH and stimulating TSH receptor antibodies share signal transduction pathways for cell activation and growth, Graves' disease is possible even upon defective Gsα signalling and resistance to TSH, suggesting alternative effector mechanisms for TSH receptor antibodies.

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P97

Primary hyperparathyroidism: clinical manifistation in Russian population

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Hypothesis

The clinical presentation of primary hyperparathyroidism (PHPT) changed lately but we don't know if more patients in our population have asymptomatic form of PHPT.

Materials and methods

Medical records of 449 patients with PHPT who were operated in three Medical Centers (Saint-Petersburg, Russia) between Jan 2011– Jun 2018 were screened. We analyzed anthropometric data, laboratory tests (PTH, 25(OH)D, Ca, iCa, P, 24-h calciuria, ALP levels) and imaging tests (US, scintigraphy or CT/MRI scan, DXA).

Results

Most of the patients were women (93.1%), F:M ratio was 13.5:1. The age varied between 23 and 87 years (mean 59), men were younger than women (55 &

60, $P=0.02$). 310 patients had symptomatic PHPT (osteoporosis (41.9%), urolithiasis (25.5%) and GI lesions), and 139 patients were asymptomatic. Patients with clinical signs were older than asymptomatic ones ($P=0.025$) and often had cardiovascular pathology ($P=0.003$). 88% of men with symptomatic PHPT had urolithiasis compared to women who mainly had osteoporosis (64%). Of 449 patients 18 had MEN1, and one had MEN2a. Asymptomatic patients were younger (58 & 60 years, $P=0.002$) and had higher 25(OH)D level (32.2 & 18.6 ng/ml) compared to symptomatic PHPT patients. Vitamin D status was assessed only for 25% of pts and most of them did not receive supplements. Correlation analysis revealed associations between PTH and serum iCa ($r=0.464$, $P<0.000001$), total Ca ($r=0.258$, $P<0.000001$), phosphorus ($r=-0.313$, $P=0.000025$) and ALP ($r=0.334$, $P=0.02$). In addition, 25(OH)D was associated with iCa ($r=-0.352$, $P=0.0007$) and Ca ($r=-0.412$, $P=0.03$). Adenoma size was associated with the disease duration ($r=-0.183$, $P=0.002$), PTH ($r=0.367$, $P<0.000001$), iCa ($r=0.334$, $P=<0.000001$). Thirty-seven patients had normocalcemic PHPT form, including ten who were asymptomatic and 27 pts with certain manifestations of the disease. The size of adenoma was smaller ($P=0.01$) and PTH was lower ($P<0.0001$) than in hypercalciemic patients. In normocalcemic group there were no patients with hypophosphatemia ($P=0.04$).

Conclusion

Study results showed that in Russian patients PHPT continues to be a symptomatic disease and only 31% of cases are diagnosed using laboratory tests. PHPT is mainly a female disease often with osteoporosis. Half of PHPT men have urolithyasis. It seems that cardiovascular diseases associates with PHPT. Serum 25(OH)D level was rarely assessed and patients did not received vitamin D supplementation.

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P98

The effect of vitamin D supplementation on sarcopenia indices: a systematic review and meta-analysis of randomized controlled trials

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Objective

To systematically review and meta-analyze the best available evidence regarding the effect of vitamin D supplementation, either as monotherapy or in combination with protein and exercise, on sarcopenia indices (muscle strength, muscle mass, muscle performance).

Materials and methods

A comprehensive search was conducted in Medline, Cochrane Central, and Scopus databases, up to December 31st, 2018. Data were expressed as standardized mean difference (SMD) with 95% confidence intervals (CI). I^2 index was employed for heterogeneity.

Results

An initial search identified 768 studies, 12 of which met the eligibility criteria for qualitative and quantitative analysis ($n=1.470$, age 78.4 ± 7.6 years, follow-up 8–24 weeks). Vitamin D dosage was either 1,600 ($n=2$), 1,404 ($n=1$), 900 ($n=1$), 800 ($n=3$), 500 ($n=2$) or 100 IU/day ($n=1$), 10.000 IU thrice/week ($n=1$) or 300.000 IU, as a single dose ($n=1$). Concerning muscle strength, vitamin D supplementation was superior compared with placebo ($n=9$, SMD 0.41, 95% CI 0.133 to 0.689, $P=0.004$, I^2 71). This was also evident when vitamin D was co-administered with protein ($n=5$, SMD 0.559, 95% CI 0.102 to 1.017, $P=0.017$, I^2 84), whereas vitamin D monotherapy had no effect ($n=4$). Concerning muscle mass, vitamin D showed a marginal positive effect compared with placebo ($n=4$, SMD 0.23, 95% CI -0.003 to 0.472, $P=0.053$, I^2 0). When vitamin D was co-administered with protein, a significantly positive effect was evident compared with placebo ($n=2$, SMD 0.371, 95% CI 0.002 to 0.740, $P=0.049$, I^2 0). Concerning muscle performance, no effect was shown ($n=2$).

Conclusion

This is the first meta-analysis providing evidence that vitamin D supplementation increases muscle strength and mass in patients with sarcopenia, only when it is co-administrated with protein. Further well-designed studies are needed to clarify the effect of vitamin D supplementation on sarcopenia.

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P99

The factors affecting balance function in patients with osteoporotic vertebral fractures

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Aim

The aim of the study was to estimate the main factors influence on static and dynamic balance function in osteoporotic patient with vertebral fractures (VF).

Methods

90 patients aged 43-80 with primary osteoporosis were enrolled. Study group comprised of 56 women and 4 men (age 65.4 ± 7.1 years, BMI 26.7 ± 4.4 kg/m^2) with at least 1 VF confirmed by X-rays. Control group included 28 women and 2 men (age 62.0 ± 5.2 years, BMI 28.7 ± 5.9 kg/m^2) with the same BMD and without any osteoporotic fracture. The examination program included stabilometry, static and dynamic balance tests (Fukuda-Unterberger test, One-leg-standing test) and 25(OH)D level evaluation.

Results

Study group was characterized by change vs control group in balance coefficient (BC) (77.2 ± 7.6 vs 85.7 ± 9.4% with opened eyes, $P=0.002$, 67.1 ± 9.8 vs 73.4 ± 9.9% with closed eyes, $P=0.03$), pressure center of media-lateral (PCML) deviation in sagittal plane (1.2 [−1.1;1.5] vs −1.2 [−1.5;1.2] mm, $P=0.025$) and PCML displacement in sagittal plane (6.8 [3.1;37.7] vs to 4.8 [1.8;10.7] mm, $P=0.01$). BC correlated with age ($r=0.41$ with opened eyes, $r=0.40$ with closed eyes, $P=0<0.01$) and BMI ($r=0.16$ with opened eyes, $P=0<0.05$). PCML deviation in sagittal plane correlated with age ($r=-0.42$, $P=0<0.01$), number of VFs ($r=0.40$, $P=0<0.001$) and femoral neck BMD ($r=-0.43$, $P=0<0.05$), and in frontal plane only with age ($r=-0.27$, $P=0<0.05$). PCML displacement in sagittal plane correlated with age ($r=-0.29$, $P=0<0.01$), number of VFs ($r=0.22$, $P=0<0.01$) and femoral neck BMD ($r=-0.38$, $P=0<0.05$) and in frontal plane only with BMI ($r=-0.15$, $P=0<0.05$). PCML deviation in sagittal plane was higher in patients with vitamin D deficiency vs subjects with normal or suboptimal 25(OH)D level ($P=0.04$). Fukuda-Unterberger test showed greater side dislocation in patients with VF vs controls (40° [25.0;45.0] vs 30° [10.0;45.0], $P=0.02$). Side dislocation correlated with number of VFs ($r=-0.30$, $P<0.05$). Patients with VF lose their balance duting One-leg-standing test faster vs controls with open eyes (5.0 [1.0;10.0] vs 7.5 [5.0;10.5] sec, $P<0.05$) and with closed eyes (2.0 [0;3.0] vs 3.5 [3.0;5.0] sec, $P<0.05$). Balance time during One-leg-standing test correlated with age ($r=-0.35$, $P<0.001$ with open eyes, $r=-0.42$, $P<0.01$ with closed eyes) and with 25(OH)D level ($r=0.25$, $P=0.01$ with open eyes, $r=0.24$, $P=0.04$ with closed eyes).

Conclusions

VFs negatively affect static and dynamic balance function that may lead increasing risk of falls and new fractures in osteoporotic patients. Elderly age, high BMI, low BMD, multiple VFs and vitamin D deficiency are main factors of balance dysfunction in osteoporotic patients with VFs.

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P100

Evaluation of trabecular bone score in men with type 1 diabetes

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Background and aims

According to modern researchers, in patients with type 1 diabetes (T1D), the presence of diabetic osteopathy and an increasing fracture risk is evident. However, the determination of bone mineral density only is not enough to adequately assess the quality of the bone. Thus, the aim of the study was to study of the lumbar spine trabecular bone score as qualitative bone characteristic in T1DM men.

Materials and methods

52 males with T1DM (mean age: 32.4 (21.2–44.9) yrs, duration of DM: 13 (7–20) yrs, age of manifestation: 19 (14–23) yrs, BMI: 23.69 (19.38–27.96) kg/μ^2; HbA1c: 8.2 (7.6–8.9) %) and 31 controls, comparable in age and anthropometric data (mean age: 30.5 (23.5–41.3) yrs, U=687.5; $P=0.707$; BMI: 24.57 (21.46–28.39) kg/μ^2, U=571.5; $P=0.119$). The research involved general clinic

examination, dual energy X–ray absorptiometry (DXA) at lumbar spine regio performed on «PRODIGY LUNAR». Bone mineral density (BMD) was taken as a quantitative assessment and trabecular bone score (TBS) was used as qualitatively parameter.). Z–score of −2.0 or less was regarded as «low bone mineral density».
Results
Low BMD was detected in 19.2% of the surveyed patients with T1DM and 6.5% of control. Lower L1–L4 BMD and TBS were significantly found in patients with diabetes compared to controls: BMD 1.13 (0.92–1.22) vs 1.25 (1.07–1.43) g/cm^2; U=411; P=0.001; TBS 1.42 (1.23–1.46) vs 1.46 (1.32–1.57); U=266.5; P=0.028), and T-score TBS −0.30 (−1.90–0.50) vs 0.10 (−1.025–0.90); U=233; P=0.042). There were no significant differences in L1–L4 Z-score TBS in T1DM men compared with control: 0.40 (−0.70–1.25) vs. −0.70 (-0.90–0.50) g/sm^2; (U=97; P=0.077). There was a definite significant correlation between BMD (L1–L4) and TBS (L1–L4) – r^2=0.41, P=0.001. However, similar results were not obtained in subgroups of T1DM men (r^2=0.32, P=0.051) and controls (r^2=0.42, P=0.051).
Conclusions
The data confirmed low bone mineral density and trabecular bone in the lumbar spine in type T1DM men. Thus mechanisms responsible for the formation of healthy bones require further research.

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P101

Association between body mass index and the risk of falls: a nationwide population-based study

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Background
This study examined the associations between body mass index (BMI) and falls in Korean adults using data from a large population-based survey.
Methods
We analyzed 113,353 men and women (aged ≥50 years) who participated in Korean Community Health Survey in 2013. The BMI groups were classified as underweight (<18.5), normal weight (18.5≤ BMI< 24.9), overweight (25≤ BMI< 29.9), and obese (≥30). Logistic regression was used to assess the relationship between BMI and falls.
Results
The mean (± standard deviation) age and BMI of all the participants were 63.8± 9.6 years and 23.2±2.9 kg/m^2. Among 113,353 study participants (52,784 men and 60,569 women), 4.5% were underweight and 1.7% were obese. Fifteen percent of men and 22% of women had a history of falls. The association between BMI and falls was different according to sex. The normal weight group showed the lowest risk of falls in women, but not in men. The odd ratio (OR) for falls associated with BMI <18.5, 25–29.9, and ≥30 kg/m^2 were 0.99 (95% CI 0.87–1.14), 1.20 (95% CI 1.11–1.29), and 1.47 (95% CI 1.22–1.75) compared with women with BMI 18.5–24.9 kg/m^2 after adjusting for multiple variables. Underweight men had a higher risk of falls compared with normal weight men (OR 1.25, 95% CI 1.05–1.47). However, there was no difference of fall risk between normal weight, overweight, and obese men.
Conclusions
Overweight and obese women had an increased risk of falls than in normal weight women, whereas there was only a significant correlation between falls and underweight status in men.

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P102

Various clinical features of Digeorge syndrome

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Background
DiGeorge syndrome (DGS) is the rare genetic disorder caused by a 22q11.2 chromosome microdeletion. The main clinical features are associated with defective development of the pharyngeal pouch system and usually include congenital heart disease, hypoplasia of thymus resulting in immune deficiency and hypoparathyroidism. Also DGS patient has characteristic long face with narrow palpebral fissures, broad nasal bridge, micrognathia and small mouth, small dysmorphic ears.
Aim
To describe the 20 years old patient with delayed diagnosis of DGS due to unspecific disease manifestation.
Clinical case
Ventricular septal defect and patent foramen ovale were diagnosed at birth and repaired when the patient was 3 years old. Since childhood pediatrics have noted moderate delay in the cognitive function and rare episodes of febrile seizures up to 3–4 times a year. However, hypoparathyroidism was diagnosed only at the age of 17 years, when the low serum calcium levels were first determined. Despite the prescribed calcium supplementation the febrile convulsions have persisted. Upon admission to our center the patient presented with periodic muscle convulsions in the upper and lower extremities, recurrent headaches, stabbing pain in the heart, weakness, memory loss. Physical examination revealed mild facial dimorphism (wide and flat nose, small low-set ears), hyperkyphosis, obesity (BMI 30.0 kg/m^2). Pathological laboratory findings were as follows: corrected calcium 1.38 mmol/L (2.1–2.55), ionized calcium 0.68 mmol/l (1.03–1.29), phosphorus 3.0 mmol/l (0.74–1.52), PTH 9.13 pg/ml (16–65). CT-scan showed the calcifications in basal ganglia. No clinical and laboratory evidence of significant immunodeficiency was found in our patient. He had been managed by combined therapy with alfacalcidol (1 μg per day), cholecalciferol (7500 IU per week), calcium (6000–8000 mg per day) for one year. The follow-up examination demonstrated the significant improvement as persistent normocalcemia, absence of convulsions and paresthesia, posture straightening, muscle weakness reduction, weight loss and increased physical activity. A genetic study identified a large chromosome 22q11.2 deletion and the diagnosis was confirmed for DGS. Besides there were found the insertion in X-chromosomal Sox3 gene that can explained the mental retardation.
Conclusion
Clinical presentation of DGS can be variable and the severity of each organ involved is wide. Although the symptoms associated with hypocalcemia suggest a wide range of diseases, DGS should be considered in children and young adults with concomitant cardiac defects, development delays and other suspicious features.

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P103

About a case of familial hypocalciuric hypercalcemia (FHH) type 3 with neurological involvement

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Background
FHH is a genetically heterogeneous condition mimicking primary hyperparathyroidism at the difference of low urine calcium excretion. FHH types 1, 2, and 3 are due to loss-of-function mutations of the CASR, GNA11, or AP2S1 genes, respectively. FFH 3, the rarest of the 3, is usually associated to 3 recurrent mutations affecting the arginine residue in position 15. The clinical phenotype has not been well described. We report a new case striking by the neurological involvement. Case: A 26-year old man was referred for fortuitously found hypercalcemia (135 mg/l, 3.36 mmol/l). The family history was not well known. The personal history included bilateral inguinal hernia and testicular fixation. The patient had followed a special schoolchild course because of mild cognitive impairment but was able to work and no further investigations were done. Biological assessment revealed moderately high calcium (115 mg/l, 2.86 mmol/l), low 25OHvitD3 (22 ng/ml), but normal phosphate (29 mg/l; N:2–45), magnesium (22 mg/l; N:20–24), and PTH (54 ng/ml; N<68) blood levels, with low urine calcium excretion (63 mg/24 H; creatininuria: 0.7 g/24 H). Nevertheless, bilateral nephrocalcinosis was present on CTscan. The Tscore (DEXA) was −1.5 (vertebral) and −1 (femoral), and remained stable over time. The diagnosis of FHH1 was considered. Frequent intron 5 polymorphism and heterozygous variant of the CASR gene were identified that could not explain biological features. At 33 years old, the patient was re-referred after surgery of calcifying right hip tendonitis with very poor results confining the patient in a wheeling-chair. Besides physical inability, the patient had now overt cognitive impairment (MMS: 25/30) confirmed by a specialized neurological evaluation showing attentional and working memory disorders (MOCA 21/30) despite a normal brain MRI. He couldn't read or work anymore and couldn't remember the birth date of his 9-month old child. The NGS completion of the genetic work-up showed a AP2S1 gene heterozygous variation (exon2: c.43C>T (p.Arg15Cys) arguing for type 3 FHH.

Conclusion
Despite similar biological and genetic features (with the most frequent p.Arg15Cys mutation), the phenotype of this case was different from that one reported in one of the largest FHH3 cohort (Vargas-Poussou JCEM 2016) since our patient had nephrocalcinosis and no osteoporosis, with evolutive cognitive impairment, as reported in some other series (Szalat Endocrine 2017; 10 patients - Hannan Human Molecular genetic 2015; 17 patients). These findings suggest that AP2S1 could play a role in neural development. Cognitive impairment in FHH should orientate towards AP2S1 gene mutation.

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P104

Verified data on parathyroid hyperplasia incidence not related to primary hyperparathyroidism in persons exposed to ionizing radiation

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During the Chernobyl nuclear power plant accident (ChNPPA) a mixture of radioactive isotopes, mainly the iodine and cesium, were released, which through inhalation and food, and in some cases along with external exposure had affected the hormone-producing cells of endocrine system. Within days and months after the accident, the thyroid and parathyroids accumulated a significant amount of these isotopes with thyroid gland becoming a secondary emitter, which further increased the exposure of parathyroids. Therefore, we expect some significant disorders in parathyroid gland system in the late period of the ChNPPA. We have developed and improved the method of ultrasound screening of parathyroids, which increases the efficiency of their visualization. We have conducted a survey of 1,534 individuals attributed to the ChNPPA survivors exposed to ionizing radiation. Thirty-two years after irradiation the parathyroid hyperplasia not related to primary hyperparathyroidism was detected on average in 34.4% of cases, namely in 28.8% of the ChNPPA clean-up workers, 71.5% evacuees from the 30-kilometer contaminated zone around the Chernobyl nuclear power plant, 41.5% residents of areas under a radiological control, 45.5% residents of Kiev city and Kiev region, and 33.3% subjects irradiated in prenatal period of life. Thus, there is a high prevalence of parathyroid hyperplasia among the population of Ukraine exposed to a range of radiation doses from the tropic iodine, cesium and strontium isotopes, including the low-dose prolonged irradiation. In most cases there were no abnormalities in serum concentration of parathyroid hormone and ionized calcium. Deficiency or lack of vitamin D was an additional factor involved in this situation. Our immediate task is to study the incidence of functional disorders of parathyroid hormone secretion and relation of parathyroid hyperplasia on vitamin D deficiency, as well as to identify any comorbid disorders in the vulnerable population groups.

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P105

Parathyroid carcinoma: identity with diagnostic difficulties and therapeutic strategies

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Blackground
Parathyroid carcinoma is a malignant neoplasm affecting 0.5 to 5.0% of all patients suffering from primary hyperparathyroidism. This cancer continues to cause challenges for diagnosis and treatment because of its rarity, overlapping features with benign parathyroid disease.
Case report
50 years-old-woman, without relevant previous history. She begins to present asthenia, weakness of lower limbs, arthralgias, cramps and appearance of a painful tumor but with progressive upgrowth at the level of the left tibial tuberosity since one year ago. Physical examination: blood pressure 100/54 mm/Hg, 55 kg, 166 cm BMI 19.9 kg/m^2, nodule in left thyroid lobe and painful tumor of 5×3 cm on palpation in left anterior tuberosity, atrophy muscular and no presence of edema in lower limbs. The rest of the exploration without findings. Blood test: Hb 12.5 g/dl, Ca 14 mg/dl (VN < 10), P 1.8 mg/dl (VN > 2.7), Mg 2.3 mg/dl, albumin 3.9 dl/l, 15 OH calcitriol 22.8 ng/ml (VN > 30), PTH 1174 pg/ml (VN < 65). Urine test: calcium / creatinine index 0.3 mg/mg. In thyroid ultrasound we observed on the lower pole of the left thyroid lobe an hypoechogenic and heterogeneous nodule of lobulated foci, predominantly solid but with a superior cystic, vascularized component, appearing to present a plane of separation with the thyroid gland with size 16.5×15×38 mm. Suggestive of parathyroid injury and whose location it was also confirmed by Tc99 m MIBI scintigraphy. The biopsy of the tibial tumor presents pathological anatomy compatible with brown tumor. Densitometry with osteoporosis in the lumbar spine T −2,6. In the surgical treatment, a left hemithyroidectomy was performed, removal of the two left parathyroid glands and ipsilateral lymph node dissection. Pathological anatomy suggestive of 2.5 cm parathyroid carcinoma infiltrating thyroid and focally adjacent fat. Contact the surgical edge. Postoperative PTH level, performed on the second day of surgery, was 95 pg/mL and calcium levels within normal. At hospital discharge we left her calcium supplements and alendronic acid to avoid hungry bone syndrome and treat osteoporosis. Monitoring should be done every 3 months with clinical examination and calcium levels during the first 3 years.
Conclusion
We observed that patients with parathyroid carcinoma are more likely to have symptoms than adenomas: appearance of neck mass, bone and kidney disease, elevated levels of calcium and PTH. When we have an early diagnosis and an early surgery, the percentage of survival can reach 67% in 10 years.

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P106

Case Report of a large family with hyperparathyroidism- jaw tumor syndrome (HPT-JT) and a deletion of the third exon of *CDC73*

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Heterozygote mutations of the gene *CDC73* are responsible for 3 types of parathyroid diseases: familial hyperparathyroidism, parathyroid carcinoma, hyperparathyroidism-jaw tumor syndrome (and uterine or kidney lesions). The goal of our study was to describe the phenotype associated with the deletion of the 3rd exon of *CDC73* found in a large family.
Patients
We have medical records for 25 patients of a large family composed of 44 individuals through 4 generations. 17 patients had a genetic analysis: the deletion was found in 11 individuals; was absent in 6 people. Additionally, 3 patients were assumed carriers of the deletion and 5 patients were children of non mutated patients. 4 patients were asymptomatic with among them, mostly children but also, one patient of 43 years. 8 mutated patients had primary hyperparathyroidism (HPT) with two acute hypercalcemic crisis (maximum calcium level 4.48 mmol/L, parathormone plasmatic level of 1100 pg/mL (N < 60 pg/mL). The median age of onset of hypercalcemia was 37 years (range from 14 to 59 years). We reported 2 patients with brown tumors (median age at onset was 37 years). Six patients had kidney diseases related to hypercalcemia: 5 urinary lithiasis (median age at onset was 41.5 years) 2 nephrocalcinosis, 3 chronic kidney failures with 1 chronic endstage kidney failure. Hypercalcemia was surgically resolved in the 8 patients and we found only a single parathyroid adenoma in each patient; no carcinoma or atypic lesion. Recurrence of moderate hypercalcemia occured in one patient after 7 years. In this family, the phenotype variability was emphasized by 2 cases: in 2 monozygotic twins, one patient is still asymptomatic at 43 years of age and the other presented with acute hypercalcemia and kidney failure. The youngest symptomatic patient was 13 years old (calcium level 3,4 mmol/L). The other lesions associated to this mutation in the family were: 1 ossifiying fibroma (surgically treated at 31 years of age, with a relapse at 36 years); and one kidney cyst. No gynecological lesions were described.
Conclusion
We report a new large family of HPT jaw tumor syndrome with deletion of the 3rd exon of *CDC73* which led mostly to HPT with a particularly severe impact on kidney. The presentation is highly variable highlighting the importance of a precocious genetic screening and a regular follow-up of the patients.

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P107

Pseudohypoparathyroidism- a tale of hypo- and hypercalcemia with a genetic solution

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Introduction
Pseudohypoparathyroidism (PHP) is a rare genetic disease characterized by renal resistance to parathyroid hormone (PTH), presenting with hypocalcemia, hyperphosphatemia and elevated PTH levels. We describe a PHP patient who presented with clinically significant hypercalcemia.
Case description
A 46-year-old woman with a prior history of hypocalcemia presented to the emergency department with new-onset hypercalcemia, renal failure and anemia. Blood gases showed a mild metabolic alkalosis. She had suffered recurrent hypocalcemic episodes throughout her life with elevated PTH levels and hypocalciuria, suggestive of PHP. Chronic medications included calcium 1800 mg/day, alfacalcidol (1α-OHD3) 3 mcg/day and cholecalciferol (vitamin D3) intermittently. A previous PTH infusion test supported the diagnosis of PHP. There were no Albright Hereditary Osteodystrophy (AHO) features, other hormone resistances or family history of calcium homeostasis dysregulation. Bearing these characteristics in mind, PHP type 1B seemed most likely and was subsequently proven by genetic testing. As for the cause of hypercalcemia, intoxication of calcium or Vitamin D was suspected and all supplements were stopped with rapid normalization of calcium levels. Laboratory 25-OHD3 and 1α,25-OHD3 levels were low. There was no evidence of malignancy. The patient subsequently became hypocalcemic and supplements were recommenced at lower doses. The patient remains normocalcemic since.
Discussion
Treatment modalities in PHP include calcium and hydroxylated vitamin D supplements. Aims of treatment include maintaining normocalcemia and normalizing PTH levels in order to avoid potentially deleterious skeletal effects of chronically elevated PTH levels. Hypercalcemia has been reported rarely in PHP, but more frequently in hypoparathyroidism due to milk alkali syndrome or vitamin D intoxication. We speculate that our patient's hypercalcemia was caused by supplement overdose although vitamin D levels were not elevated and the patient denied increasing her regular calcium dose. The mild alkalosis and renal failure may allude to milk alkali syndrome. In conclusion, close surveillance is essential in PHP to prevent potentially life-threatening electrolyte disturbances.

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P108

Generalized skeletal hyperostosis mimicking acromegaly

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A female patient presented at the age of 30 years with an incidental radiological finding of hyperostosis after a traumatic knee ligament injury. Her large facial contours with wide hands and fingers reminded acromegalic features but without typical soft tissue changes. Hormone evaluation discovered an elevated IGF-1, growth hormone (GH) was non-suppressed on glucose load, but pituitary MRI was normal. The imaging revealed remarkable cortical thickening of long bones with prominent homogenous cranial hyperostosis, large and thick facial bones, sclerotic vertebral bodies and hypertrophic metatarsal and phalangeal bones. The bone mass density was extremely increased with Z-scores values between +10 and +13. An inborn flexion contracture of the left index, clubbing fingers and dysplastic nails were observed. The intracranial space was reduced, but without significant brain compression. Beside some occasional nonspecific headaches, she has been asymptomatic with no cranial nerves damage. After being lost for follow up, her condition was re-evaluated 8 years later. Her headaches did not deteriorate. She complained of progressive exophthalmos, torus palatinus and she had worsening nasal obstruction with pronounced sleep apnea due to the extreme narrowing of the nasal cavity. The thickness of her occipital bone reached 35 mm but no evident change in intracranial compression occurred. A surgical widening of the nasal airway was performed. The modelling of orbital rims and the floor of the orbit to reduce exophthalmos was done. The reduction of the mandible and the maxilla resulted in considerable clinical and facial contours improvement and the sleep apnea was significantly reduced. The predominant craniotubular hyperostosis and digit deformities in this patient are similar to skeletal alterations found in sclerosteosis. The DNA was sent for investigation, but no known high bone mass causative mutations have been confirmed yet. We are not aware of any other family member with such a phenotype. The patient had again a hormonal profile mimicking acromegaly without typical clinical sequelae of GH over-secretion. Pituitary, thorax and abdomen imaging did not reveal any process suspicious for neuroendocrine tumour. Due to technical reasons, we could not send her blood for GH-releasing hormone determination. The disorder of the GH axis is still unresolved, but clinical data make us believe that this is not a consequence of some autonomous secretion. Hyperostotic bone diseases are very heterogeneous, usually related with mutations in the complex Wnt signaling pathway and this case might suggest an unknown interaction with the GH secretion.

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P109

Evaluation of bone quality in acromegaly and thyrotoxicosis using trabecular bone score

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Trabecular bone score (TBS) evaluates bone microarchitecture by measuring the grey-level variations from lumbar spine dual-energy X-ray absorbtiometry (DXA) images. Bone mineral density (BMD) in various endocrinopathies might not be sufficient in assessing bone fragility, especially in patients with acromegaly (ACM) but also in thyrotoxicosis. The aim of our study was to evaluate bone quality and quantity by BMD and TBS in patients with acromegaly and thyrotoxicosis.
Methods
We performed an observational, case-control study on 42 patients with acromegaly and thyrotoxicosis. Inclusion criteria were adult patients, with a positive diagnosis of acromegaly or thyrotoxicosis, with an active or residual disease, who performed DXA in our clinic. One analysis included 20 patients with acromegaly and 20 healthy controls mached 1:1 by age and gender. The second analysis was performed on 22 patients with thyrotoxicosis matched 1:1 with 22 healthy subjects, also according to age and gender. Anthropometric, biological, lumbar spine BMD, femoral neck BMD and lumber spine TBS were measured.
Results
When we compared TBS and BMD between patients with acromegaly and controls we found a non-statistically significant lower lumbar spine TBS (1.308 ± 0.140 vs 1.331 ± 0.118, $P=0.58$), femoral neck BMD (0.997 ± 0.152 vs 1.069 ± 0.319, $P=0.36$) and a higher lumber spine BMD (1.195 ± 0.170 vs 1.128 ± 0.203, $P=0.25$) in patients with acromegaly. In the second analysis, we found a lower but not statistically significant femoral neck BMD (0.774 ± 0.419 vs 0.858 ± 0.135, $P=0.37$) in the thyrotoxicosis group. Also, mean lumbar spine BMD and lumbar spine TBS did not show any difference between thyrotoxicosis and control group (0.997 ± 0.187 vs 0.999 ± 0.173, $P=0.97$ and 1.266 ± 0.164 vs 1.269 ± 0.124, $P=0.94$, respectively). In conclusion, in our study, TBS did not show superior results in evaluating bone quality alterations compared to BMD in patients with acromegaly and thyrotoxicosis.

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P110

Primary hyperparathyroidism and vitamin D

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Introduction
Several studies suggest an association between primary hyperparathyroidism (HPTP) and vitamin D deficiency. Our goal is to study the clinical and biological consequences of vitamin D deficiency in patients with primary hyperparathyroidism, and to determine the impact of Vitamin D deficiency on bone, kidney and heart functions.
Materials and methods
It is a retrospective study of 17 cases with HPTP associated with a vitamin D deficiency. We collected clinical, paraclinical, management and evolution data.

All patients underwent a biological and radiological assessment of bone, cardiac and renal functions.
Results and discussion
The mean age was 57.17 years, with a sex ratio (F/M) of 0.23. The mean vitamin D value was 11.37 ng/mL, with a mean PTH value of 391 ng/L. Patients with vitamin D deficiency had a significantly higher PTH rate than patients with normal vitamin D levels ($P=0.04$). Mean serum calcium value was 117 mg/l, with no significant association with vitamin D level. Bone assessment showed an abnormal ODM in 70% of patients, radiological abnormalities were found in 29.4% of patients, these abnormalities didn't have any correlation to the rate of vitamin D. The assessment of renal function showed that 11% of patients had renal failure, while 35.6% had urolithiasis.
Conclusion
Our study suggests that vitamin D deficiency in patients with primary hyperparathyroidism is associated with a higher rate of PTH, and occurrence of bone complications.

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P111

The coincidence of primary hyperparathyroidism and primary hyperaldosteronism is not infrequent: a retrospective case analysis

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Introduction
Primary hyperparathyroidism (PHP) has been postulated to be a cause of primary hyperaldosteronism (PHA). In fact, PTH receptors have been detected in aldosteronoma tissue. Hyperaldosteronism can also induce elevation of PTH levels, as increased circulating volume increases calciuria, with secondary elevation of PTH levels as serum calcium levels rise. We studied the prevalence of PHP in a group of patients diagnosed with PHA either following or simultaneously with diagnosis of PHP.
Methods
A retrospective study was performed. In a single Endocrine outpatient clinic of a general hospital, 46 patients were diagnosed as having PHA over a 6-year period (2010–2016), with strict application of the Endocrine Society 2008/2016 guidelines. The 25 mg captopril test was considered diagnostic when either the 2-hour aldosterone level was $\geq$130 pg/ml and/or the 2-hour aldosterone/renin ratio (ARR) was $\geq$50. Patient histories were reviewed to detect cases in which PHP had been diagnosed prior to or simultaneously with PHA. We describe the characteristics of the patients presenting PHP. Direct renin and serum aldosterone were measured by RIA and expressed in pg/ml.
Results
10/46 (21.7%) patients were diagnosed as having both PHA and PHP. 7/10 were females. The mean age was 64.3 (SD 14.3). PHP was secondary to a parathyroid adenoma in 4/10 patients and secondary to hyperplasia in 3/10. In another 3/10 patients PHP responded to vitamin D therapy and localization tests were not undertaken. Adrenal vein sampling (AVS) was performed in 7/10 patients. 2/7 presented unilateral aldosterone secretion, whereas 5/7 presented bilateral secretion (Table 1). No correlation was found between maximum calcium levels and corresponding PTH values on the one hand, and basal or 2-hour post-captopril aldosteronemias on the other hand.
Conclusions
The coincidence of primary hyperparathyroidism and primary hyperaldosteronism is not infrequent, affecting over 20% of our primary hyperaldosteronism patients. Although hyperparathyroidism has been postulated to induce an aldosterone-secreting adrenal adenoma, in our small series of patients with primary hyperparathyroidism, primary hyperaldosteronism was found to be due more often to bilateral aldosterone secretion, as indicated by AVS. The relationship between the two entities has yet to be elucidated.

Table 1 Calcium, PTH, vitamin D, and serum aldosterone values in patients with PHP and PHA.

Maximum calcium (mg/dl)	PTH (pg/ml)	25-OH Vitamin D (ng/ml)	Basal (pre-captopril) serum aldosterone (pg/mL)	2-hour post-captopril serum aldosterone (pg/mL)
11,39 (SD 0.74)	122 [IQR 74-197]	21.4 (SD 13.2)	197.5 [IQR 169-293]	211 [IQR 201-352]

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P112

Bilateral hip fractures and osteoporosis in a 40-year old man – identification of a novel *TMEM38B* mutation causing osteogenesis imperfecta

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Context
It is mandatory to rule out secondary causes of osteoporosis in young adult males presenting with osteoporotic fractures. If no such causes are identified, it is important to remember that an underlying genetic defect might explain the phenotype. This has implications for treatment, follow-up, as well as screening of family members.
Case
A 40-year old male (172 cm, 78 kg) with a past medical history of asthma and pollen allergies, initially presented to the orthopedic department with painful right groin. The pain had started 10 days after he fell on his back at work. The pain was provoked by weight-bearing and spread to both groins 1 month after the initial presentation - which on examination was pain on rotation of both hip joints. After the initial non-diagnostic pelvic radiograph and ultrasound, pelvic MRI showed bilateral stress fractures of the femoral necks. Previous history of fractures included high-energy fractures of right thumb and right fifth finger. The patient had a family history of osteoporosis (father and sister) and his father had had a femoral neck fracture at the age of 60. There was no history of fractures from the maternal side. On a DEXA scan, bone mineral density was osteopenic at the lumbar spine and right femoral neck and osteoporotic at the left femoral neck with a T score of -2.8. Primary hyperparathyroidism, and coelic disease were excluded. Serum 25-hydroxyvitamin D(3) was low at 33 nmol/L (reference range $>$ 40). Iliac crest bone biopsy showed low trabecular bone volume with a normal turnover rate, normal osteoblast and osteoclast surfaces, normal mineralising surface, but with a slightly low mineral apposition. Bone biopsy findings were consistent with normal-turnover osteoporosis. The patient was treated with calcium and vitamin D supplementation and alendronate for two years. The bilateral femoral neck fractures healed with conservative treatment but the patient continues to have bilateral hip pains and has early arthrosis of the left hip. Evaluation in Endocrine Department showed no features of Cushing's disease. Both hypercortisolism and hypogonadism were biochemically ruled out. However, genetic analysis revealed a novel mutation in *TMEM38B,* which to our knowledge is the first report of this specific mutation, which causes osteogenesis imperfecta type XIV.
Discussion
Genetic defects may underlie not only pediatric but also adult-onset fragility osteoporosis. Here, we report a novel mutation in *TMEM38B* causing type XIV osteogenesis imperfecta and bilateral femoral stress fractures in an adult male.

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P113

Hypomagnesemia induced disturbance of consciousness in alcoholic cirrhosis

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Introduction
Serum calcium (Ca) is a major regulator of PTH secretion, but serum magnesium (Mg)also can modulate PTH secretion. Intracellular Mg depletion impairs the ability of the parathyroid to secrete PTH,which subsequently cause fall in the serum Ca concentration.
Case report
A 67 year old male patient was admitted to intensive care unit because of disturbance of consciousness, due to suspected hepatic encephalopathy. In his previous history, he had only symptoms suspected on alcoholic polyneuropathy. His Glasgow coma scale was 5, with laboratory findings that indicated liver cirrhosis: hemoglobin 99 g/L, mean corpuscular volume 108 fL, platelets 78 $\times 10^9$,

glycemia 6.9 mmol/L, urea 24 mmol/L, creatinine 111 μmol/L, AST 99 IU/L, ALT 54 IU/L, GGT 267 IU/L, AP 212 IU/L, bilirubin 26 umol/l, LDH 312 IU/l, PV 20.6 s, APTT 44 s, fibrinogen 1.9 g/L, sodium 129 mmol/l, potassium 4.6 mmol/l and albumin 26 g/L. His total serum Ca was 1.12 mmol/L, and ionized Ca was 0.52 mmol/L. Ammonium was normal. Hepato-protective therapy was started with calcium replacement, but without improving the state of consciousness. Further evaluation revealed low PTH values with high phosphorus concentration, which confirmed hypoparathyroidism. By measuring magnesium, we realized hypomagnesemia (Mg 0.27 mmol/L) and add Mg supplementation. Two days after, a gradual increase in Ca, Mg and PTH concentrations lead to improved consciousness, and four days after he recovered completely. The patient developed alcoholic cirrhosis, still without elements of liver decompensation.

Conclusion

Usually hypocalcemic crisis presents with the classical symptomatology of tetany with extrapyramidal symptoms, accompanying with disturbance of consciousness leading to coma. In our patient, hypocalcemia appeared to result from transient hypoparathyroidism induced by magnesium deficiency due of prolonged alcohol abuse.

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P114

Is any body composition parameter a risk factor for symptomatic hypocalcemia after thyroidectomy?

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Objective

Postoperative hypocalcemia is one of the major concerns following total thyroidectomy as well as the most frequent cause of prolonged hospital stay. The first purpose of this study was to evaluate the relationship between body composition parameters and symptomatic hypocalcemia following total thyroidectomy. In addition, the effects of disease- and patient-related factors on hypocalcemia were investigated.

Methods

In this cohort study, a total of 144 patients were included prospectively between March 2014 and September 2017. Demographics, preoperative biochemical parameters including serum calcium, albumin, parathyroid hormone (PTH), vitamin D, and thyroid function tests, ultrasonographic features of the dominant nodule, placement of the thyroid gland, and histopathological findings were recorded. The body composition measurements including weight, height, body mass index (BMI), total body water, free fat mass, fat mass, body fat range, muscle mass, bone mass, degree of obesity, and visceral fat rating were obtained using a bioelectrical impedance analyzer. Patients who underwent total thyroidectomy were divided into two groups according to the presence or absence of hypocalcemic symptoms. Subsequently, the relationship between body composition parameters and symptomatic hypocalcemia were evaluated.

Results

Postoperative symptomatic hypocalcemia occurred in 28 patients (19.4%). Permanent hypocalcemia was not encountered in any patient in the 12-month follow-up period. Patients with hypocalcemic symptoms were more likely to have a dominant nodule larger than 40 mm (39.3% vs. 17.2%, $P = .011$), retrosternal goiter (25.0% vs. 7.8%, $P = .017$), and parathyroid autotransplantation (28.6% vs. 3.4%, $P < .001$) compared with those without symptoms. However, no differences were observed for body composition parameters between symptomatic and non-symptomatic patients. In addition to these findings, when evaluated separately, patients with a BMI ≥ 25 kg/m^2 had a similar operative time (117.8 min vs. 117.4 min; $P = 0.693$) and length of hospital stay (32.7 h vs. 31.0 h; $P = 0.461$) to patients with a BMI < 25 kg/m^2. On multivariate analysis, lower preoperative PTH levels (OR 1.05, 95% CI 0.93−1.00, $P = .028$), presence of retrosternal goiter (OR 5.26, 95% CI 1.45−19.16, $P = .012$), and parathyroid autotransplantation (OR 16.85, 95% CI 3.68−77.11, $P < .001$) were the independent predictors of symptomatic hypocalcemia.

Conclusion

This study demonstrates that patients with lower preoperative PTH levels, retrosternal goiter, and parathyroid autotransplantation are at increased risk of developing postoperative hypocalcemia. Body composition parameters have no effect on the incidence of symptomatic hypocalcemia after total thyroidectomy.

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P115

Severe diffuse tissue calcifications in a patient with pseudohypoparathyroidism type 1 A due to a novel large deletion of GNAS gene

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Pseudohypoparathyroidism type 1 A (PHP-1A) is a rare genetic disorder characterized by hypocalcemia, hyperphosfatemia, multi hormones resistance (PTH, TSH, Calcitonin, GH) associated with Albright hereditary osteodystrophy (AHO) features. The disease is caused by GNAS haploinsufficiency due to inherited inactivating mutation of GNAS-gene that codes for the stimulatory alfa subunit of G protein. A positive genotype-phenotype correlation was recently hypothesized. The purpose of this work is to describe a new family affected by PHP-1A. The proband, a 18 years old man, came for the first time to our attention in 2017 for hypocalcemia diagnosed after a tetanic crisis. Physical examination showed the typical features of AHO: round face, stocky habitus with short stature, brachydactyly and ectopic-severe ossification in the back and in the legs. Laboratory tests showed low levels of calcium, high levels of phosphate and high levels of PTH, TSH and calcitonin despite therapy with calcium carbonate, calcitriol and levothyroxine. Computed tomography showed diffuse calcifications 'rosary-like' in the cortex and scalp. Bone radiography showed diffuse soft tissue and costal cartilage calcifications and marked brachydactyly and brachimetacarpy. Family history was remarkable for hypocalcemic crisis associated with neurocognitive impairment and cerebral calcification in the brother. The genetic analysis of the GNAS gene showed a novel large deletion (encompassing exons 1–7), in the proband, in the brother and in the mother. The daily dose of calcitriol, calcium carbonate and L-thyroxine was increased with good control of hypocalcemia thereafter. At the latest evaluation, serum calcium and TSH levels were normal with a reduction of PTH levels. In conclusion, we have identified an additional PHP-1A family with severe phenotype that supports the hypothesis of a positive genotype-phenotype correlation.

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P116

Successful removal of parathyroid cancer metastasis from VI thoracic vertebra

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Background

Approximately 25% of patients with parathyroid carcinoma (PC) have metastases; the most frequent sites include cervical lymph nodes (30%) and lungs (40%). Less common are liver, bones and brain. Surgical resection of local or distant metastases (if possible) provides the best control of hypercalcemia and enhances long-term survival.

Case description

A 70-year old patient was admitted to hospital with a primary hyperparathyroidism (PH). He did not display disease specific signs or symptoms. Blood biochemistry resulted: severe hypercalcemia (total calcium – 3.21 (2.15–2.55)), elevated PTH level - 543 pg/mL (15–65). Ultrasound (US) examination and 99 mTc-Sestamibi (99 mTc-MIBI) scintigraphy detected a tumor of right lower parathyroid gland (PG) – 19 × 22 × 35 mm. A surgical treatment did not lead to remission of the PH, the parameters of phosphorus-calcium metabolism remained on the same levels. The histological examination demonstrated vascular, adipose tissue and capsular invasion regarded as PC. CT-scan showed no evidence of metastatic lesions in lungs, mediastinum, liver, kidneys and adrenal glands. However, PET/CT with 18F-fluorocholine revealed a pathological accumulation focus of 18F-fluorocholine (SUV 8.42) in the arch of VI thoracic vertebra (ThVI). The focus measured up to 20 × 12 × 25 mm. with a displacement of the structural-dural sac at this level. Normal bone tissue in this lesion was replaced by pathological soft tissue. 99 mTc-MIBI full-body scintigraphy showed a high MIBI uptake only in the ThVI. Thus, a decompression laminectomy of ThVI with transpedicular fixation of ThV-ThVII was successfully performed with normalization of PTH and Ca levels (48 pg/ml (15–65) and 2.48 mmol/l (2.10–2.55) respectively). The histological and immunohistochemical examination confirmed the parathyroid metastasis. Another 99 mTc-MIBI scan showed no pathological

uptake in the whole body. The last follow-up in a year after the surgery confirmed the disease remission (PTH 35 pg/ml, Ca 2.3 mmol/l). The patient continues regular monitoring in our center.
Conclusion
Distant local PC metastases could be successfully surgically removed to achieve laboratory remission of the disease.

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P117

Primary Hyperparathyroidism: about 34 observations

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Introduction
Primary hyperparathyroidism (PHP) is the result of excessive, independent, and inappropriate production of parathyroid hormone (PTH). The aim of this work is to study the epidemiological, clinico-biological and therapeutic aspects of PHP.
Materials and methods
This is a retrospective study of 34 patients hospitalized for the management of PHP in the Endocrinology Department of the Military Hospital of Tunis between March 1999 and July 2018.
Results
The average age of our patients was 59 years old with female predominance (sex ratio = 0.37). PHP was asymptomatic in 57% of patients and fortuitously discovered by systematic measurement of serum calcium. The diagnosis was biological: elevated PTH with hypercalcemia or normo-calcemia. Parathyroid ultrasonography/scintigraphy, performed in 90% and 83% of patients respectively, made it possible to locate the pathological parathyroid(s), with a concordant result in 65% of cases. CT/MRI imaging was used in 23.5% of cases, with 6% of patients found to have ectopic mediastinal parathyroid adenoma. Complications were mainly found in kidneys and bone: kidney stones (37%) and osteoporosis (40%). The treatment was in all cases surgical, essentially a subtotal adenomectomy or parathyroidectomy except for cases of ectopic parathyroid nodule, which were addressed in Cardio Thoracic Surgery.
Discussion and conclusion
The signs of hypercalcemia are rarely indicative of PHP but rather sought after positive biological diagnosis. Imaging plays a key role in preoperative diagnosis and surgical approach.

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P118

The clinical spectrum and endocrine profile of pseudohypoparathyroidism: ACTH resistance should not be ignored

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Backround
Pseudohypoparathyroidism (PHP) type 1A is a rare disorder characterized by end-organ resistance to the action of parathyroid hormone (PTH), resistance to other hormones that activate Gs-coupled receptors, such as TSH and gonadotropins and phenotypic features of Albright hereditary osteodystrophy (AHO), including short stature, obesity, round face, brachydactyly and subcutaneous ossifications. PHP type 1A is caused by heterozygous loss-of-function mutations in the gene encoding the α-subunit of Gs (GNAS), inherited from the mother or de novo. The clinical features and disease severity may vary considerably among affected individuals.
Objective
To describe the diversity of the clinical and endocrine features in 11 children with PHP seen in our Division between 2007 and 2018.
Methods
In the present retrospective study, the medical records of 11 PHP children were reviewed. Data collected included: a) clinical parameters: age at diagnosis, growth pattern, AHO features, abnormalities of male genitalia b) biochemical parameters: PTH, TSH, LH, FSH, PRL, ACTH, cortisol, calcium and phosphate levels, growth hormone (GH) response following GH stimulation tests, when performed c) bone age d) molecular analysis of the GNAS gene.
Results
The median age at diagnosis was 8.5 months (range: 40 days–9 years). Among 11 PHP patients ($n = 7$ males), 9 were obese (81.8%). 8 out of 9 patients manifested early onset obesity (< 2 years of age). Round face, brachydactyly and ectopic ossifications were present in 90.9%, 81.8% and 72.7% of patients, respectively. During follow-up, growth rate retardation was noted in 45.5% and adult short stature in another 18.2% of our PHP patients. 42.9% of male patients displayed abnormalities of external genitalia. Endocrine features included: increased PTH and TSH in all cases, low PRL in 80% ($n = 8/10$), increased FSH in 10% ($n = 1/10$), and elevated phosphate levels in 81.8%. Only three cases developed hypocalcemia. GH deficiency was diagnosed in 45.5% of patients. Increased ACTH levels were observed in 3 patients (27.3%). Two of them had normal cortisol concentrations. The third case, a 2-year old girl was diagnosed with adrenal insufficiency, first manifested as full-blown adrenal crisis, while undergoing adenoidectomy. Molecular analysis of GNAS gene was performed in 9 cases. Heterozygous mutations were identified in 8 patients (88.9%), one de novo and three inherited from the mother.
Conclusions
PHP disorders may exhibit wide phenotypic variability. Measurement of ACTH and cortisol levels should be always included in the assessment of PHP patients in order to promptly diagnose an associated adrenal insufficiency that can be fatal.

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P119

Biochemical and clinical features of a family with a novel mutation of CYP24A1

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Context
Mutations of cytochrome P450 24 subfamily A member 1 (*CYP24A1*) gene are associated with Idiopathic Infantile Hypercalcemia (IIH), a disease recently related to vitamin D catabolism impairment.
Aim of the study
Report of clinical and biochemical features of a large family with a novel mutation of CYP24A1.
Methods
We performed dosage of total calcium, ionized calcium, 24 h urinary calcium, PTH, 25-OH-Vitamin D (25-OH-D), and 24–25 Vitamin D, genetic analysis of CYP24A1 and abdomen ultrasound in the proband, a 44 year old man, and in first-degree relatives (Mother, Father, Sister and Two sons). Vitamin D metabolites were analyzed using liquid chromatography mass spectrometry at Queen's University Laboratory (Kingston, Canada).
Results
The proband showed high levels of total calcium, 25-OH-D, 1,25-(OH)2-D and low levels of PTH, 24,25-(OH)2D3 and 1,24,25-(OH)3D3. 25-OH-D/24-25-OH-D ratio was high (500.5). Abdomen ultrasound showed bilateral nefrolitiasis. Genetic analysis revealed a novel homozygous mutation. In first-degree relatives, serum calcium and 25-OH-vitamin D were in the upper limit of normal range and PTH low. The 25-OH-D/24-25-OH-D ratio was normal. Abdomen ultrasound showed nefrolitiasis only in the sister. Genetic analysis confirmed the mutation in heterozygosity in each member.

Family members	CYP24A1 Mutation	*Ca^{2+} (mmol/L)	*PTH (ng/L)	25-OH-D (ng/mL)	24,25-$(OH)_2$D3 (ng/mL)	*25D3/ 24,25D3	1,24,25-$(OH)_3$D3 (pg/mL)	1,25-$(OH)_2$D3 (pg/mL)	Nephro-lithiasis
Proband (M 44 yr)	c.667 A>T p.Arg223 Homozygous	1.34	6	71.89	0.14	500.5	<2	68.2	yes
Sister (54 yr)	c.667 A>T p.Arg223 Eterozygous	1.26	14	32.26	1.54	20.6	19.7	56.6	yes
Son (13 yr)	c.667 A>T p.Arg223 Eterozygous	1.33	12	37.55	1.83	20.4	15.6	97.2	no
Son 2 (11 yr)	c.667 A>T p.Arg223 Eterozygous	1.37	20	40.59	1.53	26.3	10	70.4	no
Father (85 yr)	c.667 A>T p.Arg223 Eterozygous	n.a.	n.a	38.95	1.15	33.6	10.8	41.6	no
Mother (82 yr)	c.667 A>T p.Arg223 Eterozygous	n.a.	n.a	48.93	2.37	20.5	17.2	38.3	no

n.a.: not available*Ca2+: normal range 1,12–1,32 mmol/L * PTH: normal range 8-40 ng/L *25D3/24,25D3: normal range < 30.

Conclusions
We report the biochemical and clinical features of a family with a novel CYP24 A1 mutation. Preliminary data suggest that the new mutation is associated with a mild phenotype. However, genetic and environmental factors could contribute in the clinical outcome.

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P120

A case of primary hyperparathyroidism in a patient with Lobstein's disease

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Introduction
Osteogenesis imperfecta also known as Lobstein's disease (LD) is a rare disorder of type 1 collagen characterized by an increased susceptibility to bone fractures. Its coexistencewith primary hyperparathyroidism (PHP) was rarely described. Herein we report a new case of a primary hyperparathyroidismin a patient with a history of Lobstein's disease.
Observation
A 35-year-old woman was referred to our departmentfor hypercalcemia. Her past medical history included osteogenesis imperfecta type I diagnosed at the age of 8 years and recurrent urinary tract infections due to a vesicoureteral reflux. She presented with nausea, vomiting, constipation, bone pain, muscle weakness and depression. On examination, she had a body weight of 70 kg, a short stature, a body mass index of 28.39 kg/m^2, a blue sclera, a blood pressure of 100/60 mmHg and a regular pulse of 75 beats/min. The laboratory investigations showed a serum calcium level of 114 mg /L(normal range: 85–105), a urinary calcium level of 330 mg/24 h, a phosphate level of 17 mg/l (normal range: 25–45), a creatinine level of 7 mg/l, a magnesium level of 21 mg/l (normal range:16–26 mg/l) , a serum albumin of 34 g/L (normal range: 38–56), a Vitamin D deficiency (25 OH Vitamin D level of 5,5 µg/L, normal range: 30–80 µg/L) and an elevated parathormone level of 626 pg/ml (normal range: 10–65 pg/ml). Radiographs of long bones showed cortical bone thinning and excessive trabecular bone transparency. Bone densitometry revealed osteoporosis. Cervical ultrasound and parathyroid scintigraphy were normal. Cervical computed tomography disclosed a left superior parathyroid adenoma. Parathyroid adenomectomy was performed to the patient. After surgery, serum calcium and PTH level were normal (91 mg/l, 29 pg/ml, respectively).
Conclusion
PHP and LD are two disorders affecting the skeletal system and the calcium metabolism. Their coexistence seems to be a chance occurrence. However, it has been suggested that LD may predispose to PHP. In fact, the lifelong disorder of skeletal homeostasis in LD may lead to a secondary hyperparathyroidism and then to autonomous parathyroid tumor formation.

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Diabetes, Obesity and Metabolism 1

P121

Lifestyle modification strategies to prevent diabetes in individuals who participated in a medical health check

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Several lifestyle modification strategies have been suggested to prevent lifestyle-related diseases. However, the situation may be different for health check participants and outpatients. This study aimed to determine suitable lifestyle modification strategies to prevent diabetes in individuals who participated in a medical health check using retrospective cohort study. Individuals who participated in a medical health check in Fukuyama, Japan every year from 2011–2015 were investigated. Laboratory data between 2011 and 2015 were compared and the association between current lifestyle and onset of diabetes in the next 5 years was assessed via Cox proportional hazard model, controlling for age, sex, and body mass index (BMI). Disease onset was defined as the year of starting relevant medications. BMI was not different between 2011 and 2015. By contrast, waist circumference, systolic blood pressure, diastolic blood pressure, plasma glucose, and hemoglobin A1c levels were significantly higher in 2015 compared with those of 2011. Onset of diabetes was related to current smoking. In addition, 'eating quickly' was relevant to the onset of diabetes in the next 5 years. Medical professionals generally use 'less calories and more exercise' as advise to patients with lifestyle-related diseases. However, recommended lifestyle modification for those undergoing health checks and those in an outpatient-setting should be modified as appropriate, as they may have different characteristics from those who already have lifestyle-related diseases.

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P122

Effects of ginger powder supplementation on glycemic status and lipid profile in newly diagnosed obese patients with type 2 diabetes mellitus

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Diabetes is a huge problem affecting 387 million adults by a global prevalence of (8.3%) which is expected to rise to (10.1%) by 2035. Type 2 diabetes, a growing public health problem, is associated with increased morbidity and mortality.
Aim
To evaluate the effects of ginger powder supplementation on glycemic status, lipid profile and beta-cell function in obese Egyptian patients with new-onset type 2 Diabetes Mellitus.
Design
A randomized, single blind, placebo-controlled clinical trial, was performed on 80 subjects newly diagnosed with T2DM conducted at the National Institute of Diabetes and Endocrinology. Subjects were randomly divided into: Group 1: Ginger Group (GG), consumed three capsules daily, each capsule containing: 600-mg of ginger powder (total daily dose was 1.8 g), they also underwent certain diet and physical activity changes, and also received metformin as one 850-mg tablet twice a day with meals for a duration of 8 weeks. Group 2: Placebo Group (PG), which received capsules of the same color, size, and number as (Group 1) but containing wheat flour, they also underwent the same diet, physical activity, and metformin dosage as (Group 1) during the 8 weeks of the study.
Results
Ginger powder supplementation significantly reduced body mass index, fasting blood glucose, 2-hour postprandial blood glucose, glycated hemoglobin, total cholesterol, low density lipoprotein cholesterol, triglycerides, fasting insulin levels, and homeostasis model assessment-insulin resistance index(HOMA2-IR). Ginger also significantly increased high density lipoprotein cholesterol levels, beta cell function index (HOMA2-%β) & insulin sensitivity index (HOMA2-%S) in comparison to the placebo group.
Conclusion
Ginger supplementation could be an effective adjuvant therapy for patients with T2DM.

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P123

Effects of lemon and cumin on premature atherosclerosis in obese patients

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Background
Obesity is a multifactorial chronic disease that leads to a cardio-metabolic disease, with increased incidence of atherosclerosis.
Aim
Our aim to evaluate premature atherosclerosis in those patient and the impact of different diet on ameliorating its course.
Methodology
100 obese patients were subjected to Hb A1c, Fasting blood glucose, lipid profile, carotid artery duplex, and Brachial artery flow media dilation divided into five groups each group includes 20 patients, mean age 30–45y. group 1 without regimen diet considered as a control group, group 2 on diet regimen, group 3 diet plus cumin, group 4 diet plus lemon, group 5 diet plus cumin and lemon.

Results
There was statistically significant difference in flow mediated dilation of the brachial artery between all groups and group 1 with better values in group 3 yogurt with lemon and cumin group, however there was no differences between other groups. There was statistically significant difference between all groups and group 1 in intima media thickness, LDL, cholesterol, triglycerids, BMI, glucose level, HA1C, serum creatinine with higher values in group 1, and between all groups and group 1 in HDL with lower values in group 1. There was statistically significant difference in those use lemon and cumin and all other groups in HDL with higher values in first group.
Conclusion
Combination of lemon and cumin raise the protective effect of either component alone in preventing premature atherosclerosis in obese patients.

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P124

Management of acute charcot arthropathy

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Aims/objectives
The aim of this retrospective audit on MANAGEMENT OF ACUTE CHARCOT ARTHROPATHY was to assess the current practice at King's Mill hospital against the latest National institute of clinical excellence guidelines.
Methods
A retrospective audit of 22 patients with diabetes presented with acute Charcot neuro-arthropathy, between January 2016 and August 2018 to the specialist diabetes foot team at KMH. The data was collected from the hospital software systems ICE, ORION, EPRO and patients' files.
Results
Of These 22 patients 16 were males, 18 patients (31.82%) were type 2 diabetics. 31.82% patients had diabetes duration >20 years, 27.28% for 10 to 19 years, 31.82% patients 5 to 10 years whereas 9.09% patients had less than 5 years. 59.09% patients had associated ulcer on foot. 27.27% patients had history of fracture of the affected foot in the past, whereas 36.36% patients had history of previous amputation. 81.82% patients were known to have peripheral neuropathy and 40.91% had history of CKD. 72.27% patients were known to have hypertension, 45.45% hyperlipidemia and 40.91% patients had history of cardiovascular disease. Charcot was on right side in 72.73%. All the patients had clinical suspicion which was later confirmed on MRI in 54.55%, whereas 22.73% had single X-ray. Temperature difference was not documented in 4.55%. 54.55% had less than 3 degrees difference whereas remaining had more than 3 degrees difference. 90.91% patients had documented advice of weight off-loading. 50% had removable cast and 50% had non-removable ones. 90.91% patients had serial temperatures documented and 4.55% patients had serial x-rays done. 50% patients had complete resolution of acute arthropathy, whereas others had partial resolution so far.
Conclusions
The audit demonstrated that all the patients were given cast (removable or non-removable) and were followed up in MDS Diabetes Foot Clinic. Temperature difference on presentation was documented in 95.45%. However the two key concerns were that only 4.55% patients had serial X-rays done for monitoring and 09.09% patients did not have documented advice of weight off-loading. It is really important to check and document temperature difference and do serial X-rays during follow up of these patients in order to bridge the gap between current recommendations and clinical practice.

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P125

Non-Governmental Organizations (NGO's) & Diabetes – advocacy for support services in resource-poor nations

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Background
Diabetes-support services facilities available only in few city hospitals. Especially diabetics in rural India lack comprehensive diabetes care plan. NGO's play key role in psychosocial-support/Counseling/rehabilitation in remote towns of India. Our Project aimed to formulate policy for trained personals to give better & cost-effective Diabetes-support services.
Methods
We mobilized training resources from local primary Health-centers. Training in Counseling & diabetes care imparted to nurses. Team consisted 2 social worker, 4 nurse & one physician. Local traditional faith-healers & community leaders involved for more effective diabetes awareness/education programs. Aim was to provide physical-comfort to patient, improve relationship with diabetics family members, gradually we prepared patient/family for long term diabetes care needed by patients. Discomfort/anxiety decreases overall treatment efficacy. 51 Patients enrolled during community out-reach-programs. Data collected on feedback-questionnaire. Most difficult tasks is discussing cost of long term therapy & non-availability of newer insulin preparations in rural/tribal areas.
Results
Diabetes Counseling/ support services must be made more accessible in rural-areas. Our NGO's approach is also very cost-effective. Due to non-availability of trained-personal in rural areas this approach crucial in resource poor nations. We noted 86% responded favorably to counseling/nursing care programs, 79% showed willingness to motivate fellow patients to facilitate supportive-care-program of NGO-volunteers. Infact 17 patients themselves became regular active facilitators in our NGO's Diabetes-care workshops. Our Holistic approach helped overcome hopelessness/fear depression. supportive care emerged very serious issue affecting QOL in diabetics. NGO's need to Improve access to drugs by collaboration with national diabetes societies.
Conclusion
In no extra cost our NGO's performed good job of Counseling/rehabilitation for diabetics. Restricted resource-limitations didnot permit us to take study large-sample-size, but we can collaborate with other NGO's & diabetic associations for larger effort.

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P126

Microvascular and macrovascular complications in a cohort of patients with type 2 diabetes mellitus

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Objective
To assess the prevalence of complications In a cohort of patients with type 2 diabetes mellitus (T2DM).
Material and methods
Prospective cohort study. 465 patients with T2DM who were not followed-up at an endocrinology clinic were included. The follow-up was carried out during 26 weeks. The prevalence of complications was evaluated throughout the study. This

Table 1 Associated factors with DN, OD and MD in the multivariate logistic regression analysis.

	OR			95% CI			P		
	DN	OD	MD	DN	OD	MD	DN	OD	MD
Age (years)	1	1.1	1.1	0.9–1.1	0.9–1.2	1–1.2	0.104	0.074	0.002
Male	2.8	1.1	4.1	1.4–5.8	0.5–2.2	1.9–8.8	0.0004	0.809	<0.0001
Time of evolution ≥ 5 years	1.7	3.7	0.9	0.8–3.7	1.4–9.7	0.4–2.2	0.208	0.008	0.883
Initial HbA1c (%)	1.7	0.7	1.2	1.1–2.7	0.4–1.1	0.8–1.7	0.029	0.124	0.474
HbA1c in the previous two years (%)	2	1.9	0.9	1.2–3.4	1.1–3.1	0.6–1.4	0.006	0.014	0.568
HT	2.5	0.7	2.1	1.1–6.3	0.4–1.1	0.8–5.9	0.043	0.124	0.144
DL	1.3	1.1	15.7	0.5–2.9	0.5–2.6	3.4–72.5	0.597	0.808	<0.0001
Smoking	1.3	0.9	1.4	0.5–3.3	0.4–2.6	0.5–3.8	0.524	0.986	0.502
Obesity	1.8	–	–	0.9–3.7	–	–	0.088	–	–
OD	3.1	–	0.8	1.5–6.5	–	0.3–1.9	0.002	–	0.628
MD	1	0.8	–	0.–2.2	0.3–1.7	–	0.95	0.51	–
DN	–	2.4	1.5	–	1.1–5.1	0.7–3.2	–	0.021	0.336

study was approved by the Ethics and Clinical Research Committee of the University Hospital of Guadalajara (Spain).
Results
Mean age was 63.4 ± 12.5 years and 61.5% were males. Time of evolution of T2DM was ≥5 years in the 69.9%. Initial HbA1c was 8.3% ± 1.8 and the HbA1c at the 26th week of the follow-up was 6.6% ± 0.9 (difference of mean 1.7; 95% CI 1.4–1.9; $P < 0.0001$). The 80.6% of patients had hypertension (HT), 83.1% had dyslipidemia (DL), 61.5% had obesity and the 16.8% were smokers. 25.1% of patients had diabetic nephropathy (DN), 21.9% had ocular disease (OD) (retinopathy and/or macular edema) and the 6.9% had diabetic foot or amputation. Regarding to macrovascular disease (MD), the 4.9% had cerebral vasculopathy, 7.7% had peripheral arterial disease and 19.8% had coronary disease. The factors that were independently associated with the presence of complications are shown in Table 1.
Conclusions
• The prevalence of cardiovascular risk factors is high in the cohort of patients and microvascular complications are more frequent than macrovascular ones.
• Poor metabolic control of T2DM is associated with the presence of microvascular complications among other factors. However, it is not associated with the presence of macrovascular disease.

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P127

Calbindin-D9k ablation cause endoplasmic reticulum stress induced β cell death

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Cellular Ca^{2+} signals have been proposed to activate signal for hormone secretion. In pancreatic β cell which produce insulin, Ca^{2+} signals have been known contributing insulin secretion. Prior to conduct this study, we confirmed Calbindin-D9k (CaBP-9k) which responsible for regulation of the distribution of free calcium in the cytoplasm. We confirmed Insulin-secreting β cell express CaBP-9k and assumed that CaBP-9k play a certain role in β cell insulin synthesis or secretion. Using CaBP-9k knock out (CaBP-9k KO) mice, we demonstrate ablation of CaBP-9k induces reduction of insulin secretion and hyperglycemia. Furthermore, to find the role of CaBP-9k in pathophysiologic condition, we evaluate the pathophysiology of aged wild-type and CaBP-9k KO mice. Compare to the aged wild-type mice accumulates abdominal fat, CaBP-9k KO mice does not. CaBP-9k mice showed decreased expression of PPARγ in liver, results in decreased lipid synthesis. Furthermore, CaBP-9k KO ablation induces endoplasmic reticulum (ER) stress, which increase insulin resistance. CaBP-9k KO mice showed more increased level of ER stress marker protein than wild type mice. Taken together, we assumed that CaBP-9k play a certain role in glucose homeostasis accompanying decreased lipid metabolism.

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P128

Serum 25-hydroxycholecalciferol and the A allele of rs2228570 of the vitamin D receptor locus reduce the risk of type 2 diabetes mellitus in Jordan

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Diabetes mellitus (DM) is a disease of epidemic proportions. Most of DM patients are classified as type 2 diabetes mellitus (T2DM) that is linked with resistance to insulin action on target tissues. In 2015, 415 million people were living with DM worldwide with the highest prevalence rates recorded in the Oceania and the Middle East and North Africa (MENA) regions. In Jordan, a MENA country, the prevalence of DM has increased from 13% to 17% over a 10-year period (1994–2014). This highlights the need to identify risk factors associated with the current DM epidemic. This will better inform the public health policy of potential preventive measures to control the disease. Vitamin D, cholecalciferol, is a fat-soluble vitamin and a hormone. Vitamin D traditional role is to maintain calcium homeostasis and bone health. Vitamin D is increasingly recognized for its' 'extra-skeletal' activities including a role in regulating insulin action on target tissues. Vitamin D elicits its action via binding to the vitamin D receptor (VDR). VDR, a nuclear receptor, mediates its action through transcriptional regulation of target genes. Vitamin D deficiency was reported in T2DM patients in several populations but not in Jordan. Herein, we recruited 125 T2DM patients and 125 healthy controls matched by gender and body mass index (BMI). We found that 25-hydroxycholecalciferol (25(OH)D) levels were lower in T2DM patients ($P = 0.0306$). We also genotyped subjects for the following VDR SNPs (rs2228570, rs1544410, rs7975232 and rs731236). We showed that under a dominant inheritance model, the A allele of rs2228570 reduces the risk of DM ($P = 0.0432$; OR 0.597; 95% CI 0.362-0.984). This effect was independent of age and 25(OH)D levels. Haplotype analysis of VDR rs2228570, rs1544410, rs7975232 and rs731236 showed that the ACAA and GAAG haplotypes both reduced the risk of DM in our population ($P < 0.05$). Our findings indicate that vitamin D deficiency/insufficiency may be a risk factor of T2DM in Jordan. Normalizing 25(OH)D levels in the general population may be a feasible and well-tolerated approach to reduce T2DM burden in Jordan.

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P129

Long term functional prognosis is worse in patients with chronic hyperglycemia

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Diabetes and acute hyperglycemia are known to increase stroke volume and disability in stroke patients, and deliver worse outcomes after reperfusion therapies. Chronic glycemic status has recently been linked to stroke functional outcome, but its impact on long term prognosis of stroke has rarely been studied. We conducted a study to investigate the impact of glycosylated hemoglobin (HbA1c) levels on functional outcome 1 year after stroke.
Methods
Patients with acute stroke or TIA were prospectively included. Sociodemographic factors, premorbid conditions, and clinical, biochemical and hematological parameters that were considered as possible prognostic factors in previous studies were collected, as well as modified Rankin Scales (mRS) scores at different times. Multivariate logistic regression analyses were conducted to identify factors related to achieving functional independency 12 months after stroke. HbA1c levels higher than 6.4% were considered as pathologic.
Results
382 patients were included. In 217 of them (56.81%) mRS was 2 or less 12 months after stroke, while 167 (43.19%) had a mRS ≥ 3. Medium HbA1c on admission was 6.6 ± 1.55% (6.29 ± 1.43% vs 6.76 ± 1.70%; $P = 0.032$). Additionally, 130 patients (34.03%) had HbA1c levels higher than 6.4% (23.08% vs 44.76%; $P < 0.001$). In multivariate analysis for functional independency, elevated HbA1c level was an independent predictor of functional dependency 1 year after stroke (OR 0.190; CI 95% 0.064–0.568; $P = 0.003$).
Conclusions
Chronic glycemic status is an independent prognostic factor for long term outcome after stroke, as patients with higher HbA1c are more frequently disabled one year after the event. We propose that HbA1c levels should be determined in all stroke patients to help physicians predict functional status after stroke.

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P130

Role of blood catecholamine in cases with dysmetablolic iron overload syndrome (DIOS) in patients of Metabolic Syndrome

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Background
Dysmetabolic iron overload syndrome (DIOS) is characterized by elevated ferritin and normal transferrin saturation level. Iron metabolism may be linked to the sympathetic overactity. DIOS is seen in 15–20% of the metabolic syndrome cases.
Aim
This study aimed to test the hypothesis linking the increased baseline sympathetic drive to the hypertension seen in dysmetablolic iron overload syndrome in cases of metabolic syndrome.
Subjects
64 hypertensive patients with metabolic syndrome diagnosed based on the criteria of National Cholesterol Education Program (NCEP)compared to 37 hypertensive controls without metabolic syndrome.
Methods
History and general examination including height, weight, BMI and waist circumference measurements were done for both cases and controls. Panel of assay (CRP, cholesterol, triglycerides, uric acid, glucose, creatinine, ALT and GGT). Iron, transferrin, ferritin, insulin and catecholamines (adrenaline, noradrenaline and dopamine) were measuredfor both groups. Transferrin saturation and HOMA-IR were calculated as well.
Results
Six patients were found fulfilling criteria of DIOS represented 9.3% of metabolic syndrome patients. Demographically DIOS patients were shown to be statistically older when compared to non-DIOS patients (P value$=0.026$). BMI of DIOS patients (mean$=28.2$, SD$=2.5$) was found to be statistically lower than non DIOS patients (mean$=33.7$, SD$=6.2$) (P value $=0.033$). 4 out of 6 DIOS cases were females. No significant difference was found between the cases presenting with DIOS versus the Non DIOScases as regard to assayed catecholamines (adrenaline P value $=0.4$, noradrenaline P value $=0.68$, dopamine$=0.516$).
Conclusion
9.3% of metabolic syndrome cases were diagnosed as dysmetabolic iron overload syndrome. Thus, iron profile and liver MRI should be done routinely in these cases for early diagnosis of liver cirrhosis and hepatocellular carcinomas. Further research on more mass population should be continued to assess the role of age, gender and BMI in the pathogenesis of DIOS.

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P131

Incidence of obesity, overweight and hypertension in children and adolescents in Ahvaz southwest of Iran

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Objective
The purpose of this study was to investigate the incidence of obesity, overweight and Hypertension in children and adolescents aged 10–15 in Ahvaz.
Methods
This is a epidemiologic study performed on 176 people aged 10–15 in Ahvaz. In 2009, 300 people underwent weight, height and blood pressure measurements. Five years later, the same people were reassessed for obesity, overweight and hypertension, of whom a total of 176 people agreed to repeat the procedure.
Results
The study included 100 (57%) males and 76 (43%) females. Mean BMI was 22.1 ± 4.3 kg/m^2 in year 2014, without any significant difference between the two sexes ($P=0.518$). In the same year, the prevalence of obesity and overweight was 26 (14.8%) and 13 (7.4%), respectively. After 5 years, BMI increased significantly ($P<0.001$). Of the 150 norma participants with normal BMI in 2009, 15 (10%) and 6 (4%) became overweight and obese in 2014 respectively. The mean systolic and diastolic blood pressures increased significantly over 5 years $P=0.042$ and $P<0.001$.
Conclusions
This study shows an increase in mean BMI and mean systolic and diastolic blood pressures after 5 years among people aged 10–15 in Ahvaz.

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P132

Association of serum lipid profile and insulin resistance in polycystic ovary syndrome (PCOs) women in Ahvaz, Iran

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Polycystic ovary syndrome is a common endocrine disorder in women was associated with lipid disorders with increased risk of cardiovascular disease and obesity are associated. This study aimed to compare the lipid profile and fasting plasma glucose levels, insulin resistance in women with polycystic ovary syndrome is done with the control group.
Methods
This case–control study on 153 women with PCOS and 449 healthy control subjects from 4 cities in the province of Khuzestan) was performed. Serum lipids, fasting plasma glucose and serum insulin levels associated with BMI, HOMA IR, Lipid Accumulation Product Index and Body Adiposity Index in the two groups were compared using appropriate statistical tests.
Results
Prevalence of low HDL and total cholesterol$>$ 200 in women with polycystic ovary higher than the control group (respectively $P=0.032$ and $P=0.001$). Average levels of total cholesterol, triglycerides, HDL, LDL, glucose and indicators HOMA IR, LAP and BA in between the two groups showed no significant difference. In PCOs women with BMI <25 and BMI between 25 and 30, mean total cholesterol was higher than the control group, the PCOs subjects with BMI$>$ 30 had average triglycerides and glucose higher than women in the control group respectively $P=0.029$, $P=0.010$.
Conclusion
The level of triglycerides and glucose in obese women with polycystic ovary syndrome were more than healthy women. PCOs non-obese women had a total cholesterol level higher than healthy women.

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P133

A1c level in people with newly diagnosed type 2 diabetes during screening

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Background
There are about 50% of people living with undiagnosed diabetes worldwide. Moreover, by the time of diabetes diagnosis, chronic disabling complications are already present.
Aim
To assess level of A1c by the time of type 2 diabetes diagnosis.
Material and methods
We analyzed results of type 2 diabetes screening in three regions of the Republic of Uzbekistan among 2521 people aged 35 or older without known carbohydrates metabolism disorders. A1c was tested using method of immune precipitation with anti-human and anti-mouse A1c antibodies (Human), oral glucose tolerance test was performed with 75 g glucose. Diabetes was diagnosed according to IDF recommendations.
Results
Average fasting glycemia in people with newly diagnosed diabetes was 9.6 ± 0.3 mmol/l ($P<0.001$ comparing to people without carbohydrate metabolism disorders), average 2h post-load glycemia was 13.7 ± 0.5 mmol/l ($P<0.001$). Average A1c level was $9.4 \pm 0.24\%$ ($P<0.001$). 49% of people with newly diagnosed diabetes had A1c level $\geq 9\%$, and 33% had A1c $\geq 10\%$.
Conclusion
By the time of type 2 diabetes diagnosis, average A1c level is very high, and almost in half of patients demand as a minimum double (16%) or triple (33%)

combination therapy (according to international algorithms), including injectable medicines. Informational campaign in population about first clinical symptoms and signs of diabetes is essential as well as regular screening in high diabetes risk groups.

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P134

Metabolic syndrome is associated with peripheral endothelial dysfunction amongst men

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Background
Metabolic syndrome (MetS) and peripheral endothelial dysfunction (PED) are both independently associated with an increased risk of cardiovascular disease (CVD). PED provides prognostic information beyond that provided by conventional risk factors. However, the association between MetS and PED remains uncertain. We evaluated the association between MetS and PED.
Methods
We performed a retrospective analysis of patients who were referred to Mayo Clinic between 2006 and 2014 for evaluation of chest pain and/or an assessment of CVD risk that included an assessment of PED measured with reactive hyperemia peripheral arterial tonometry (index <2.0 defines PED). MetS was defined as the presence of at least 3 of the following: body mass index $\geq 25\ kg/m^2$, impaired fasting glucose or diabetes, high blood pressure, hypertriglyceridemia, or low high-density lipoprotein cholesterol.
Results
Six hundred seventy eight patients were included (mean age 51.9 ± 13.5 years, 418 (61.6%) women), of which 293 (43.2%) had PED, and 249 (36.7%) had MetS. In multivariable analyses adjusted for age, sex, presence of obstructive CVD, smoking status and elevated low-density lipoprotein, MetS was significantly associated with PED (Odds Ratio (OR) 2.06; $P=0.0090$). Of the individual MetS components, only being overweight and MetS range high density lipoprotein had a similar association. After stratifying by sex with adjustment for the same confounding variables except sex, the association between MetS and PED persisted only in men (OR 3.16, $P=0.0094$).
Conclusions
MetS is associated with PED in men undergoing an assessment of chest pain and/or CVD risk. Identifying PED in individuals with MetS could provide an abridged assessment of risk, potentially allowing for earlier and more intensive management of risk factors.

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P135

The frequency of Cushing's disease, ACTH independent Cushing's syndrome, and autonomous cortisol secretion among turkish patients with obesity

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Objectives
The frequency of Cushing's disease (CD), ACTH independent Cushing's syndrome (CS) and autonomous cortisol secretion (ACS) in patients with obesity is not well known and the results of the studies are heterogeneous. Therefore, in the present study, we aimed to assess the frequency of CD, CS, and ACS among patients with obesity.
Methods
In this study, 813 consecutive patients [683 female, mean age 46.47 ± 14.23-year-old, mean BMI $37.31 \pm 6.50\ kg/m^2$] who were admitted due to obesity between January 2010–December 2015, were retrospectively analyzed. All patients who admit due to obesity to our institution are evaluated for Cushing's syndrome by clinical and laboratory evaluations. The diagnosis of obesity was made according to BMI and the obesity was classified further to grade 1, 2 and 3, according to the BMI. Serum cortisol levels failed to suppress to $< 1.8\ \mu g/dl$ after overnight 1 mg dexamethasone suppression test (DST) in 44 (5.4%) patients. These patients were evaluated further by 2 days 2 mg DST, 24 hours urinary free cortisol excretion, late-night salivary cortisol, and plasma ACTH levels. The patients with CD, CS and ACS and those without these conditions were compared in terms of gender, age, diabetes, hypertension, and hyperlipidemia.
Results
Forty-four (% 5.4) out of 813 patients were diagnosed as CD, CS or ACS. Five (0.6%) of the patients were lost to follow-up. According to the laboratory, pituitary and upper abdominal MRI results, CD, CS, and ACS were diagnosed in 4 (0.4%), 2 (%0.2) and 33 (4%) out of 39 patients, respectively. Among patients diagnosed as CD, CS and ACS, 4, 2 and 2 patients underwent transsphenoidal surgery and unilateral adrenalectomy, respectively. When patients with CD, CS, and ACS were compared to those without these conditions, older age at diagnosis, and the presence of stage-1 obesity, hypertension, diabetes and uncontrolled DM (Hgb A1c $>$ 7%) were significantly higher in patients with CD, CS and ACS ($P=0.001$, $P=0.007$, $P=0.004$, $P=0.038$ and $P=0.026$, respectively).
Conclusions
According to the results of this study, the frequency of CD, CS, and ACS are high among patients with obesity. Therefore, all patients with obesity, particularly patients older than 50 years of age with grade-1 obesity, who also have type-2 diabetes and hypertension, as well as those with uncontrolled diabetes, should be evaluated in terms of CD, CS or ACS.

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P136

Higher level of astrocyte elevated gene 1 expression in peripheral blood monocytes in adults with newly diagnosed type 2

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Background
Diabetes mellitus or more appropriately type 2 diabetes mellitus (T2DM) is the most heterogeneous form of diabetes which is caused by complex interactions between genetic and environmental factors. Although genome-wide analysis has found several single nucleotide polymorphisms (SNPs) in association with T2DM, their documented role is ambiguous and very few studies have reported about the correlation of particular gene expression with T2DM. In this study, we aimed to examine the correlation of AEG-1 gene expression in peripheral blood monocytes with type II diabetes.
Methods
This cross sectional study includes 17 newly diagnosed T2DM patients and 16 healthy nonglycemic control subjects of Bangladeshi origin without any current treatment regimen. Peripheral blood monocytes (PBMCs) were sorted from the whole blood and RNA was extracted followed by Q-RT PCR analysis to study the gene expression patterns.
Results
Our study suggests that Aeg-1 gene expression in peripheral blood monocytes of newly diagnosed patients with type II diabetes is significantly higher than control subjects. Aeg-1 gene expression is positively correlated with BMI index and increased level was observed in patients with BMI index of 30 or more.
Conclusion
Our study indicates that elevated expression of AEG-1 gene is a novel risk factors for type II diabetes.

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P137

The EMPA-REG OUTCOME, a real cardiovascular benefit or a play on words?

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Introduction
The EMPA-REG OUTCOME is a cardiovascular safety study with empaglifozin that has shown a reduction in cardiovascular mortality and a decrease in hospitalization for heart failure. Our work is based on the analysis of the protocol

that recognized five changes, the last, 3 years after the start of the study and which affects the definitions of the elements of the primary composite, and following these modifications, we find that the mortality Cardiovascular was increased by 67% in favor of empaglifozin, and myocardial infarction was underestimated, which leaves some doubt about the reality of cardiovascular benefit in this study.
Method
Our work is based on the analysis of the protocol that recognized 5 changes, these changes affect the definitions of the elements of the primary composite
1) Cardiovascular mortality: undetermined cause mortality is considered as a presumed cardiovascular death.
2) myocardial infarction: silent myocardial infarction is excluded from myocardial infarction.
Results
1) cardiovascular mortality: this is the only cardiovascular safety study that has considered undetermined cause mortality to be presumed cardiovascular mortality, which has increased cardiovascular mortality by 67%, and this increase is 53% higher in the placebo arm compared with the empagliflozin arm.
2) myocardial infarction: in this study silent myocardial infarction is excluded from myocardial infarction, but the problem, we can not evaluate the impact of this change, because the results of silent myocardial infarction reported, only affects 53% of the population studied.
Conclusion
The play on words used to define cardiovascular mortality for the benefit of empagliflozin, and the retention of information about the number of the silent myocardial infarction, leave some doubt about the real cardiovascular benefit of this study, whose results have been taken into consideration to make cardiovascular safety a criterion in the therapeutic choice in the latest recommendations of ADA EASD 2018.

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P138

Diabetic nephropathy and arterial stiffness in patients with type 1 diabetes mellitus

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Background and aims
In 2005, experts from the IDF assigned the risk of developing coronary heart disease in patients with type 1 diabetes mellitus (DM1) at age of 30 and over or patients with DM1 with kidney damage equal to the patients with type 2 diabetes mellitus. The need for a non-invasive preclinical marker for identifying patients with the increased risk of cardiovascular disease is obvious. The assessment of arterial stiffness can play a role of such marker. The aim of this study was to assess the effect of microvascular complications of DM1 on arterial stiffness in patients with DM1.
Materials and methods
We examined 73 patients with DM1 (age 28.1 ± 6.4; HbA_1c $8.9 \pm 1.8\%$) with normoalbuminuria AER in the morning urine <20 mg/l ($n=40$); microalbuminuria AER <199 mg/l ($n=24$); macroalbuminuria AER ≥ 200 mg/l ($n=9$). The decrease of glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 was noted in eight patients, and GFR ≥ 60 ml/min/1.73 m^2 was registered in 65 patients. Control group included 25 healthy subjects (age 26.3 ± 4.2). The study included an evaluation of the contour pulse wave analysis with the determination of the stiffness index of the arterial wall-the augmentation index (Alx75) on the unit. Additionally, all patients were assessed the thickness of the intima-media complex (TIM) and general clinical studies. Statistical analysis was performed with SPSS22.0, $P<0.05$.
Results
There was no statistical significant differences Alx75 between the DM1 group and the control group. Alx75 was significantly higher in patients with DM1 and diabetic nephropathy compared to patients without nephropathy ($P=0.000$). In the group of patients with GFR <60 ml/min/1.73 m^2, Alx75 was higher in comparison with the group with GFR ≥ 60 ml/min/1.73 m^2 ($P=0.009$). An increase of Alx75 was noted in patients with microalbuminuria compared to patients with normoalbuminuria ($P=0.006$), however, there were no significant difference during comparison of patients with DM1 without nephropathy with the control group. Alx75 was higher in patients with diabetic retinopathy compared to the patients without retinopathy($P=0.000$), while no statistically significant difference was found during comparison the patients with type 1 diabetes without retinopathy and the control group ($P=0.093$). Alx75 was correlated positively with TIM ($R=0.490$; $P=0.000$); age ($R=0.326$; $P=0.007$); duration of DM1 ($R=0.441$; $P=0.000$); and albumin/creatinine ratio ($R=0.369$; $P=0.004$), Alx75 was correlated negatively with GFR ($R=-0.301$; $P=0.015$). Smoking status and arterial hypertension was not independently associated with increased arterial stiffness in patients with DM1.
Conclusion
An increase of the arterial stiffness index in the early stages of microvascular complications may be an early marker of macrovascular lesions even in patients without arterial hypertension.

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P139

Evaluation of perior-operational safety and efficiency of the laparoscopic gastroplication procedure compared to laparoscopic handle gasstroektomia in patients with overweight and metabolic syndrome

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The aim of the study
Laparoscopic sleeve gastroectomy is now the gold standard for bariatric surgery for the treatment of obesity and metabolic syndrome. Laparoscopic gastroplasty is a relatively innovative procedure that has recently been used throughout the world. The purpose of the study was to assess the perioperative safety and outcome of procedures in 2 years.
Materials and methods
Sixty two patients with a body mass index of 35 kg/m^2 to 50 kg/m^2 who were undergoing surgical barrier intervention. Laparoscopic gastroplasty was performed for thirty-eight patients, and 24 patients chose gastro-enteromatous sleeve. Patients were monitored for 2 years after surgery. During this period, both groups studied the percentage of loss of overweight, early and late complications, and improved comorbid conditions associated with obesity and nutritional disorders.
Results
Both groups did not have fatalities, and there was no significant difference in the results of early and late morbidity in both groups (11% after laparoscopic gastroplasty and 12.5% after sleeve gastroectomy). Losing weight was much better after sleeve gastroectomy. During 2 years of observation, the percentage of loss of overweight reached 46% after laparoscopic gastroplasty and 62% after sleeve gastroectomy. There was no significant difference in the overall improvement of concomitant diseases. Nutrient deficits were similar in both groups, with the exception of vitamin B12 deficiency, which was more common after sleeve gastroectomy.
Conclusions
Sleeve gastroectomy and laparoscopic gastroplasty are equally safe and effective for the improvement of concomitant diseases. Sleeve gastrectomy has a better result of overweight loss, whereas laparoscopic gastroplasty is associated with fewer postoperative metabolic deficiencies, without correction. The use of laparoscopic gastroplasty requires additional research to prove the reliability and metabolic efficiency of the new procedure.

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P140

Predictors of incident hypertension in healthy, non-diabetic postmenopausal women with normal renal function

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Introduction
The aim of this study was to investigate the incidence of hypertension and to identify potential risk factors in healthy, non-diabetic recently postmenopausal Greek women with normal renal function.

Patients and methods
In this retrospective cohort study, we evaluated 141 recently postmenopausal women at baseline and annually thereafter (follow-up time: 1 to 8 years). Blood samples were obtained and ultrasound evaluations were performed at baseline. A detailed medical history, anthropometric parameters, blood pressure and cardiovascular risk factors were recorded for every woman at each visit. Incident hypertension was defined as first occurrence of systolic or diastolic hypertension, measured at 2 different visits within 2 months, or initiation of antihypertensive medication.
Results
Incident hypertension was diagnosed in 30 out of 141 women (21.3%). Median time to incident hypertension was 3.5 years after menopause. Obesity, elevated cholesterol and triglyceride levels, insulin resistance and parity were positively associated with incident hypertension. In multivariate analysis, however, obesity and insulin resistance were the only statistically significant variables associated with more than 3fold and 2fold respectively increased risk of incident hypertension (obesity: OR = 3.746, P value = 0.019, HOMA-IR: OR = 1.988, P-value = 0.043).
Conclusions
A large proportion of women entering the menopause present incident hypertension and this is mostly associated with obesity and insulin resistance.

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P141

The role of sodium glucose co-transporter inhibitors in patients with acromegaly and diabetes: is there an additive effect beyond glucose control? A clinical hypothesis

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Acromegaly represents a rare chronic disease mainly caused by GH pituitary adenoma with increased levels of GH and IGF-I. Diabetes mellitus was shown to increase cardiovascular morbidity and mortality in patients with acromegaly. Management of diabetes in acromegaly represents a challenging matter and deserves special considerations due to multiple factors that might be implicated in hyperglycemia including: i) the etiology of diabetes, which could be related to acromegaly per se. ii) the treatment modality applied for controlling disease activity, such as pasireotide long acting release (PAS-LAR) with remarkable increase rate of hyperglycemia and worsening of preexisting diabetes. iii) the disease activity and the tumor burden taking into consideration the negative effects of GH excess other than hyperglycemia such as weight gain, water retention. Sodium glucose cotransporter inhibitors (SGLT2is) are vastly administrated in patients with T2DM. Despite their cardiovascular safety and superiority this class is not recommended for patients with acromegaly and diabetes. Taking into consideration at least three positive aspects of this class: i) cardiovascular superiority beyond glucose control, ii) weight reduction and osmotic diuresis and iii) decreased insulin levels which might play an important role in GH receptor (GHR) expression and as a result decreased IGF-I levels. The aim of this paper is to focus on the role of SGLT2is in this group of patients and the potential‘ additive effect’ of this novel class beyond glucose control.

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P142

Irisin level in type 2 diabetic patients and its relation to glycemic control and diabetic complications

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Background
Irisin is a new myokin and adipokine related to human obesity and insulin resistance status.
Aim
To assess serum irisin level as well as to investigate whether serum irisin is related to glycemic indicators, and micro and macrovascular complications in patients with T2DM.
Methods
The study included 60 T2DM patients and 30 healthy controls. Anthropometric measures, neurological assessment and fundus examination were done to all patients. Correlations of serum irisin and blood glucose, glycosylated hemoglobin (HbA_{1C}), urinary albumin, estimated glomerular filtration rat (eGFR), C-reactive protein (CRP), and carotid intima media thickness (CIMT) were analyzed using Spearman's correlation coefficient.
Results
There was no significant difference of irisin level between T2DM patients and healthy controls (0.18 ± 0.10 vs. 0.16 ± 0.05 ng/ml, $P = 0.940$). In diabetic patients, there was negative correlation between irisin level and duration of diabetes ($r = -0.302$, $P = 0.023$), BMI ($r = -0.663$, $P < 0.001$), HbA_{1C} ($r = -0.528$, $P < 0.001$), urinary albumin ($r = -0.439$, $P < 0.001$), CRP ($r = -0.692$, $P < 0.001$), and CIMT ($r = -0.807$, $P < 0.001$). Levels of irisin were significantly lower in patients with peripheral diabetic neuropathy (PDN) compared to those without PDN (0.11 ± 0.05 vs. 0.22 ± 0.11 ng/ml, $P < 0.001$). Levels of irisin was not significantly different between patients with diabetic retinopathy and those with normal fundi.
Conclusions
Serum irisin levels were not different between T2DM subjects and controls. In T2DM patients, negative correlations between irisin and $HbA_{1C,}$ urinary albumin, CIMT were found. Patients with diabetic neuropathy had lower irisin levels.

Keywords: Type 2 diabetes, irisin, carotid intima media thickness, nephropathy, neuropathy
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P143

Clinical importance of determination of glytoxic methylglyoxal in nafld and type 2 type

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Introduction
The formation of oxidative stress in the biological reaction of inflammation is accompanied by the formation of methylglyoxal (MG), which initiates the glycosylation reaction of proteins. When hyperglycemia MG content significantly increased. MG interacts with the amino groups of lysine and arginine to form further glycation end products (CNG). Glycation is due to the ability of glucose to form irreversible chemical compounds of CNG with amino groups of proteins. During inflammation, MG covalently binds to proteins, enzymes, lipids, and DNA, in violation of their physiological functions. CNG causes complications of diabetes, damaged proteins in the glomeruli of the kidneys, retina and peripheral nerves. The formation of covalent bonds with the amino groups of collagen is the cause of the loss of vascular elasticity.
Purpose of the study
To determine the level of MG in serum by the method of high performance liquid chromatography according to Titov V.N. 2014 in our modification in patients with NAFLD and type 2 diabetes.
Materials and methods
Surveyed 98 patients with NAFLD and 52 patients with type 2 diabetes and 22 healthy volunteers. Age 57.3 ± 5.2 years. IMT 34.85 ± 1.79. The diagnosis was established on the basis of clinical laboratory data and examination results. The level of POL was determined by the content of malonic dialdehyde (MDA).
The results
In patients with NAFLD, the MG content in the serum was 520.75 ± 114.35 in the control 69.02 ± 6.67 nM/l $P = 0.001$. For T2DM, the content of MG292 is 11 ± 16.34 nM/l. With hyperglycemia and excessive accumulation of lipids, the processes of lipid peroxidation enhance, which leads to an increase in the activity of PLA2. In apoptosis, the function of cellular membrane phospholipids is impaired, the function of mitochondria is disturbed, fibrosis develops and steatohepatitis is formed. The correlation of MDA and PLA2 in the serum $r = -0.578$ $P = 0.001$ was noted. MG and MDA are in the correlation dependence $r = 0.495$. The content of PLA2 correlates with the level of nitric oxide $r = 0.625$ $P = 0.001$.
Conclusion
In patients with NAFLD there is a significant increase in MG in serum by 7 times compared with the control. MG damages arginine residues of proteins, the insulin signaling is disturbed, and enzymes are inhibited. MG plays a key role in the development of IR and hyperglycemia. Quantitative determination of MG in serum by HPLC is a prognostic and diagnostic test.

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P144

The psychometric adaptation of the Russian version of the Diabetes Eating Problem Survey–Revised (DEPS-R)

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Objectives
Eating disorders often co-occur with diabetes, and this comorbidity is associated with severe medical complications. The DEPS-R is a 16-item diabetes-specific self-report measure of disordered eating that can be completed in <10 min. The purpose of the study was to translate and validate the Russian version of the Diabetes Eating Problem Survey–Revised (DEPS-R).
Methods
372 patients with diabetes mellitus using insulin injections participated in the research (109 patients with type 1 diabetes mellitus and 273 patients with type 2 diabetes mellitus). The participants completed the DEPS-R and EAT 26 questionnaires. Clinicians provided data on height, weight, A1C, and insulin dosing.
Results
The factor analyses of the Russian version of the Diabetes Eating Problem Survey–Revised (DEPS-R) identified 3 subscales 'disordered eating behavior', 'preoccupation with thinness or weight', 'concept of maintaining high blood glucose values to lose weight'. The reliability was confirmed by the Cronbach's Alpha $=0.74$. Analysis of internal consistency of the responses pointed out a good homogeneity for the scale DEPS-R. It correlates positively with the EAT-26 ($r=0.524$; $P\leq0.01$).
Conclusion
The data confirmed the good reliability and validity of the Russian version of the Diabetes Eating Problem Survey–Revised. Although it cannot be used alone to establish a diagnosis of eating disorders, the scale is a reliable instrument for assessing the risk of eating disorders among patients with either type of diabetes.

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P145

Retinol binding protein 4-marker insulin resistance in patients with diabetes mellitus 2 types and NAFLD

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Introduction
Retinol binding protein (RSP) is a member of the adipokine family associated with insulin resistance (IR). With an excess of free fatty acids, the binding of insulin by hepatocyte receptors decreases and hyperinsulinemia develops. RSP is a transport protein for retinol, synthesized in hepatocytes and adipocytes. The level of RSP increased in patients with obesity, diabetes mellitus and non-alcoholic fatty liver disease (NAFLD) correlated positively with the severity of the inflammatory process and fibrosis. RSP regulates the action of insulin in tissues, skeletal muscle and liver.
Purpose of the study
To determine the CPR in patients with NAFLD and type 2 diabetes. To compare the results of CPR with inflammatory markers of lipoprotein associated phospholipase (PLA2) and nitrogen oxide (NO), which inhibits the proliferation of collagen and regulates hepatic blood flow.
Material and methods
A total of 208 patients with NAFLD and T2DM (120zh/88m) were examined. The average age is 57.3 ± 5.2. Of these, patients with type 2 diabetes are type 76 patients and 132 have impaired glucose tolerance (IGT). BMI over 30 kg/m^2 (34.85 ± 1.79). Patients underwent clinical, biochemical, and instrumental research methods. RSP was determined in 89 patients with type 2 diabetes using the ELISA method in blood serum. The control group consisted of 15 healthy individuals. FLA was determined by ELISA. NO metabolites were determined by the express method.
The results of the study
The RSP content in the control group was 26.15 ± 1.31 μg/L. In patients with type 2 diabetes without NAFLD (group 1), it was reduced by 12.8% and amounted to 20.34 ± 3.8 μg/l. In 49 patients with NAFLD and type 2 diabetes (group 2), the RSP content was significantly increased by 48.9% and amounted to $38,96\pm11.47$ μg/l. The content of PLA2 was increased by 4.78 times compared to the control in group 2 and the level of stable metabolites of nitric oxide increased parallel to the activity of hepatic enzymes. A direct positive correlation between PLA2 and NO is noted. The correlation coefficient was $r=0.625$ $P=0.001$.
Conclusion
The level of CPR was significantly increased in patients with type 2 diabetes and NAFLD compared with controls and group 1. An increase in the content of inflammatory markers was accompanied by an inflammatory process in the liver with an increased activity of liver enzymes and severity of morphological changes.

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P146

Metabolic profile and diabetes in prison

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Introduction
The prison environment is a space that involves certain restrictions on prisoners. The diabetic subject requires, however, special attention. The aim of this work is to evaluate the impact of this medium on the glycemic balance and the metabolic profile.
Patients and method
Descriptive cross-sectional study carried out on a health campaign day in a penitentiary center, in the men's sector, and concerned patients with known diabetes from the institution.
Results
The prevalence of diabetes was 12%, diagnosed in a penitentiary environment in 3 cases. The average age was 42.3 years and type 2 diabetes was found in 93.1% of cases. The average duration of diabetes was 6.15 years, 76.4% of patients were on oral treatment. Mean HbA1c was 8.2%. The mean capillary blood glucose level on examination was 1.92 g/L and pathological waist circumference in 32% of cases. Hypertension and dyslipidemia were associated in 26% of cases. Patients complied with the rules of hygiene and diet (physical activity and diet) in 36% of cases.
Discussion
In prison, the health care system deals with a vulnerable population. In our study, diabetes was more common than in the general population. The exclusive male sex is a cardiovascular risk factor in its own right. The detention environment involves limited physical activity and imposed nutrition. However, the institution tries to encourage a healthy lifestyle. Also, access to care and treatment is available and provided by the penitentiary pharmacy.

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P147

The treatment of fertile age women with obesity

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The aim of investigation to study of optimization of treatment of women of childbearing age with metabolic syndrome.
Material and methods
Under supervision were 20 women with a metabolic syndrome who applied for infertility in Center of Endocrinology from 2014–2015. The control group consisted of 20 women without obesity and without disturbances of the menstrual cycle. The age of patients ranged from 20 to 39 years and averaged 28.3 ± 0.64 years. All patients underwent a set of studies, including General clinical (General blood and urine analysis), biochemical (blood glucose, glucose tolerance test), hormonal (LH, FSH, prolactin, estradiol, progesterone, free testosterone,

dehydroepiandrostenedione (DHEA), 17-oxyprogesterone (17 OKS), antimuller hormone (AMG), insulin on day 14 of the cycle), determination of cortisol in the blood and free cortisol in the daily urine. Patients to decrease body mass was appointed non-pharmacological and etiopathogenetic therapy. Etiopathogenetic therapy included therapy for 6 months: was assigned to a combination Metformin 1000 mg per day + veroshpiron 50 mg twice a week + lodmarin 100 mg in the morning + levothyroxine 50 mg in the morning + antiandrogens (Yarina, Jess, dexamethasone, etc.)+ antidepressants courses (amitriptillin, rexetin, etc.).
Results
It was found that after 6 months after treatment, patients had a significant decrease in BMI of 1 and 2 degrees after 6 months of treatment. In addition, fertility recovery and pregnancy were achieved in patients in 19.5% of cases (10 patients).
Summary
Thus, the inclusion of the drug 'Siofor' (Metformin) in the traditional treatment of patients with obesity of different groups contributes to a significant improvement in clinical indicators - a decrease in BMI, which indirectly indicates that in the study groups of women obesity is one of the manifestations of the metabolic syndrome.

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P148

Prevalence and risk factors of hepatic steatosis among patients with chronic hepatitis B

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Introduction
Chronic hepatitis and NAFLD represent a global public health problem since they are two common cause of chronic liver disease. Hepatic steatosis (HS) is becoming highly prevalent worldwide and its association with hepatitis B, although controversial previously, is increasingly encountered and thought to be related to host factors.
Aim and methods
The aim of this retrospective study is to determine the prevalence of HS in chronic hepatitis B (CHB) patients and to investigate causes of fatty liver. This study included 80 patients diagnosed with CHB between 2010 and 2018. Liver Biopsy was performed in each patients. Clinical, biochemical, and histological characteristics were examined. Patients with alcohol intake were excluded. Pathological data that were collected from biopsy reports included presence of steatosis (>5% of hepatocytes), presence of fibrosis according to Metavir staging, steatosis type and area.
Results
Thirty-eight men (48%) and 42 women (52%) were enrolled. The average age was 49 years. Most of patients (80%) was infected by mutant virus B, common type in Tunisia. the average level of viral DNA was 10881 IU/ml. 57% of patients had Metavir score >=F2 and 25% were cirrhotic. HS was present in 18% of patients ($N=15$). Their mean age was 47 years. 58% of patients with SH had Metavir score >=F2 but none was cirrhotic. Diffuse steatosis was found in 25% of cases. Our data showed that HS was not associated with age, sex, HBeAg, viral load, amount of fibrosis, transaminase levels, or alkaline phosphatase. Conversely, HS was significantly associated with type 2 diabetes ($P<0.001$), hypercholesterolemia ($P=0.01$) and body mass index BMI ($P=0.02$).
Conclusion
Concomitant hepatic steatosis and hepatitis B is relatively common in daily practice, although this association remains less frequent than observed in chronic hepatitis C. In our study overall HS prevalence was 18%. HS was significantly associated with metabolic factors, such as obesity, dyslipidemia and does not seem to influence the progression of liver fibrosis.

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P149

Negative regulation of AMPK-related kinase MPK38/MELK activity by protein phosphatase 5 (PP5)

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Murine protein serine-threonine kinase 38 (MPK38), also known as maternal embryonic leucine zipper kinase (Melk), is a member of the AMP-activated protein kinase (AMPK)-related kinase family and regulates multiple cellular processes, including cell cycle, stem cell self-renewal, apoptosis, carcinogenesis, and metabolism, and is activated in response to apoptosis signal-regulating kinase 1 (ASK1)/TGF-β/p53 signals. A serine/threonine protein phosphatase PP5 has been suggested to negatively regulate the functions of ASK1 and p53. Here, PP5 is found to be a binding partner of MPK38 in cells. The association of PP5 and MPK38 is mediated via the N-terminal domain of PP5 and the C-terminal domain of MPK38. PP5 dose-dependently suppressed the kinase activity and functions of MPK38, as determined by *in vitro* kinase assays, reporter assays, and apoptosis assays, by destabilizing MPK38. The inhibitory effect of PP5 on MPK38-dependent ASK1/TGF-β/p53 signaling is also confirmed in MEF cells that were null (-/-) for PP5. Consistently, PP5 overexpression by an adenoviral delivery worsens obesity-associated metabolic disturbances in high fat diet (HFD)-fed C57/BL6 mice. However, such adverse effects are not observed in MPK38-deficient obese mice. These findings suggest that PP5 physiologically functions as a specific inhibitor of MPK38 that may participate in obesity metabolism.

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P150

Effects of diabetes mellitus and autoimmune thyroiditis on features of rheumatoid arthritis

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Background
It is known that rheumatoid arthritis (RA) can be a part of autoimmune polyglandular syndrome and be combined with endocrine diseases.
Objectives
To study the effects of autoimmune thyroiditis (AIT) and diabetes mellitus (DM) on the clinical and laboratory manifestations of RA.
Methods
The study included two groups of patients. The first group of patients included 24 patients (20 women and 4 men, mean age - 68.37±1.75 years) with a combination of RA and DM. The second group included 24 patients (20 women and 4 men, mean age - 59.1±2.13 years) with a combination of RA and AIT. In the group of patients with a combination of RA and DM 2 patients were with type 1 diabetes, 22 with type 2 diabetes. In a group of patients with RA and AIT 15 patients had euthyroidism, 8 had hypothyroidism, and 1 had hyperthyroidism. Patient groups were compared by statistical treatment and correlation analysis method for the following indices of rheumatoid arthritis: detection of rheumatoid factor in blood serum, presence of erosion on radiographs of the hands/feet, radiographic stage and on a scale of activity DAS-28.
Results
In both groups of patients similar data were obtained on the average results for the studied parameters (detection in the serum of the rheumatoid factor was noted in 75% and 87.5% of patients, erosion in 87.5% and 83% of patients, in 50% and 54% identified III X-ray stage of rheumatoid arthritis, a high degree of activity of rheumatoid arthritis was detected in 67% and 50% patients). However, using the Spearman correlation analysis in the first group of patients (combination of RA and DM), a direct relationship between the presence of erosion and the degree of activity of rheumatoid arthritis (DAS-28, $R=0.39$, $P<0.05$), as well as between the detection of rheumatoid factor in the blood and the degree of disease activity ($R=-0.63$, $P<0.05$). In the second group of patients (a combination of RA and AIT), a direct relationship was found between the detection of rheumatoid factor and the degree of disease activity ($R=0.39$, $P<0.05$).
Conclusions
Thus, in the first group of patients there is a stronger correlation between the clinical and laboratory indicators of RA, including the severity of bone destruction, than in patients with a combination of RA and AIT. This fact can speak about synergistic enhancement of damage to the joint tissue pathogenetic mechanisms inherent in both diabetes and RA.

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P151

'Killing two birds with one stone' treating porphyria patient with diabetes with SGLT2 inhibitors - a case report

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Background
Acute intermittent porphyria (AIP) is characterized by attacks of abdominal pain and neuropsychiatric symptoms. This disease is more frequently and more severely affecting women. Hem deficiency in the liver of AIP patients stimulates an increase in ALA-synthase which triggers an escalating metabolic chain reaction, leading to an increase in the porphyrin content. Treatment of AIP is carbohydrate-rich diet and by treating the attacks with intravenous infusions of glucose or hem. This presents difficulty in treating patients with diabetes mellitus. SGLT2 inhibitors drugs are a class of medications that inhibit *reabsorption of glucose in the kidney* and therefore lower *blood sugar*.
Method
A case report
Result
We present a 60 years old female diagnosed with porphyry seven years ago, which presented with acute abdominal pain and positive porphyrin in urine. She was treated with carbohydrate-rich diet and was symptom free for three years. She complained polydipsia and polyuria, her blood sugar lever were over 11 mmol/L in her profile and HbA1c 6.5%. Diagnosis of diabetes mellitus was made and she started using metformin. For the last year her abdominal pain attacks are more often, Other reasons for chronic abdominal pain were examined. Her ultrasound of abdomen, MR enterography and MR colonography were normal. Antibodies for celiac disease and calprotectin were in referent range. As we don't have hem treatment in our country and its used for only attacks she started using carbohydrate rich diet which caused bad regulation of her diabetes (HbA1c 7.5…8.3%). We decided to start treatment of diabetes mellitus with SGLT2 inhibitors. Blood sugar profiles values range from 5.1 to 6.4, and her HbA1c on the last control was 6.1, as far as her abdominal pain attacks, frequency of attacks reduces almost double and intensity of pain is lower.
Conclusion
Treating porphyria patients with diabetes is a two-edged sword, while carbohydrate help a lot patient with porphyria, they cause bad regulation of diabetes. With using SGLT2 inhibitors and their mechanism it is possible to keep both diseases under control.

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P152

Effect of glucocorticoid on agouti-related protein deficient mice

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Purpose
Agouti-related protein (AgRP) is known as an orexigenic neuropeptide which is expressed in the hypothalamic arcuate nucleus. It's possible AgRP is an important molecule in glucocorticoid (GC) induced obesity (e.g. Cushing syndrome), because GC positively regulate hypothalamic AgRP. To clarify the role of AgRP in GC-induced obesity, we investigate here the effect of GC on AgRP deficient mice.
Methods
Male wild-type littermates ($n=20$) and AgRP deficient mice (AgRP-KO, $n=20$) were randomly divided into two groups, and were implanted subcutaneously with either placebo or corticosterone (CORT) pellet. Their body weight and food consumption were measured every day. They were decapitated on day 14, and trunk blood, hypothalamus and fat tissue were collected for further examination.
Results
There were no differences in body weight between WT and AgRP-KO before treatment (WT 21.5 ± 0.3, AgRP-KO 21.9 ± 0.5 g), and CORT treatment increased circulating CORT levels compared with placebo in both groups. In WT group, CORT administration increased epididymal fat weight compared with placebo (Placebo 271 ± 22, CORT 486 ± 42 mg, $P<0.05$), but not their body weight (Placebo 25.2 ± 0.7, CORT 24.9 ± 0.6 g). In AgRP-KO group, CORT administration increased epididymal fat weight (Placebo 310 ± 20, CORT 727 ± 63 mg, $P<0.05$) and body weight (Placebo 25.2 ± 0.4, CORT 29.4 ± 0.5 g, $P<0.05$) compared with placebo.
Conclusion
These results suggest that AgRP is not necessary in GC-induced obesity. On the other hand, accumulated evidences support GC clearly increase AgRP, and it's reported GR (GC receptor) deficient in AgRP neuron shows obesity resistant phenotype. Therefore, the role of AgRP in GC-induced obesity should be further examined.

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P153

Insulin content and activity of inflammatory markers in patients with nonalcoholic fatial liver disease and diabetes of the second type

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Pathogenesis of Non-alcoholic fatty liver disease in 90% combined with diabetes mellitus (DM) of the second type. Factors cutting: abdominal obesity, excessive content of free fatty acids. Development of insulin resistance through protein kinase. Violation of the transmission of insulin signal leads to damage to the endothelium. Glycation of nitric oxide synthase leads to the development of diabetic complications and violates the sensitivity of the insulin receptors.
Purpose of the study
To determine the level of insulin, metabolites of nitric oxide, malonic dialdehyde, activity of lipoprotein-associated phospholipase A2 (PLA2), in the serum of patients with NAFLD and type 2 diabetes and impaired glucose tolerance.
Material and methods
74 patients with NAFLD and type 2 diabetes were examined; 30 with NAFLD and impaired glucose tolerance. The age of patients is 55.6 ± 2.2 years. The body mass index is 34.85 ± 1.79 kg/m^2. Phospholipase A2 was determined by the method of chemiluminescent immunological analysis on a Siemens device. Fatty acids were determined by the enzyme method using test systems (England). Nitric oxide metabolites were determined by the method of Metelskoy VA, Malondiy aldehyde was determined by the Andreeva method.
Results
Insulin was determined in 74 patients. Hyperinsulinemia was observed in 30 patients with low glucose tolerance. 34.65 ± 4.16 μIU/ml. Control group: 8.3 ± 1 μIU/ml. In patients with diabetes, insulin content: 6.28 ± 0.4 ($P=0.001$), which caused the expression of phospholipase A2 3 times in diabetes and twice in violation of glucose tolerance. With NAFLD, the content of nitric oxide is increased: the level of metabolites increased in parallel with the activity of hepatic enzymes. The content of malondialdehyde in diabetes in patients with diabetes increased and amounted to 24.12 ± 1.64 μmol/l. In case of violation of glucose tolerance: amounted to 16.91 ± 3.87. (the norm is 9.94 ± 1.62 μmol/l). $P=0.001$. A negative correlation between insulin and malonic dialdehyde was detected. ($R=-0.31$). The interrelation of the peroxide and phospholipase mechanism of lipid damage to the membranes of hepatocytes FLA2 and MDA $r=-0.53$; $P=0.001$; between NO and FLA2 $=0.625$. $P=0.001$.
Conclusions
High activity of inflammatory markers in patients with NAFD with diabetes mellitus is an early diagnostic criterion for the activity of non-alcoholic steatohepatitis (NASH).

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P154

The role of bile acids in the pathogenesis of NAFLD

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Obesity affects on the composition of bile: the lithogenicity of bile increases, biliary sludge and cholelithiasis are developing. Under the influence of the active form of oxygen, abnormal forms of bile acids are formed, which negatively affects the development and progression of the pathological process. With the development of inflammation in the liver and pancreas, disturbances in the membrane proteins of glucose transporters occur, the activity of nuclear receptors for the synthesis and conjugation of bile acids decreases. Ursodeoxycholic acid activates nuclear receptors, improves sensitivity to insulin, leptin, ghrelin, adiponectin, increases the activity of glucose transporters, lipoproteinlipase and other enzymes.

Objective
To determine the effect of inflammation markers (NO, LPS, FLA2, MDA) on the synthesis and transport of bile acids in patients with NAFLD and diabetes.
Materials and methods
158 patients with NAFLD: 46 patients with DM2 and 112 patients with IGT were examined. Activation of LPO stimulates fibrogenesis and progression of the pathological process in the liver. The level of LPO was determined by the content of MDA. NO metabolites- by screening FLA2, LPS- by chromogenic end point method using LAL test. Pharmacotherapy with Ursosan in 50 patients with NAFLD.
Results
Group I included 59 patients with NAFLD and DM in which the content of bile acids was lower by 45% compared with the control group was 2.97 ± 1.02 μmol\l the control group consisted of practically healthy persons without disorders of carbohydrate metabolism of 56 patients with the LCD level of 5.4 ± 1.8 mmol\l. group II: NAFLD patients with IGT, $n = 21$;LCD 8.88 ± 4.94 mmol/l, $P = 0.0001$. MDA in group I (24.12 ± 1.64 μmol\l) was increased compared to the control (9.94 ± 1.62 μmol\l). NO metabolites in group I was increased (137.7 ± 35.96 μmol\l). The activity of FLA2 at CD2 median 605 (504–826) ng\ml and LPS = 3.69 EE\ml, at NTG median 430 (324–497) ng\ml ($P = 0.001$), LPS = 1.43 EE\ml. A negative correlation $r = -578$ (FLA2/MDA). After 12 weeks treatment with Ursosan, inflammation markers decreased, biochemical parameters improved.
Conclusions
In patients with NAFLD with DM there is a decrease in the synthesis of bile acids and a violation of bile acid transport, which is associated with damage to cell membranes, inhibition of enzyme systems and inflammation. Accumulation of products of lipid peroxidation leads to the damage of hepatocyte membranes, impaired synthesis of bile acids in the liver, it inhibits the transporters of bile acids. Replacement therapy with Ursosan is recommended in NAFLD.

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P155

Improvement of human pancreatic islet quality after co-culture with human adipose-derived stem cells

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Introduction
Pancreatic islet transplantation is an effective treatment for patients with type 1 diabetes mellitus (T1DM) with unstable metabolic control. However, the quality of islets isolated from a donor is negatively affected by the inflammatory environment related to the donor's brain death and by the stress related to islet isolation and culture. To overcome islet quality loss, some studies have co-cultured islets with mesenchymal stromal cells (MSCs). Considering that MSCs release growth factors, cytokines and chemokines that support cell survival and function, we therefore hypothesized that MSC-secreted molecules would induce a trophic effect in islets during culture conditions, attenuating inflammation and decreasing apoptosis of islets. To date, no study has co-cultured human islets with human adipose-derived stem cells (ASCs) in an indirect contact environment. Thus, the aims of this study were to investigate whether co-culture of human islets with human ASCs can improve islet viability and function *in vitro*, and to evaluate which factors are related to the protective effect of ASCs against islet dysfunction.
Methods
Human islets were isolated according to the well-stablished method described by Ricordi *et al*. (1989), while human ASCs were isolated from lipoaspirates using the protocol established by Zuk *et al*. (2001). Islets and ASCs were cultured in three experimental groups for 24, 48 and 72 h: i) indirect co-culture of islets with an ASC monolayer (Islets/ASCs); ii) islets cultured alone; and iii) ASCs cultured alone. Islet viability was evaluated using fluorescein diacetate/propidium iodide staining, and function was assessed by glucose stimulated-insulin secretion. Growth factors, cytokines and chemokines in supernatant of all conditions were quantified using an ELISA multiplex kit. Expressions of inflammation-, oxidative-stress-, apoptosis- and endoplasmic reticulum stress-related genes in islets were quantified using qPCR.
Results
The percentage of viable islets was higher in islet/ASC group compared to islet alone in all times analyzed ($P < 0.001$). In the same way, islets from islet/ASC group showed improved beta-cell function ($P = 0.001$). VEGF, HFG, IL-6, IL-8, IL-10, MCP-1, IL-1β and TNF levels were increased in the supernatants of islet/ASC group compared to islet alone, mainly after 24 h of culture. Moreover, *VEGF*, *IL-6*, *MCP-1*, *HIF-1a*, *CHOP*, and *NFKBIa* genes were differentially expressed in islets from the co-culture condition compared to islet alone.
Conclusion
Co-culture of islets with ASCs seems to promote an improvement in islet viability and function, probably due to protective trophic factors secreted by ASCs.

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P156

The association between lipoprotein (a) and metabolic syndrome

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Background
Lipoprotein (a) (Lp(a)) is a low-density lipoprotein like particle which has proatherogenic and a prothrombotic properties. Therefore, increased Lp(a) levels have been reported to be associated with a higher cardiovascular risk in numerous studies. However, the association between Lp(a) and metabolic disorders such as diabetes or metabolic syndrome (MetS) is still controversial. This study aimed to examine the association between Lp(a) levels and presence of MetS in a large cohort.
Methods
A total of 10,150 Korean participants (men: 60.5%, mean 51.6 years) who underwent the health checkup in 2006–2013 were included in this cross-sectional study. MetS was defined using a revised National Cholesterol Education Program definition, which adopted an Asian-specific waist circumference threshold suggested by the International Diabetes Foundation. Logistic regression analyses were performed to determine the significance of the association between baseline Lp(a) levels and presence of MetS.
Results
The overall prevalence of MetS was 7.1% and the proportion of the participants with MetS decreased across the Lp(a) quartiles (P for trend < 0.001). In a multivariate model, the highest quartile of Lp(a) levels (> 37.0 mg/dl) was significantly associated with a reduced risk of MetS (odds ratio (OR) 0.63, 95% CI: 0.49–0.80; P for trend < 0.001) compared with the lowest quartile (< 12.2 mg/dl). When we analyzed log-transformed Lp(a) level as continuous variables, elevated Lp(a) level was also associated with a lower MetS risk. Serum Lp(a) levels inversely correlated with waist circumference, body mass index, blood pressure, fasting glucose, insulin, index of insulin resistance, and the number of MetS components, while it correlated positively with C-reactive protein.
Conclusions
Serum Lp(a) level showed a significant inverse correlation with MetS prevalence and individual components of MetS.

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P157

Relationship study between blood groups, rhesus factor and the risk of diabetes type 2 in a population of the Sidi Othmane district, Casablanca

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Introduction
Blood groups and the Rh factor are involved in several pathologies. Some studies have also identified them as risk factors for diabetes. The objective of this work is to evaluate the possible association between ABO blood groups, rhesus (Positive, Negative) and the risk of diabetes.

Patients and methods
This is a case-control study involving 257 diabetic patients followed in the hygiene department and 266 controls followed at Sidi Othmane Hospital. Blood groups were taken from medical records and blood glucose was determined. Statistical analysis is performed using SPSS software 23.
Results
523 subjects were included in this study, of whom 71.2% are women and 28.8% are men with an average age of 50.62 ± 14.93. The mean fasting blood glucose level was 1.57 ± 0.78 in diabetic subjects and 1.01 ± 0.11 g/l in controls. The distribution frequency of group O in the population is 45.5%, while that of non-O (A, B and AB) is 54.5% with (31.4% of group A, 5% of the AB group and 16.6% of the B group). The distribution of ABO blood groups in diabetics by sex (women vs men) is respectively A (73.3% vs 26.7%), AB (81.2% vs 18.8%), B (83, 8% vs. 16.2%) and O (82.2% and 17.8%). On the other hand, among controls, it is 65.2% vs 34.8% for group A, 77.8% vs 22.2% for AB, 78% vs 22% for B and 51.4% and 48.8%, 6%) for O. 94.4% of the control population and 91.1% of the diabetic population consisted of Rh+. Analysis of the association between diabetes and blood group O and non-O revealed a low but significant correlation ($r = 0.093$, $P = 0.034$, OR = 1.452, CI = 1.027–2.051), with an effect protective agent for blood group O (OR = 0.861, CI = 0.676–0.986) and a pejorative effect for non-O blood groups (OR = 1.185, CI = 1.185–1.388) and with a significant difference by female gender. In addition, no association was observed between diabetes and Rhesus factor ($P = 0.098$).
Conclusion
Our study showed a slight association between blood group O and the risk of diabetes probably related to the female sex. Further studies are needed to support it.
Keywords: ABO blood groups, Rhesus, diabetes
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P158

Case-control study on the obesity prevalence in a population of diabetic's consultant at the health department of Sidi-Othmane district, Casablanca: Morocco

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Introduction
Obesity is a risk factor for cardiovascular disease and diabetes. The objective of this work is to study the prevalence of obesity among a consultant population at the Hygiene Service of the Sidi-Othman District (ASO) in Casablanca.
Patients and methods
This is a case-control study of subjects consulting the Sidi Othmane hygiene service. Socio demographic, anthropometric data (weight, height, waist circumference, hip circumference, body mass index (BMI)) blood pressure and pulse were collected. Capillary blood glucose and a lipid profile were performed. Arterial age and cardiovascular risk were estimated by the Framingham score. The data was analyzed by the SPSS software 23.
Results
1281 subjects were included in this study, of which 236 are diabetics. The average age is 49.11 ± 15.46 years. The mean fasting blood glucose level is 1.89 ± 0.68 in diabetic subjects and 0.90 ± 0.15 g/l in controls. Compared to controls, the prevalence of hypertension and dyslipidemia was 40.7%–66.5% for diabetics and 23%–56.2% for controls, respectively. In addition, the mean arterial age is higher in diabetics (66.26 ± 14.47 years) than in controls (54.02 ± 16.67 years). Diabetics were more likely to have cardiovascular risk (14.15%) than controls (8.2%). The average BMI of the population is 28.92 ± 5.95 kg/m^2. The distribution of BMI classes in diabetics vs controls is as follows: overweight (36% vs. 33%), class I obesity (28.4% vs. 25.2%), class II obesity (10.6%) % vs. 11.5%), class III obesity (6.4% vs 3.3). Obesity is slightly higher in diabetics than in controls (45% vs. 40%); especially the distribution of abdominal fat (Obesity android) (61.8% vs 43.3). The correlation coefficients of Pearson are significant, on the one hand, between classes of BMI and diabetes ($P = 0.001$); and on the other hand between diabetes and dyslipidemia ($P = 0.0001$).
Conclusion
The correlation observed in this study between diabetes and BMI classes makes it possible to understand that the primary prevention of diabetes in this population goes, for the most part, by the fight against obesity and even against overweight. The distribution of obesity/overweight for both populations follows the same pattern with higher values for diabetics. We can expect today's witnesses to be the diabetics of tomorrow.
Keywords: Diabetes, Obesity, Overweight, BMI
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P159

Vitamin D: cardiovascular risk marking? About 290 patients

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Introduction
The question of the relationship between vitamin D and cardiovascular disease is still open to debate. Recent, exciting and preliminary evidence suggests that vitamin D may play a role in the occurrence of cardiovascular events.
Materials and methods
Patients of both sexes, involving 290 patients recruited between September and March, aged between 40 and 80 years, with type 2 diabetes mellitus after informed consent. We excluded patients with pathologies responsible for hypovitaminosis D. We studied the relationship between cardiovascular risk factors and vitamin D level, then an experimental therapeutic test over a period of 24 weeks was performed in 42 patients divided at random in two groups: a group under vitamin D 3 and a control group without treatment. The purpose of this test is to determine the effect of vitamin D 3 supplementation on risk factors for cardiovascular risks; Diastolic systolic blood pressure, lipid profile (HDL, LDL, TG, and cholesterol).
Results
We found no significant relationship between vitamin D levels and cardiovascular risk factors.
Conclusion
Numerous studies have demonstrated the link between hypovitaminosis D and cardiovascular risk. Until the role of vitamin D is explored at the cardiovascular level, it is possible that more emphasis is placed on vitamin D levels, especially in people at risk, including the elderly, obese and those with diabetes.
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P160

Complementary-alternative medicine & diabetes treatment adherence

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Issues
In resource-poor-settings, Unlike Western nations monitoring DIABETES-treatment Adherence is low priority due to lack of training modules/funds/expertise. we analyzed experiences in using locally available Complementary Alternative Medicines [CAM] in rural/tribal areas.
Aims
Facilities for diagnosis/treatment located in major cities &are unaffordable to >85%. ADR's & social stigma worsened situation. CAM must be incorporated along with standard ARV's to reduce ADR's & control symptoms to get better DIABETES-Treatment-Adherence. Provide CAM to Traditional-faith-hearers. To assess CAM response to pain, fatigue, Mayalgia, wt loss, feeling of hopelessness. Hence combine CAM with ARV's.
Methods
80 subjects aged 40–65 years enrolled. 40% females, 60% males. 20% returned to villages after incomplete therapy in city hospitals on allopathic drugs. 10% has severe ADR's. Mud therapy 10%, Bach-flower 30%, Acupressure/Acupuncture 40%, Hydrotherapy 10%, Hypnotherapy 40%, ayurvedic therapy 80%, 20% on Unani, 60% Homeopathic.
Results
Patients treated in 11 CAM sessions. responses evaluated by feedback Performa periodically to modify treatment. Our NGO functioning shown graphically [pictorial display]. Symptom relief 60%, Psychosocial mood elevation 70%, willingness to shift back to ARV therapy 80%. CAM 50% cheaper compared to drugs. CAM available locally & high acceptance in patients.
Conclusion
62 patients used & preferred CAMs. Hence CAM effectively compliments DIABETES-treatment-adherence. Community NGO's must be part of such efforts to evolve newer concepts in Adherence. Realizing divergent versions of

CAM multicentre study needed. We shall form group with researchers to substantially improve DIABETES care policy.

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P161

Diabetes and QOL: strategies we need to work on

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Background
Cultural/psychological/spiritual/social factors influence quality-of-life (QOL) of population with diabetes [PWD]. We correlated spiritual well-being, religiosity, QOL, depression, and end-of-life despair in terminally ill PWD. We also explored stigmatized-issue of sexual-desire of PWD.
Aim
Evaluate spirituality and its relation to depression and the QOL. Analyze impact of anxiety/mental-fatigue due to DIABETIES-diagnosis on sexuality/desire.
Patients and methods
We surveyed 62 PWD through questionnaires. [FACIT-Sp QOL questionnaire & Beck-Depression-Inventory, Hamilton-Depression-Rating-Scale (HDRS), Memorial-Symptom-Assessment-Scale, Duke-UNC Functional-Social-Support-Questionnaire]. Evaluated correlations between variables with Chi-square-Fisher and ANOVA-tests. Multiple regressionanalysis to evaluate if depression and spirituality would independently correlate with QOL.
Results
$n=62$. 56 participants completed-study. [4-died, 2-dropouts]. Mean-age 50-65years. 45-males, 11-female. 37-married. 82% felt religious-faith/spirituality most-important-factor to cope with HIV. no statistical-correlations between FACIT-Sp-scores & demographic-variables. significant correlations between higher-scores of spirituality (ANOVA $P<0.001$) with absence-of-depression. By multiple-regression-analysis both spirituality-dominion of FACIT-Sp and Beck-depression-inventory-score correlated independently and significantly with general-QOL measured by FACT-G-questionnaire's score ($P=0.023$ and $P=0.003$, respectively).Strong-negative-association observed between FACIT-Spiritual-Well-Being-Scale and HDRS.
Conclusion
QOL/Mental[wellbeing of PWD enhanced by spirituality/psycho-social-support. religion provide solace reducing depression. spirituality/psycho-social-support emerging new hope for PWD. Spiritual well-being prevents end-of-life-despair. Effect of spiritual/psycho-social-community support fertile ground for further investigations. We need to work-together/share-experiences to further ground work on this issue among patients community with a larger sample size. We aim at improving spiritual-health and general-QOL among PWD.

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P162

The relationship between glycated hemoglobin, postload blood glucose levels and non-hdl cholesterol among 75 gram oral glucose tolerance test applied women

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Aim
Diabetes and prediabetes become prevalent day by day, likewise their complications are also as important as they are. Lipid profile is also evaluated for cardiovascular diseases which are the major complications of diabetes and prediabetes. Non-HDL cholesterol has begun to be taken as one of the treatment goals, especially in diabetics, with respect to the recent dyslipidemia guidelines. The aim of this study is to compare non-HDL values in women with normal or impaired glucose tolerance or diabetes mellitus according to the results of 75 g oral glucose tolerance test (OGTT) and to analyse the relationship between 0- and 2- hour blood glucose values with HbA1c and non-HDL.
Materials and methods
Glucose, OGTT 0- and 2-hour blood glucose values, HbA1c, total cholesterol, triglyceride, HDL, LDL and non-HDL cholesterol results of 75 g OGTT applied women in Bakırköy Dr. Sadi Konuk Education and Research Hospital, were evaluated retrospectively. Patients were grouped according to OGTT results. The relationship of the parameters in each other for each group and the differences between groups were examined. Pearson correlation coefficient and, for ANOVA and Post-Hoc information Bonferroni test were applied as statistical methods.
Results
34, 85 and 14 of 133 women were determined as normal, prediabetic and diabetic in our study group, respectively. For whole group, OGTT 0-hour variable was determined as 41% and 38.6% correlated with OGTT 2-hour and HbA1c, respectively; OGTT 2-hour variable was 36.5% correlated with HbA1c; HbA1c was 17.2% correlated with non-HDL positively and these were statistically significant. In diabetic group, non-HDL averages were found as significantly higher when compared to impaired glucose tolerance, statistically. In whole group, proportion of individuals who reached to target LDL values and non-HDL targets were 34.6% and 47.4%, respectively.
Conclusion
Glucose metabolism states of individuals should be determined and precautions should be taken to avert complications within the context of preventive medicine. The risk should be identified by evaluating lipid profile in the scope of cardiovascular diseases. Non-HDL cholesterol should be considered as secondary treatment target, especially for diabetics.

Keywords: Cardiovascular diseases, diabetes mellitus, HbA1c, non-HDL cholesterol, oral glucose tolerance test, prediabetes

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P163

Diabetes-, sex-, and BMI specific associations of genetic variants in PRRG1 with cardiovascular surrogates in a large cohort at CV risk

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The proline rich and Gla domain genes PRRG1-4 encode for short transmembrane proteins. PRRG proteins contain a Gla domain with glutamic acid residues which are gamma-carboxylated in a vitamin-K-depend manner. In a previous study, we were able to show a decrease in PRRG1 gene expression during intima thickening in atherosclerosis. In this study, we investigated the association of single nucleotide polymorphisms (SNPs) in the vitamin-K-dependent protein PRRG1 with cardiovascular parameters (pathologic intima media thickness (IMT), left atrial volume index (LAVI), left ventricular mass index (LVMI) or pulse wave velocity (PWV), and relative wall thickness (RWT) groups) in three diabetes stages (no diabetes, prediabetes and type 2 diabetes), in lean and overweight persons and males vs. females. We investigated the BioPersMed cohort ($n=1025$), a prospective cohort study of asymptomatic patients with one cardiovascular risk factor. Determination of PRRG genotypes was done by GSA array (Illumina Inc., USA). Pulse wave analysis was done using a SphygmoCor device (Atcor Medical, Australia) and echocardiographic measurements were performed using the Vivid 9 device (GE Healthcare Austria GmbH & Co OG, Austria). Type 2 diabetes (T2DM) and prediabetes were defined according to ADA criteria. Persons with a BMI <25 were defined as lean. RWT groups showed concentric (>0.42) or eccentric (≤ 0.42) hypertrophy. A LAVI <29 ml/m^2, a LVMI ≥ 96 (females) or 116 (males) g/m^2, an IMT >0.9 mm and a PWV <10 m/s (end organ damage) were considered pathologic. No associations were seen with these SNPs and parameters in the other patients' groups (data not

shown). Chi-square analysis revealed significant associations of PRRG1 SNPs in females and males with RWT groups. These associations might implicate a possible role of PRRG1 and vitamin K-dependent proteins in the modulation of important cardiovascular parameters and thus contribute to cardiovascular risk.

Table 1 Significant associations of PRRG1 with cardiovascular parameters in various patients' groups.

ID of genetic variation	no diabetes		pre-diabetes		T2DM	lean			overweight
	IMT	LVMI	LAVI	RWT group	PWV	LAVI	LVMI	RWT group	LVMI
rs113362444	0.034	0.002	ns	0.028	0.020	0.059	0.076	ns	0.003
rs5917507	0.063	0.017	0.015	0.009	0.059	0.046	ns	0.025	0.027
kgp22829647	0.063	0.013	0.018	0.008	0.047	0.048	ns	0.010	0.014
kgp22738694	0.094	0.028	ns	0.050	ns	0.041	ns	0.002	0.012
rs5917212	0.038	0.083	ns	0.049	0.067	0.073	0.035	0.002	0.099
rs6610168	0.037	0.085	ns	0.048	0.075	0.066	0.038	0.004	0.087
kgp22730765	0.010	Ns	ns	0.039	ns	ns	0.094	ns	0.082

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P164

CGI-58 gene expression is decreased in the subcutaneous adipose tissue of patients with obesity

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Background and aims
In adipose tissue, excess of energy is stored inside cytosolic lipid droplets as triglycerides. During fasting or exercise, the stored fat is mobilized for utilization as free fatty acids and glycerol via lipolysis. The complete lipolysis of triglycerides is mediated by the orchestrated activation of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase, which have been associated with obesity. There is compelling evidence that the protein comparative gene identification 58 (CGI-58) markedly enhances ATGL-mediated lipolysis. However, to date, only few studies have evaluated the association between CGI-58 and obesity, with inconclusive results. Thus, here, we compared *CGI-58* expression in subcutaneous adipose tissue (SAT) of subjects with different body mass index (BMI) categories. We also evaluated if *CGI-58* correlates with body composition parameters, resting energy expenditure (REE), insulin resistance (IR), and lipid and glycemic profiles.
Methods
SAT biopsies were obtained from 59 individuals who underwent bariatric surgery or elective abdominal surgery. Patients were divided in Group 1 ($n=8$; BMI <25.0 kg/m^2), Group 2 ($n=22$; BMI 30.0 – 39.9 kg/m^2) and Group 3 ($n=29$; BMI ≥ 40.0 kg/m^2). *CGI-58* expression in SAT was quantified using real-time PCR (qPCR).
Results
CGI-58 expression was decreased in Group 3 [median 0.60 (0.56 – 0.82, 25th–75th percentiles)] and Group 2 [0.89 (0.70 – 1.10)] compared to Group 1 patients [2.48 (1.64 – 3.23)] ($P<0.00001$). Accordingly, *CGI-58* expression was negatively correlated with BMI values ($r=-0.424$, $P<0.001$). Moreover, after BMI adjustment, *CGI-58* expression was negatively correlated with waist circumference ($r=-0.525$, $P<0.001$), fat-free mass ($r=-0.290$, $P=0.030$), insulin ($r=-0.266$, $P=0.047$), HbA1c ($r=-0.379$, $P=0.003$), and triglycerides ($r=-0.521$, $P<0.001$), while it was positively correlated with adiponectin levels ($r=-0.277$, $P=0.044$).
Conclusion
CGI-58 expression is decreased in patients with obesity, being associated with worse metabolic profile.

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P165

Results at 2 years of bariatric surgery in patients with type 2 diabetes mellitus

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Objectives
1. To evaluate the effect after two years of bariatric surgery on comorbidities in patients with diabetes mellitus type 2 (DMT2) and obesity grade II or higher.
2. Analyze the surgical complications in these patients.
Material and methods
Cohort study with intrasubject measures (before-after) in patients with grade II or higher obesity and T2DM, who underwent bariatric surgery (gastric bypass or vertical gastrectomy) at the Puerta del Mar Hospital in Cádiz during the period from 2005 to 2015. We analyzed anthropometric parameters, cardiovascular risk factors and complications related to surgery at baseline and 2 years after the intervention.
Results
Of the 333 patients who underwent bariatric surgery in that period, 87 had T2DM prior to surgery. 63.2% ($n=55$) women, with a mean age of 44.20 ± 10.24 years and a BMI prior to surgery of 50.72 ± 7.81 Kg/m^2 and 32.67 ± 6.12 Kg/m^2 after surgery. The percentage of overweight lost was $63.51\pm18.61\%$. 54% ($n=47$) were operated on by gastric bypass and 46% ($n=40$) by vertical gastrectomy. The resolution rate of diabetes was 77.6% ($n=66$). In most cases, the duration of diabetes was less than 10 years and there were no known chronic complications. The average HbA1c prior to surgery was $7.48\pm1.52\%$ and $5.66\pm0.98\%$ at two years. 29.1% ($n=25$) are smokers, 71.3% ($n=62$) have high blood pressure and 69% ($n=60$) have dyslipidemia. The resolution of these comorbidities occurred in 61.7% and 71.7% of the cases respectively ($P<0.001$). 12% ($n=10$) of the patients presented early surgical complications and 14.8% ($n=12$) developed late complications.
Conclusions
In patients with obesity grade II or higher and T2DM, bariatric surgery is shown in our environment as an effective tool in the early resolution of diabetes, in addition to its beneficial effects on the rest of associated metabolic comorbidities and with a rate of surgical complications similar to other series.

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P166

Assessment of the functional activity of neutrophilic granulocytes in patients with metabolic syndrome

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Introduction
Metabolic syndrome (MS) is a common disease with up to 25% of the total adult population and more than 45% of those over 60 years of age. When MS develops a complex of metabolic disorders that contribute to the development of vascular atherosclerotic diseases, such as abdominal obesity, hypertension, insulin resistance, dyslipidemia. Exchange disorders in MS are associated with the development of inflammation in organs and vessels, while the role of neutrophils in MS cellular reactivity is not fully understood.
Aim
To study the characteristics of neutrophil chemiluminescent activity in patients with MS in dynamics.
Materials and methods
We studied 30 patients with MS and 30 practically healthy individuals. The groups did not differ in age and sex. The intensity of the synthesis of reactive oxygen forms NG was determined by chemiluminescence analysis.
Results
The study of luminol-dependent chemiluminescence showed a significant increase in the intensity of spontaneous and induced luminescence in patients with MS, regardless of the degree of obesity. The area under the spontaneous chemiluminescence curve in patients with MS was significantly increased. In the study of zymosan-induced chemiluminescence, the area under the curve is increased in all groups of patients, while in patients with grade III obesity, the total production of reactive oxygen species is significantly higher than in grades I and II. After undergoing a course of treatment, the chemiluminescent activity of neutrophils in MS patients tended to decrease, not reaching the indicators of the control group.
Conclusion
In patients with MS before treatment, there was an increase in neutrophil chemiluminescent activity regardless of the degree of obesity, and after treatment, there was a tendency to decrease, which indicated the effectiveness of the therapy.

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P167

Hygienic-dietetic habits in a group of patients with morbid obesity waiting for bariatric surgery and in a group already intervened

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Objectives
To determine the lifestyle in patients with morbid obesity in a previous group and in a group after performing bariatric surgery.
Material and methods
Cross-sectional study in two groups of patients with morbid obesity one before and one after bariatric surgery attended in the Clinical Management Unit of Endocrinology and Nutrition of the Puerta del Mar Hospital in Cádiz. The clinical and analytical data of the patients, the sociodemographic characteristics and lifestyles are collected.
Results and conclusions
Some 111 patients with morbid obesity were collected before and after the surgical intervention: (31.5% males, 68.5% females) and operated patients (29.9% males and 70.1% females). Before surgery, the average weight was 133.4 kg (SD 24.4) and the BMI 48.6 kg/m^2 (SD 7.0), and in the patients treated, it was 94.9 kg (SD 19.8) and BMI 34.5 kg/m^2 (6.5). There are statistically significant differences between both groups in terms of habits and lifestyle: tobacco consumption (21.1% vs 7.1%), alcohol consumption (21.1% vs 17.4%), physical exercise (55.0% vs 82.6%), hours of physical exercise (4.75 h/week vs 5.9), eating habits such as snacking (35.5 vs 19.8%), fast food consumption (56.5% vs 11.9%), and increase in meals/day from 3 to 5. We observed statistically significant differences in lifestyle both before and after bariatric surgery, which could contribute to maintenance, improved prognosis and good patient evolution.

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P168

Challenges in managing patients with type 1 diabetes and hypersensitivity reaction to insulin

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Patients with type 1 diabetes (T1DM) and insulin hypersensitivity reaction of any type are at high risk of acute and chronic long term complications of hyperglycaemia and glycaemic variability. Such patients are challenging to manage. We present a case report. A 57 year old lady with T1DM for 21 years managed with insulin pump for 7 years reported new onset intermittent skin reaction at the pump infusion site over the last two years. She described her skin becoming swollen and hard and sometimes itchy and red within 4–12 hours of starting NovoRapid insulin via a new cannula. The reaction persisted up to a week and swelling subsided without any intervention. The reaction continued with the new types of cannula or with Humalog or Apidra in the pump. The reaction also happened with subcutaneous injections of quick, intermediate and long acting insulin. The reactions seemed to be more pronounced during infections. Skin prick and intradermal testing to all human, bovine and porcine insulins were negative. Specific IgE to insulins were negative and mast cell tryptase was normal. She was diagnosed to have type 3 hypersensitivity reaction to insulin molecule. Antihistamines would help minimise itching but no other treatments were deemed suitable as reactions were intermittent and satisfactory glycaemic control was maintained. She will be considered for trial of DiaPort, peritoneal insulin delivery system in future if reactions become more persistent and/or glycaemic control is affected. Insulin hypersensitivity presents a management challenge for patients with insulin dependent diabetes. Its incidence has reduced since the invention of human insulin. Most common type is immediate or less commonly biphasic IgE medicated type 1 local or systemic reaction. Type 3 hypersensitivity is less common and usually presents with a slightly delayed local reaction. Management of hypersensitivity reactions involves switching to different insulin, antihistamines, glucocorticoids or desensitisation although type 3 hypersensitivity is more difficult to treat. It is important to note that the hypersensitivity could either be due to insulin itself or other substances in the insulin injections therefore it is critical to recognise the exact allergen. DiaPort system of insulin delivery through peritoneum is a promising option for such patients if other treatments fail or are deemed unsuitable.

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P169

Relationship between liver fibrosis and diabetes-related complications in type 2 diabetic patients

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Introduction
Type 2 diabetes has a relationship with fatty liver. Fatty liver can progress to liver fibrosis. This study examined relationship between liver fibrosis and diabetes-related complications in type 2 diabetic patients.
Methods
This study analyzed data from the 2007 to 2015 the Korea National Health and Nutrition Examination Survey (KNHANES) in South Korea. Which included values of c-peptide, fasting blood sugar, AST, ALT, and platelet to calculate parameter of homeostasis model assessment (HOMA) and fibrosis-4 scores (FIB-4). We compared FIB-4 scores by groups of normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and diabetes. We also compared frequencies of diabete-related complications depending on the presence of liver fibrosis among diabetic patients.
Results
A total of 16,420 subjects were analyzed. Diabetes group showed higher FIB-4 scores than NGT or IGT groups (1.4 ± 0.9 vs 0.9 ± 0.6 vs 1.1 ± 0.8). Among diabetes patients, liver fibrosis group (Fib-4 ≥ 1.45) had more hypertension (40.9% vs 17.8%), hypercholesterolemia (13.3% vs 6.5%), stroke (3.2% vs 1.4%), cardiovascular diseases (5.1% vs 1.4%), cataract (11.6% vs 4.5%) and glaucoma (1.5% vs 0.7%) than non-fibrosis group. Particularly, liver fibrosis increased risk of cardiovascular diseases such as myocardial infarction or angina (OR 11.01, 95% CI 1.64–73.94) by multivariate regression analysis.
Conclusion
Diabetes patients are more accompanied by liver fibrosis. Liver fibrosis increased risk of diabetes-related complications. Thus, early screening of liver fibrosis and fatty liver in diabetic patients is needed. And appropriate treatment would be helpful to prevent progression of diabetes-related complications.

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P170

Study on compositions of lipids in tissues of rats with alimentary obesity

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Obesity is considered as a major factor of insulin resistance and diabetes mellitus risk. Study on lipid composition of tissues in obesity is relevant in understanding of mechanisms underlying insulin resistance.
Aim
The work was initiated to study lipid composition of liver and skeletal muscles tissues in rats with alimentary obesity.
Materials and methods
Obesity was induced in rats leading an inactive lifestyle with prolonged high calorie diet (standard diet + fat, sugar and margarine). After the animals' weight of 400–500g was achieved they were sacrificed; their liver and skeletal muscles were removed for study. Lipids were extracted by Kates (1975) and fractionated by thin layer chromatography.

Results
In livers of rats with induced alimentary obesity cholesterol and triglycerides were found to increase by 23% and 48%, respectively, total phospholipids were found to decrease from 1039 ± 37.2 μg of phosphorus per gram of tissue to 878.6 ± 32.1 μg of phosphorus per gram of tissue documented in the control animals. Changes in the fraction composition of liver phospholipids were found in rats with the induced alimentary obesity too. Thus, lysophospholipids, cardiolipin and phosphatidic acid were found increased by 280%, 7.1% and 29%, respectively, while phosphatidylcholines, phosphatidylethanolamines and sphingomyelins were found to decrease by 9%, 34% and 31%, respectively. In the skeletal muscles of rats with alimentary obesity cholesterol and triglycerides were found to increase, while total phospholipids decreased; changes in some phospholipid fractions were oppositely directed.
Conclusions
Changes in concentrations of neutral lipids, total phospholipids and some of their fractions registered in rats with the induced alimentary obesity are thought to be caused by fluctuations in lipid metabolism and activation of lipolytic enzymes. The changes in lipid composition of tissues under study could underlie insulin resistance in alimentary obesity.

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P171

Dopamine Receptor and Dopamine Transporter in Obesity: A Meta-analysis

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Objectives
The brain plays a major role in controlling the desire to eat. We performed a meta-analysis to assess the association of dopamine transporter (DAT)/dopamine receptor (DR) availabilities from neuroimaging studies with obesity.
Methods
We performed a systematic search of MEDLINE and EMBASE for English-language publications. Data were extracted from the publications independently by two reviewers. Effect sizes were correlation coefficient between BMI and the availabilities of DR or DAT from both controls and obese subjects. To investigate DR availability ratio of obese subjects to controls, mean DR availabilities and mean BMI of each group were extracted.
Results
8 (DR) and 3 (DAT) studies including 332 (DR), and 358 (DAT) subjects were eligible for inclusion in this study. DR availabilities were weakly correlated with BMI (correlation coefficient 0.239, 95% confidence interval 0.164 ~ 0.311, $P < 0.001$, $I^2 = 26.7\%$). DR availability ratios decrease as the BMI increases in subjects with BMI more than 40kg/m^2. However, the pooled data did not show the significant association between DAT availabilities and BMI (correlation coefficient 0.0277, 95% confidence interval −0.130 ~ 0.184, $P = 0.732$, $I^2 = 74.9\%$).
Conclusions
DR availability was positively correlated with BMI, however, DAT availability was not associated with BMI. DR availability from subjects with BMI of approximately 35 kg/m^2 was higher than that from controls, however, DR availability from subjects with BMI more than 40 kg/m^2 was lower than that from controls, which is consistent with the hypothesis of reward deficiency syndrome in severe obesity.

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P172

Cerebral glucose metabolism and Cerebral blood flow in Hypothyroidism and Hyperthyroidism: An activation likelihood estimation Meta-analysis

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Objective
Thyroid dysfunction is frequently associated with functional disturbances of the brain. We performed a meta-analysis of previous positron emission tomography and single-photon emission computed tomography studies using a coordinate-based technique of activation-likelihood estimation (ALE) to investigate the potential background of neuropsychiatric complications in patients with hypo- and hyperthyroidism.
Methods
We performed a systematic search of MEDLINE and EMBASE for English-language publications using the keywords of 'positron emission tomography', 'single-photon emission computed tomography', and 'thyroid'. The software GingerALE ver 2.3.6 was used to transform all reported coordinates into stereotactic Montreal Neurological Institute space. A threshold of uncorrected $P < 0.001$ (minimum volume of 200 mm^3) was applied to the resulting ALE map.
Results
Six studies were eligible for inclusion in the study; 4 studies of cerebral metabolic rate of CMRglu, and 2 studies of CBF. In hypothyroidism, significant decreases in CMRglu were identified in 3 clusters including left anterior cingulate, right inferior occipital gyrus, and right cuneus. In hyperthyroidism, a significant decrease in CMRglu was identified in right superior frontal gyrus. In hypothyroidism, a significant decrease in CBF was observed in left postcentral gyrus.
Conclusions
Several brain regions showed altered CMRglu and CBF in patients with thyroid dysfunction compared with euthyroid controls. These findings might account for underlying mechanisms of thyroid hormones on psychological and physiological effects on brain.

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P173

Biomarkers of myocardial fibrosis at coronary heart disease in the presence and absence of diabetes mellitus type 2

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Combination of coronary heart disease (CHD) with diabetes mellitus type 2 significantly increases the risk of left ventricular remodeling. The objective of the study was to determine the association of biomarkers of myocardial fibrosis with the level of glycaemia at CHD in patients with and without DM type 2.
Methods
We have examined 104 patients with CHD of average age 64.9 ± 0.3 years old, 27 of them were with DM type 2; 77 patients were without DM type 2.
Results
The levels of glycaemia and HbA1c differed depending on the presence of DM type 2: 5.16 [4.7; 5.48] vs 6.70 [5.39; 7.40] mmol/l ($P < 0.001$) and 5.70 [5.40; 5.93] vs 6.60 [5.80; 7.50]% ($P < 0.001$). In the case if the CHD wasn't combined with DM type 2, a correlation was found between the level of glycaemia and IL-1β ($r = -0.30$; $P = 0.007$); IL-2 ($r = -0.26$; $P = 0.024$); HbA1c with BNP ($r = -0.42$; $P < 0.001$), galectin-3 ($r = -0.30$; $P = 0.008$), IL-6 ($r = -0.24$; $P = 0.032$), IL-12 ($r = -0.26$; $P = 0.023$). When CHD was combined with T2DM, a correlation was found between the level of glycaemia and aldosterone ($r = 0.57$; $P = 0.002$); HbA1c with IL-1β ($r = 0.42$; $P = 0.027$), IL-6 ($r = 0.55$; $P = 0.003$) with aldosterone ($r = 0.56$; $P = 0.002$).
Conclusion
Patients with CHD showed a correlation between glycaemia and HbA1c levels with a number of biomarkers of myocardial fibrosis, regardless of the presence of DM type 2, which indicates the necessity to determine critical points of glycaemia and HbA1c, and perhaps of glycemia variability, which influence the myocardial fibrosis development.

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P174

Prevalence of vitamin D deficiency in a population of patients with prediabetes and type 2 diabetes mellitus

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Objective
Vitamin D deficiency has been related to extraskeletal manifestations such as insulin resistance, type 2 diabetes mellitus (DM) and obesity. The objective of this study was to assess the prevalence of vitamin D insufficiency and deficiency in a population of patients with prediabetes and with type 2 DM already established, and to see if there were differences according to different parameters.
Material and methods
Cross-sectional study, in which a total of 460 patients were selected, 230 of them with prediabetes and another 230 patients with type 2 DM, controlled in Endocrinology consultations. 50% of each group were women. The main variables determined were: weight, body mass index (BMI), abdominal perimeter, fasting glucose levels, and 25-OH vitamin D levels. Serum 25-OH vitamin D levels considered as sufficiency were >30 ng/ml; insufficiency was considered between 20–30 ng/ml, and deficiency <20 ng/ml.
Results
The prevalence of vitamin D deficiency was 85.7%, being higher in women (92.8%) than in men (79.3%) ($P<0.05$). In patients with type 2 DM, the prevalence of vitamin D insufficiency was 7.1% and the prevalence of deficiency was 84.2%; while in patients with pre-DM, 5.7% had vitamin D insufficiency and 64.3% had deficiency of this vitamin ($P<0.05$). A greater deficiency was also observed in patients older than 65 years (88.3% vs. 76.1%, $P<0.05$); in patients with a higher BMI (91.2% of patients with BMI >30 kg/m^2 had deficiency compared to 78.1% of those with BMI <30 kg/m^2), and a greater abdominal perimeter (90.1% if abdominal circumference was >110 cm, compared to 81.3% in those with abdomen perimeter <110 cm).
Conclusions
There is a high prevalence of vitamin D deficiency in population with type 2 diabetes mellitus, being higher in women, in patients with higher BMI and greater abdominal perimeter, and in those with established type 2 DM compared to patients with prediabetes.

Table 1 Studied variables in patients with pre-DM and established type 2 DM.

	Prediabetes	Type 2 Diabetes Mellitus	*P*
Age (years)	59.1 (+*4.1*)	60.3 (+*5.5*)	>0.05
BMI (kg/m^2)	31.4 (+*4.9*)	33.5 (+*4.3*)	>0.05
Abdominal perimeter (cm)	103.8 (+*12.4*)	123.1 (+*11.1*)	0.01
25-OH vitamin D levels (ng/dl)	19.3 (+*4.2*)	14.1 (+*3.6*)	0.02
Fasting glucose levels (mg)	115 (+*12.6*)	132 (+*13.8*)	0.01
Glycated hemoglobin (%)	5.8 (+*0.6*)	6.9 (+*0.9*)	0.01

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P175

Genealogical analysis in diabetes mellitus risk assessment

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Prevention of familial diabetes mellitus is a most urgent problem in diabetology. Genetic susceptibility is a leading factor in diabetes mellitus onset.
Aim
The work was initiated to assess potentiality of diabetes mellitus risk prediction based on genealogical analysis.
Materials and methods
For the purpose of the study, 53 patients with diabetes mellitus were examined. The probands' mean age was 14.4 years. Genealogical medical history was assessed by establishing breeding background with number of generations not less than 3. Index of hereditary burden was calculated as the quotient from total number of diabetes mellitus cases and total number of a proband's relatives to establish orientation of family medical history by diabetes mellitus. The index of hereditary burden less than 0.4 meant the absence of the hereditary burden by diabetes mellitus.
Results
Clinical-genealogical analysis of breeding background showed hereditary burden by diabetes mellitus in 74.2% of patients examined in the study with index of hereditary burden 0.5. The onset of diabetes mellitus in a proband was determined by the number of his affected relatives. If parents are healthy, the probability ranges from 5 to 10%. Diabetes mellitus in one parent implies its risk in 10–20%. If both parents are diabetic, the risk can increase up to 40%. The disease risk in children of the proband may range by the affection of his parents ranging from 10 to 20%.
Conclusions
Analysis of genealogical tree for patients with diabetes mellitus demonstrated multifactor character of the pathology confirmed by mode inheritance non-conformity with Mendelian laws which are general for the monogenic characters. Type I diabetes mellitus was demonstrated to develop in the offsprings of patients with type II diabetes mellitus which is an activating factor to a mutant gene capable of triggering mechanism for the hereditarily associated diabetes. Thus, clinical genealogical analysis allows identifying groups at higher risk of diabetes mellitus and performing timely interventions.

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P176

The waist-to-hip ratio is a better obesity index than body mass index and waist circumference for screening for nonalcoholic fatty liver disease in postmenopausal women

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Background/Objectives
Although it has been well-established that menopause causes a shift in body fat, thereby eliciting metabolic disturbances in women, there has been no study conducted yet to examine the best obesity parameters to predict the risk of nonalcoholic fatty liver disease (NAFLD) in this population. Thus, the aim of this study was to compare the efficacy of body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) for screening NAFLD according to menopausal status.
Subjects/Methods
This cross-sectional analysis included 620 healthy women between 20 years and 80 years of age recruited from the Health Promotion Center of Korea University Guro Hospital. NAFLD was diagnosed by abdominal ultrasonography.
Results
All receiver operating characteristic curves of BMI, WC, and WHR for NAFLD were established statistically above the diagonal nondiscrimination line. In premenopausal women, there were no statistical differences in area under the curve (AUC) values among the three obesity indices, whereas, in postmenopausal women, the AUC value of WHR was significantly larger than those of either BMI ($P=0.005$) or WC ($P=0.007$). Furthermore, in postmenopausal women, the combination of WHR with BMI or WC significantly increased predictive power of NAFLD when compared to using BMI or WC alone. The optimal cutoff values for BMI, WC, and WHR for detecting NAFLD were 23.9 kg/m^2, 69 cm, and 0.81 in premenopausal women and 22.9 kg/m^2, 74 cm, and 0.86 in postmenopausal women, respectively.
Conclusion
In premenopausal women, BMI, WC, and WHR hold similar potential in predicting the risk of NAFLD, whereas, in postmenopausal women, WHR is the most useful discriminative indicator for NAFLD. Women's optimal cutoff values for NAFLD were different according to menopausal status.

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P177

The severity of different components of metabolic syndrome in hypertensive patients depending on IRS-1 gene polymorphism

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Objective
To establish possible associations of the polymorphism of the insulin receptor substrate−1 (IRS-1) gene with the severity of various components of metabolic syndrome in patients with arterial hypertension (AH). We examined 187 patients with AH aged 45–55 years (with history of hypertension less than 5 years, unsystematic administration of antihypertensive drugs and/or failure to achieve target blood pressure (BP) levels when prescribing drug therapy). The control group consisted of 30 individuals matched for age and sex.
Methods
Anthropometry, reactive hyperemia, color Doppler mapping, biochemical blood analysis, HOMA-insulin resistance (IR), glucose tolerance test, enzyme immunoassay (determined levels of adiponectin, interleukin-6 (IL-6), C-reactive protein (CRP)) and molecular genetic method (genotyping of polymorphic marker Gly972Arg of IRS-1gene).
Results
It was found that among the hypertensive patients, 103 had abdominal obesity, 43 – type 2 diabetes mellitus (established less than 2 years ago), 131 – increased blood triglycerides ($\geq$150 mg/dL), 19 – decreased high density lipoproteins (HDL, $<$40 mg/dL in men and $<$50 mg/dL in women), 59 – prediabetes (33 – fasting hyperglycemia and 26 – impaired glucose tolerance), 126 had IR, assessed by the HOMA-IR. At the same time, hypertensive patients had the following distribution of IRS-1 genotypes: Gly/Gly −47.9%, Gly/Arg −42.2% and Arg/Arg −10.7%, whereas in practically healthy individuals the distribution of genotypes was significantly different: Gly/Gly −86.8% ($P<0.01$), Gly/Arg −9.9% ($P<0.01$) and Arg/Arg −3.3% ($P<0.05$). At the next stage, associations of the IRS-1 gene polymorphism with anthropometric, metabolic and hemodynamic parameters in hypertensive patients were evaluated. It was found that hypertensive patients with Arg/Arg and Gly/Arg genotypes had significantly higher levels of glucose ($P<0.05$), insulin ($P<0.05$), HOMA-IR ($P<0.01$), triglycerides ($P<0.05$) than patients with the Gly/Gly genotype. At the same time, body mass index, waist circumference, levels of BP, adiponectin, HDL, IL-6, CRP, total antioxidant activity, degree of endothelium-dependent vasodilation, as well as the frequency of occurrence of impaired glucose tolerance did not differ significantly with various IRS-1 genotypes.
Conclusions
In hypertensive patients, the genetic polymorphism of IRS-1 gene is associated with such components of metabolic syndrome as hypertriglyceridemia and fasting hyperglycemia; this polymorphism is not associated with proinflammatory state, endothelial dysfunction, dysglycemia, an increase in waist circumference and decrease in HDL.

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P178

The association of fibroblast growth factor 23 with other factorsof mineral and bone disorder in chronic kidney disease

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Introduction
Chronic kidney disease (CKD) is growing problem nowadays. Disorder of mineral metabolism occurs in initialCKD and includes the changes of bone metabolism. Fibroblast growth factor 23 (FGF23) plays an important role in phosphate metabolism. Bearing in mind this physiological role of FGF23, but also it's role in pathophysiology of mineral and bone metabolism, there is a growing interest in conducting clinical studies in patients affected by CKD. Our aim was to investigate the potential relationship among FGF23 and other chronic kidney disease-mineral and bone disorder (CKD-MBD) participants in the clinical setting.
Methods
Eighty-seven CKD patients were involvedin our cross-sectional study, including all causes of the disease. The mean estimated glomerular filtration rate (eGFR) was 40.1 (3–110) mL/min/1.73 m^2. Evaluation of renal function and mineral methabolism condition were perfomed by using standard biochemical protocols. Serum intact FGF23 (iFGF23) level determination was accomplished by utilizing ELISAtechnique. The concentration of iFGF23 in serum greater than 50 ng/L was defined as elevated levels. Descriptive and analytical statistics were used to analyze the data acquired from the study.
Results
The mean iFGF23 level was 80.53$\pm$43.59 ng/L and was increased from CKD stage 1. Serum iFGF23 correlated negatively with eGFR ($P<0.05$) and positively with the levels of serum creatinine ($P<0.05$). Increased level of PTH was seen in stage 3 CKD. Hyperphosphatemia was present from stage 4 CKD, while serum calcium levels remained mostly in reference range. No correlation was seen between iFGF23 with serum calcium, phosphate and parathyroid hormone (PTH) levels.
Conclusion
Initial CKD shows elevated serum iFGF23 levels, whereas other CKD-MBD parameters are mostly within reference range. No significant association was seen between iFGF23 with other markers of CKD-MBD.

Keywords: iFGF23, mineral and bone disorder, CKD, biomarker
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P179

Delivery in the diabetic women

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Purpose
To determine the frequency of *trial of labor* after *caesarean delivery* and the success rate of this trial in women with diabetes as well as in a *control population*.
Materials and methods
This is a retrospective *case-control study* involving 400 cases: 200 diabetic women compared to 200 non-diabetic women conducted in obstetrics and *gynecology* department of the university hospital center of Monastir over 5 years.
Results
The rate of patients with a scarred uterus was 29% (53 cases) in diabetes group against 15% (30 cases) in the control group. The trial of labor is accepted in 24 women in the diabetes group against 26 women in the control group. The failure of the trial of labor was noted in 17% of cases (4 cases) in diabetic women and 38% of cases in non-diabetic women (10 cases).
Conclusion
The rate of elective *cesarean* in case of scarred uterus can be decreased among women with diabetes and expanding indications for the trial of labor. The success rate of trial of labor is high among diabetic, this is explained by the fact that those women with *high-risk pregnancies* are better selected before passing this test.

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P180

Peripheral arterial disease in Asian Type 2 diabetes mellitus under 65 years old and its risk factors

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Objectives
Peripheral arterial disease (PAD) is the macrovascular complications of type 2 diabetes mellitus, and type 2 diabetic patients with PAD may have higher incidence of foot amputation and coronary heart disease. We conducted a clinical-based cohort study in northern Taiwan in order to assess PAD in diabetes and its associated risk factors.
Methods
This study enrolled type 2 DM patients not older than 65 years old who were seen in diabetes clinics in Chang Gung Memorial Hospital (Keelung, Taiwan). Body mass index (BMI) was measured and relevant laboratory investigations were performed. We also checked serum Vitamin D level in each patient. Ankle brachial index (ABI) was obtained for each leg. The lower value obtained for the two legs was taken as the ABI value. A cut off of $<$ 0.9 was used to define PAD. Brachial-ankle pulse wave velocity (baPWV) was measured to assess arterial stiffness.
Results
We studied 182 patients (85 men and 97 women; mean age 55.5$\pm$7.6 years ranging from 30 to 65 years old; mean duration of diabetes 9.4$\pm$6.1 years). The prevalence of PAD was 6.6%. PAD subjects had a significantly higher prevalence of proteinuria (33.3% vs 12.4%), and a lower baPWV values than those without PAD (R:1617.5$\pm$184.2, L:1575.5$\pm$219.8 vs R:1631.8$\pm$315.7, L:1634.5$\pm$321.9). Otherwise, we did not find a correlation between age, serum vitamin D levels, A1c, duration of diabetes, BMI and PAD.
Conclusion
The low prevalence of PAD in these diabetes patients was due to relatively young age. Our data shows type 2 diabetes patients with proteinuria are at higher risk of PAD. Type 2 diabetes patients with PAD had lower baPWV values than those without PAD. However, more study subjects are needed in the future to enhance the significance of the study.

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P181

Gestational diabetes mellitus and continuous glucose monitoring: glycemic patterns and pregnancy outcomes

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Introduction
Gestational diabetes mellitus (GDM) is associated with an increase risk of neonatal and maternal complications. Continuous glucose monitoring (CGM) detects glycemic patterns, which could help predict the development of maternal-fetal complications.
Objective
To analyze the different glycemic patterns obtained with CGM and to correlate them with the appearance of maternal-fetal complications in GDM.
Methods
Women with GDM at 26–32 gestational weeks were allocated a 6-day CGM system (Ipro^{TM}2) right after diagnosis in an observational prospective study. The following parameters were analyzed by CGM: percentage of time that glucose is above or below range before and after breakfast, lunch, dinner and night. Glucose targets: before meals 70–95 mg/dL, after meals 70–140 mg/dL and night 70–120 mg/dL. Multivariable binary logistic regression was performed to identify independent risk factors associated with both neonatal and maternal outcomes. Value of P 0.05 were considered statistically significant.
Results
$n=87$. Maternal age 33 ± 4.26 years (>35 years$=39\%$). Pregestational body mass index 26.2 ± 4.7kg/m^2 (>30 kg/m$^2=22.1\%$). Insulin treatment 23.4%. *Maternal and neonatal outcomes*: caesarean 28.6%, macrosomia13%, large gestational age (LGA) 8.2%, small gestational age 6.5%, neonatal hypoglycemia 22.1%, neonatal hyperbilirubinemia 7.8%, need for supplemental oxygen in the neonate 7.8%. *Glucose time above and below range (%):* before breakfast: $>95=25.75\%$, 70–95$=66.79\%$ and $<70=7.36\%$; after breakfast:$>140=18.49\%$, 70–140$=80.71\%$ and $<70=0.77\%$; before lunch: $>95=20.43\%$, 70–95$=70.16\%$ and $<70=90.48\%$; after lunch: $>140=11.08\%$, 70–140$=85.87\%$ and $<70=3.18\%$; before dinner:$>95=35.81\%$, 70–95$=58.55\%$ and $<70=5.47\%$; after dinner: $>140=8.18\%$, 70–140$=88.89$ and $<70=2.94\%$; night: $>120=7.84\%$, 71–120$=81.79\%$ and $<70=90.40\%$. *Multivariate binary logistic regression:* Glucose time above range after lunch was an independent factor for macrosomia (Odds ratio 1.041, 95% confidence interval [1.002–1.081]; P value 0.035) and LGA (Odds ratio 1052, 95% confidence interval [1.012–1.094]; P value 0.010). It was not found another independent risk factor for maternal or neonatal outcomes.
Conclusions
There is a correlation between hyperglycemia after lunch at diagnosis of GDM and macrosomia and LGA, although a predominance of preprandial hyperglycemia is observed, especially before dinner. The use of CGM could help identify those patients with higher risk of maternal-fetal complications. However, further studies with a larger number of patients are required.

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P182

Evaluation of leptin levels in diabetic and nondiabetic patients with increased BMI

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Objectives
Leptin is an adipokine responsible for controlling appetite and fat accumulation. The role of leptin in pathophysiology of obesity and diabetes mellitus is an area of active investigation.The aim was to study leptin levels in diabetic and nondiabetic patients with increased body mass index (BMI).
Methods
A sample of 246 patients with type 2 diabetic mellitus and 86 age and BMI-matched controls were examined. The mean age of the participants with diabetes mellitus was 58.24 (53–66) years, healthy adults 51.23 (40–63) years. The mean BMI of diabetic patients was 31.26 (28.08–34.68) kg/m^2 vs controls 30.4 (27.28–34.92) kg/m^2. Blood samples were taken from participants after fasting for 12 hours. For diabetic patients antidiabetic drugs were given 12 hours before.
Results
We found no statistical differences in serum leptin levels in the examined groups. Leptin levels in diabetic patients were 32.37 (14.93–43.67) ng/ml, in healthy adults 27.05 (12.42–38.2) ng/ml, $P=0.109$. These may be the result of increased levels of BMI in diabetic and nondiabetic patients and the absence of significant differences in BMI between two groups. Study of gender differences in fasting serum leptin concentrations revealed statistically higher concentrations of leptin in diabetic females 38.22 (19.61–40.62),ng/ml than in diabetic males 16.09 (9.24–20.3) ng/ml, $P=0000.1$ and in healthy females 31.02 (17.4–42.98) ng/ml vs healthy males 14.74 (8.19–17.6) ng/ml; $P=0.001$.
Conclusion
The data revealed no statistical differences in leptin levels in diabetic and non diabetic patients with increased BMI, but suggest gender dichotomy in both groups.

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P183

Adiponectin concentrations in type 2 diabetes mellitus patients compared with healthy controls

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Objectives
Adiponectin is an adipokine that play an important role in glucose metabolism and energy homeostasis. The aim of our study was to evaluate adiponectin levels in type 2 diabetes mellitus patients compared with healthy controls.
Methods
A sample of 246 patients with type 2 diabetic mellitus and 86 age and BMI-matched controls were included. The mean duration of diabetes was 9.54 (5–13) years. The mean glucose level was 8.14 (5.56–9.9) mmol/l in diabetic patients, 5.48 (4.9–5.78) mmol/l in healthy controls.
Results
No statistical differences were revealed in adiponectin levels of the examined groups. Fasting concentration of adiponectin in diabetic patients was 3.44 (1.6–4.44) ng/ml vs 4.03 (1.62–6.28), ng/ml in healthy adults, $P=0.25$. However the study identified gender differences in serum adiponectin concentrations. The level of adiponectin in women with type 2 diabetes mellitus was 3.74 (1.84–4.72), ng/ml, in male 2.61 (1.32–3.17) ng/ml; $P=0.001$. In the group of healthy women adiponectin concentration was 4.47 (1.92–6.72), ng/ml; in healthy men 2.65 (1.54–3.77) ng/ml; $P=0.039$.
Conclusion
The study did not found statistical differences in adiponectin levels in diabetic and nondiabetic patients. The level of adiponectin was higher in female than in male regardless of the presence of the disease.

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P184

Diagnosis of type 1 DM in a patient with Hydroxymethylglutaric aciduria: Case report

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Introduction
Hydroxymethylglutaric aciduria is a rare metabolic disease that is caused by the deficiency of the enzyme 3-hydroxy-3-methylglutaryl-CoA lyase, which participates in the metabolism of leucine and in the formation of ketone bodies. The symptomatology usually occurs in the first two years of life and consists of nausea, vomiting, diarrhea, hypotoniaanddepressed level of consciousness. Metabolic acidosis occurs during crises as a result of the accumulation of metabolites and hypoglycaemia.The crises are triggered by infections or prolonged fasting.

Case report
A 18-month-old female who comes to the hospital due to seizures andhypotonia, with the suspicion of encephalitis. The blood test shows hypoglycaemia (19 mg/dL) and non-ketotic metabolic acidosis with high anion GAP. A study of hypoglycaemia in children is performed with the following results: marked increase of the excretion of leucine metabolites, decreased levels of free carnitine and normal levels of total and esterified carnitine. The diagnostic suspicion is Hydroxymethylglutaric aciduria, which is confirmed by a skin biopsy. Treatment is started with a diet low in proteins of high biological value, carnitine, and a leucine-free nutritional supplement. We also indicate to avoid prolonged fasting. With the adjustments, the patient showed a good evolution having only one admission due to a hypoglycaemia associated with a rotavirus gastroenteritis. In the follow-upthe genetic testindicates alikely pathogenic variant in apparent homozygotes: c.575T>C (p.Phe192Ser) in the HMGCL gene. At the age of 21, the patient debuted with diabetes with associated cardinal symptoms, which led to the initiation of insulin in basal-bolus therapy. Blood test results: GAD65-Ab >250 IU/mL, C-peptide 0.54 ng/mL and negative anti-IA2 and anti-Insulin antibodies. Currently the patient has good metabolic control with glycosylated hemoglobin of 6.1%.
Conclusions
We present a patient with type 1 DM who cannot present with metabolic ketoacidosis due to the deficit of the HMGCL enzyme. The association of both diseases is not previously described in the literature. Could an SGLT2i be used safely in this case? Is it beneficial that she cannot have ketoacidosis?

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P185

Novel clusters of adult-onset Diabetes: Casuistic from an Endocrinology Department

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Introduction
Type 2 diabetes (T2D) is a heterogeneous disease for which causal mechanisms are incompletely understood and subclassification may improve patient management. In the latest assessment of patients with adult-onset diabetes, *Ahlqvist and colleagues (2018)* defined five new subgroups: an autoimmune form, two severe forms (insulin-deficient and insulin-resistant diabetes) and two mild forms (obesity and age-related diabetes).
Objectives
To stratify patients with T2D into subgroups and assess the impact of the clusters on outcomes and therapeutics.
Material and Methods
We conducted a cluster analysis of patients with T2D ($n=1280$) in an Endocrinology department. Clusters were based on three variables (presence of antibodies, age at diagnosis and BMI) and data from patient records was collected on development of complications and therapeutics.
Results
We identified 4 clusters of T2D, with significantly different patient characteristics. Cluster 1 (autoimmune) consisted of 2% of patients, Cluster 3 (obesity-related diabetes) of 63%, Cluster 4 (age-related diabetes) of 13% and Cluster 2 the remaining 22%. Clusters 1 to 4 presented a mean age at diagnosis of 46, 52, 54 and 72, respectively. The remaining clusters presented a mean BMI of 24.4 kg/m^2. Cluster 3 presented the highest mean BMI value (31.7 kg/m^2). Cluster 1 had the highest mean HbA1c (7.3%), while Cluster 4 the lowest (6.6%) (*P*-value 0.033). Nephropathy was the most common complication in this population. Retinopathy was most frequent in Clusters 1 (18%) and 2 (16%) (*P*-value 0,001). Insulin was prescribed to most patients in Cluster 1. Monotherapy was the trend in Cluster 4. Combination therapy was required more often in clusters 2 and 3 (*P*-value <0.001). The majority of patients in Clusters 2 and 3 (60%) presented family history of diabetes.
Discussion and Conclusions
Clusters 1 and 2 were characterized by early-onset disease, higher HbA1C and low BMI. Furthermore, they presented the highest prevalence of retinopathy. Cluster 3 presented the highest BMI. Combination therapies were more common in clusters 2 and 3. Cluster 4 was characterized by late-onset disease, low HbA1c and low BMI. Also, monotherapy was the treatment of choice. Nephropathy was the most common complication. This new classification is easily replicable in a real word setting, especially amid general practioners. It will be exciting to explore whether individuals respond differently to medications based on the pathway predominantly disrupted or whether they have a variable rate of progression and diabetic complications.

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P186

Relationship between cortisoluria and the presence of metabolic syndrome among HIV-infected patients

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Introduction
People living with human immunodeficiency virus (HIV) are at increased risk of developing metabolic disorders, such as obesity, dyslipidemia, insulin resistance, diabetes and hypertension; which may also be associated with hypercortisolism. Due to the similarity between the metabolic changes present in these two clinical situations, several studies have evaluated whether HIV-infected patients have increased levels of cortisol, but the results are not consensual. Urine free cortisol (UFC) is a screening test for hypercortisolism.
Purpose
We aims to determine the relationship between cortisoluria and the presence of metabolic syndrome (MetS) and assess the relationship between the UFC and each components of MetS in HIV-infected patients.
Methods
As part of a cross-sectional study, 219 Caucasian, non-institutionalized, HIV-1 infected adults under cART (combined antiretroviral therapy) were evaluated. For each patient the following data were collected at baseline: demographic data (age, gender), weight, height, waist and hip circumferences and UFC levels. For non-normally distributed continuous variables, we used Mann–Whitney U tests for comparison between two groups. To evaluate the association of anthropometric parameters with UFC we performed adjusted logistic regression models for the confounding variables (sex, age, duration of disease and cART. We excluded the patients without UFC and with the diagnosis of Cushing's syndrome or under corticotherapy. The presence of MetS was defined according to the harmonized International Diabetes Federation criteria of 2009.
Results
Of the 219 patients observed, 61.4% were males, with a mean age of 46.33 ± 11.46 years, BMI of 25.41 ± 5.00 kg/m2, waist circumference of 92.12 ± 12.59 cm and the hip circumference of 95.45 ± 9.66 cm. The median disease duration was 8.11 ± 4.01 years and the cART median duration was 6.67 ± 3.90 years. The median UFC values in patients with SMet were 38.4 μg/day [7–127.3] and in those without SMet of 50.1 μg/day [8.9 – 208.6]. No significant difference in UFC levels in HIV-infected patients with and without MetS ($P=0.147$), even after adjusting for confounding variables, was observed. The presence of obesity, diabetes, hypertension or dyslipidemia wasn't associated with UFC levels ($P=$ 0.509, 0.611, 0.675 and 0.778, respectively).
Conclusion
In our population of HIV-infected patients, MetS was not associated with higher levels of UFC, contrary to previous data in the general population. These findings suggest that the pathophysiological mechanisms of the metabolic syndrome in HIV patients could be different of uninfected population, where the MetS is associated with higher cortisol levels.

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P187

Complication of bariatric surgery as a reason of unsuccessful hypothyroidism and hypoparathyrosis treatment

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Background
Bariatric surgery remains the most effective method of weight loss and can result in partial or complete resolution of multiple obesity-related comorbidities. Bariatric surgery should be performed in conjunction with a comprehensive preoperative assessment and a follow-up plan consisting of nutritional, behavioral, and medical programs. The bariatric surgical procedures are associated with significant long-term complications, primarily malnutrition.
Clinical case
A 56-year-old woman was presented with complaints about tingling in her fingertips, painful muscle cramps, and difficulties with finger extension. It was found out from medical history that total thyroidectomy with parathyroidectomy because of papillary thyroid cancer was performed in 2007 and oral levothyroxine was prescribed. Bariatric surgery SADI-S (sleeve gastrectomy, duodeno–ileal anastomosis) was performed because of morbid obesity in September 2018. On

physical examination Chvostek and Trousseau signs were noted. BMI was 39 kg/m^2. Laboratory examination was carried out. Increased level of TSH and decreased value of calcium and 25-OH vitamin D were revealed. Laboratory results demonstrated postoperative hypothyroidism decompensation due to abnormal gastric acid secretion because of sleeve gastrectomy and postoperative hypoparathyrosis decompensation due to reduced calcium absorption because of duodeno–ileal anastomosis. So, the dosage of calcium, vitamin D and levothyroxine was increased. Also 10% calcium gluconate was prescribed. But compensation of postoperative hypothyroidism and hypoparathyrosis was not achieved. Thus, reconstructive operation was recommended due to ineffective medical treatment of hypothyroidism and hypoparathyrosis.

Conclusion

This clinical case demonstrates that lack of comprehensive preoperative assessment indications to bariatric surgery leads to complication in compensation of comorbid states, such as postoperative hypothyroidism and hypoparathyrosis.

References

1. Nancy Puzziferri, MD, MS, Thomas B. Roshek III, MD, Helen G. Mayo, BS, MLS, Ryan Gallagher, BA, Steven H. Belle, PhD, MScHyg, and Edward H. Livingston, MD Long-term Follow-up After Bariatric Surgery: A Systematic Review. *JAMA*. 2014 September 3; 312(9): 934–942.

2. Improved levothyroxine pharmacokinetics after bariatric surgery. *Thyroid* 2013; 3; 23: 414–9.

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P188

Assessment of asymptomatic coronary aretry disease using myocardial perfusion scan in diabetic patients

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Purpose

Coronary artery disease (CAD) is more common and severe in diabetic patients. The aim of this study is to assess the frequency of silent myocardial ischemia in asymptomatic diabetitics by myocardial perfusion scintigraphy and to correlate the results with risk fators.

Methods

We prospectively studied 50 (25 men and 25 women) diabetic patients asymptomatic and without known history of CAD. The minimum duration of diabetes was 15 years for the type 1, 10 years for type 2. The average age was 61.4 years ranging from 43 to 80 years. All these patients had a first stress Myocardial Tomoscintigraphy (MTS) 99mTc-MIBI. MTS has enabled a study of myocardial perfusion, wall motion abnormalities and LV function. If MTS showed severe ischemia, further exploration was carried out by coronary angiography. It was performed in 5 patients in our study. These patients were recruited over a period of 8 months and have received specialized follow-up of 12 months post MTS.

Results

Positive MTS screening results were obtained in 20 patients (40% of cases) and showed ischemia in 65%, necrosis in 20% and mixed abnormalities in 15% of cases. lschemia is minimal in 8 patients (40%), moderate in 4 patients (20%) and severe in 8 patients. In the latter two cases there were at least 4 factors of cardiovascular risks. For the 8 patients with severe ischemia, the stress test (ST) was positive in only 10% of cases. Perfusion abnormalities sit at the inferior wall in 43%, concern the right coronary artery in 53%, and reach a single territory in 55% of cases. Coronary angiography was normal in one case, while the MTS objectified hypo perfusion. Moreover, the MTS abnormalities observed were consistent with coronary angiography. For six negative MTS, ST was negative in 80% of cases and doubtful in 20% of cases. Positive MTS patients have had therapy reinforcement or revascularization procedures. The SMI was more frequent in the group of male subjects, aged over 60 years for type 2 diabetes and over 45 years for the type 1, unbalanced, smoking, dyslipidemic.

Conclusions

MTS is a reliable tool for diabetic SMI screening. Its prognostic value can stratify the cardiac risk and guide therapeutic strategy. Improving this prognosis is based more on the intensive correction of risk factors than on possible revascularization procedure. Through better management of radiation risks, MTS is most appropriate.

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P189

HbA1c as a marker of glycemic control in patients with thalessemia HbH disease

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Hemoglobin A1c (HbA1c) is formed from the addition of a glucose residue to the N terminus of the Beta chain of a hemoglobin molecule via a non-enzymatic glycation pathway. Its levels correlate with the ambient plasma glucose concentration. The 120-day life span of red blood cells makes HbA1c a useful tool to approximate the diabetic control of patients over three to four months. It has also been found to be an accurate predictor of the microvascular and macrovascular complications of DM. The measurement of HbA1c works on the principle of separating and quantifying glycated hemoglobin chains. Several techniques have been developed for daily clinical use including High Pressure Liquid Chromatography (HPLC) via ion exchange and immunoassay techniques. However, there are caveats to their uses with some limitations. Several factors can cause assay interference including hemoglobinopathies. Hemoglobinopathies such as Thalessemia (HbH) disease can affect HbA1c results through both HPLC and immunoassay methods. We report a case of a patient with a falsely low HbA1c in a patient with known Thalessemia (HbH disease) and DM. The error occurred on both HbA1c assays available in our local hospital. His HbA1c was discordant with his home serial blood glucose monitoring (SBGM) and real-time interstitial glucose monitoring. This posed an important clinical management challenge. Further evaluation and analysis of the HPLC chromatogram revealed an inaccurate estimation of HbA1c via the HPLC method. It is important to recognise such pitfalls. While HbA1c may be a popular marker to assess patients' long-term glycemic control, clinical judgement needs to be exercised in situations where serial blood glucose monitoring does not correlate. In patients with Thalessemia HbH disease, other markers of glycemic control such as fructosamine should be considered.

References

1. Pravatmuang P, Sae-Ngow B, Whanpuch T, Leowattana W. Effect of HbE and HbH on HbA1C level by ionic exchange HPLC comparing to immunoturbidimetry. *Clinica Chimica Acta*. 2001; 313(1–2):171–178.

2. Agilli M, Yaman H, Aydin FN, *et al*. Hb H interference on measurement of HbA1c with ion-exchange HPLC. *Acta Inform Med*. 2013;21:216–218.

3. Khera R, Singh T, Khuana N, Gupta N, Dubey AP. HPLC in characterization of hemoglobin profile in thalassemia syndromes and hemoglobinopathies: a clinicohematological correlation. *Indian J Hematol Blood Transfus*. 2014;31(1): 110–5.

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P190

HbA1C as a marker of retrograde glycemic control in diabetes patient with co-existed beta thalassemia: Case report

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Introduction

A number of studies reported that almost every fifth patient with thalassemia hav e diabetes. Various factors could contribute to inadequate retrograde glycemic control in thalassemia patients co-existed with diabetes. According to published data, HbA1C seems to be an insufficient marker of the quality of diabetes control in thalassemia patients.

Case report

We present a male 67 years old type 2 diabetes patient with disease history for 15 years, who is under oral treatment and has microvascular diabetes complications on peripheral nerves and small distal arterial vessels. A retrograde glycemic control determined by HbA1C measurement was unexpectedly satisfied. The patient has been admitted to the hospital because of chronic distal neuropathic pain, right toe trophic ulcer, and electromyography (EMG) finding of distal sensorimotor polyneuropathy. In past medical history, the patient reported a

discus hernia (L1-5) surgery and later on noticed the presence of blood transfusions-independent thalassemia. Additionally, his daughter is also a beta thalassemia-heterozygous carrier. Five-point glycemic profile revealed moderate postprandial hyperglycemia and no hypoglycemic episodes. Despite the fact of already EMG confirmed distal polyneuropathy, retrograde glycemic control was optimal (HbA1C 6.5%). The thorough patient examination did not reveal any other chronic micro- or macrovascular diabetes complication. Laboratory analyses show microcytic anemia, mild biochemical syndrome of liver necrosis and remodeling and moderate hepatosplenomegaly detected by abdominal ultrasound. After the introduction of insulin and treatment by hyperbaric oxygen, the patient was discharged slightly improved in regard to actual glycemic control and right toe trophic ulcer healing. Some neuropathic complaints alleviation was achieved by use of alpha lipoic acid, pregabalin and amitriptyline.
Discussion and conclusion
When different factors can interfere with HbA1C measurements in diseases such as thalassemia and hemoglobinopathies, the discrepant findings of profile glycemic control and HbA1C values could be expected. In such patients, it is necessary to measure HbA1C with another method or to use fructosamine as a more reliable marker of retrograde glycemic control. When the 5-point glycemic profile is acceptable, HbA1C can be cautiously used in the estimation of retrograde glycemic control, preferably accompanied by fructosamine.

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P191

Clinical determinants of mean platelet volume in patients with abdominal obesity from different age groups

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There is growing evidence that platelet indices correlate with functional status of platelets and with the risk of cardiovascular events. In this study we aimed to assess clinical correlates of mean platelet volume (MPV) in patients with abdominal obesity from different age groups. We investigated 111 adults with abdominal obesity, not receiving antiplatelet therapy. Abdominal obesity was defined in accordance with IDF criteria (2006). Group 1 included 44 patients aged 26–45, group 2–67 patients aged 46–65. We evaluated clinical history, serum levels of lipid fractions, homocysteine, creatinine, eGFR, C-reactive protein, total and free testosterone (in men only), insulin, HOMA-IR index, and 25-hydroxyvitamin D. Mann-Whitney U-test and Spearmen's correlation coefficient (rs) were used for statistical analysis. Groups were found to have no significant differences when compared on the basis of sex composition, BMI, waist-to-hip ratio, HOMA-IR index, platelet level, and MPV. In both groups MPV was not interconnected with age, BMI and eGFR. In group 1, MPV correlated positively with the level of C-reactive protein ($rs = 0.390$, $P = 0.009$) and negatively – with total testosterone ($rs = -0.387$, $P = 0.042$) and free testosterone ($rs = -0.637$, $P = 0.001$) in men. In group 2, MPV had the only negative correlation with the level of 25-hydroxyvitamin D ($rs = -0.299$, $P = 0.015$). The results of the study suggest that different age groups of patients with abdominal obesity are characterized by different clinical determinants of MPV. In younger adults MPV is interconnected with C-reactive protein and testosterone levels (in men), while in people aged 46-65 it is significantly related to the level of 25-hydroxyvitamin D.

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P192

Large phenotypic variability of diabetes due to *ABCC8* gene mutation illustrated by the paradigm of a family

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Background
Monogenic Diabetes is relatively rare, representing only 1–2% of total diabetes cases; nevertheless, it is often misdiagnosed primarily as Type 1 Diabetes, leading to unnecessary insulin therapy and delayed recognition of affected family members.
Methods
Case report.
Results
We describe a case of a young patient who presented with hyperglycemia in the absence of ketosis and following genetic testing, he proved to harbor the R1352H mutation in the *ABCC8* gene, inherited from his mother. This mutation has been previously described in patients with Congenital Hyperinsulinism. Furthermore, different mutations in the *ABCC8* gene have been linked with MODY 12, Type 2 and Gestational Diabetes; however, to the best of our knowledge, this is the first report that associates this specific mutation with diabetes phenotype. We present our diagnostic and therapeutic approach and suggest a theoretical framework to explain the association between the cellular alterations resulting from genetic variation and the clinical presentation of the described case.
Conclusions
Given that there is no definite consensus regarding the management of such cases and that relative clinical data are still inadequate, close clinical follow-up and individualized treatment are required, in order for these patients to achieve metabolic targets and avoid long-term diabetic complications.

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P193

Find prevalence of type 2 diabetes mellitus (DM) in age, BMI, symptoms and comorbidities (hypertension, dyslipidimia) in Indian scenario

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Objective
To Find Prevalence of type 2 diabetes mellitus (DM) in Age, BMI, Symptoms And Comorbidities (Hypertension, Dyslipidimia) in Indian Scenario.
Methods and plan
This is retrospective observational multicentric Study carried out in our four (4) centres of DIA CARE, Ahmedabad during September to December 2018, We divided patients with newly-diagnosed DM in BMI, Age,Symptoms, Comorbidities(Hypertension, Dyslipidimia). We studied consecutive patients with newly-diagnosed DM during September 2018 -December 2018. We recorded data regarding BMI and Age of newly diagnose patients and recorded symptomatic or Asymptomatic and Comorbidities, We recorded data newly diagnosed DM with blood pressure (BP) and Cardiovascular risk factor like dyslipidimia. Data are presented as mean ± S.D. or median (interquartile range).
Results
We studied total 150 newly diagnosis diabetes patients 4 centres at Dia Care, Ahmedabad, Gujarat, India (Tables 1–5).

Table 1 Data Recorded between Age – 50 ± 15.

Male	88
Female	62
Age	Patients
Above 55	
45-55	(55%)83
30-45	(25%)-37
Less than 30	(20%)-30

Table 2 Data Recorded Symptomatic or Asymptomatic. Symptoms (Polyuria, Polydipsia, Polyphagia, Weight loose, etc).

Symptomatic	Asymptomatic
93 (62%)	57 (38%)

Table 3 Data recorded According to BMI.

BMI	
Overweight	57 (38%)
Obese class 1	23 (15%)
Obese class 2	12 (8%)
normal	58 (39%)

Table 4 Data Recorded of Hypertensive/Non Hypertensive.

Hypertension	Hypertension Simultaneously	Normotensive
52 (35%)	30 (20%)	68 (45%)

Table 5 Dyslipidimia (High LDL, Low HDL, High TG).

Dyslipidimia	Normal
97 (65%)	53 (35%)

Conclusions
Study Indicates High Prevalence in Age between 45–55 age. In BMI high prevalence seen in Over Weight People. We found 35% hypertensive, 20%. Simultaneously, 45% Normotensive and 65% Dyslipidemic and 35% Normal in Newly Diagnosed Diabetes type 2 Patients.

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P194

Clinical case of insulin autoimmune syndrome

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Introduction
Insulin autoimmune syndrome (IAS) is characterized by the development of hypoglycemia due to insulin and insulin autoantibodies (IAA) interaction. The disease has a strong association with certain alleles of *HLA* gene. In most cases the disease affects predisposed persons who take drugs containing the sulfhydryl groups. The IAA are also noticed in patients with other autoimmune pathology and in patients with multiple myeloma or monoclonal gammopathy. In case of mild course of disease the treatment is not necessary, but in some cases the glucocorticoids may be prescribed.
Clinical case
A 46-year-old female patient with obesity (BMI 36.0 kg/m^2) received the Thioctic acid since November 2017. Since December 2017 the patient had the episodes of dizziness and feelings of fear which occurred 2–3 hours after meals and accompanied by hypoglycemia to 2.1 mmol/l. The drug was discontinued. The results of examination in a non-specialized clinic: HbA1c 5.4%, insulin $>$600 mIU/l. Abdominal ultrasound and MRI did not reveal insulinoma. Since February 2018 no hypoglycemic episode appeared. In April 2018 the patient was firstly examined in Endocrinology Research Centre. During the 72-hour fast, mixed meal test and oral glucose tolerance test the normoglycemia was recorded according to the continuous glucose monitoring system. The results of examination: insulin 330.7 mIU/l, C-peptide 4.96 ng/ml, glucose 5.2 mmol/l, HOMA-IR 76, IAA 102.4 U/ml, antibodies (AB) to insulin receptor 4.156 ng/ml, AB to 21-hydroxylase, thyroid peroxidase, thyroglobulin, receptor for thyroid-stimulating hormone, glutamate decarboxylase, islet cell AB, islet antigen 2 AB, zinc transporter 8 AB were not increased. The electrophoresis and immuno-chemical study of serum and urine proteins did not reveal any pathologic findings. HLA-typing was carried out: *DRB1*: *03, 04*; *DQA1*: *0301, 0501*; *DQB1*: *02, 0302*. There were no other autoimmune pathology in patient or any autoimmune pathology in her relatives. We diagnosed the IAS, induced by Thioctic acid. The examination in November 2018 revealed: insulin 143.1 mIU/l, C-peptide 4.91 ng/ml, glucose 4.87 mmol/l, IAA 35.26 U/ml, AB to insulin receptor 3.821 ng/ml. Thus, after discontinuation of Thioctic acid the levels of insulin and IAA gradually decreased, hypoglycemia was not recorded.
Conclusion
IAS should be excluded in any patient with hyperinsulinemic hypoglycemia to determine the appropriate tactics for subsequent examination and treatment. Imaging study of the pancreas is not required for patients with IAS. The detailed survey on the use of drugs and a thorough analysis of laboratory examination data are necessary.

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P195

Evaluation of distance learning activities for healthcare professionals in diabetes management in Albania

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Background and purpose
The rising incidence of diabetes mellitus in Albania intensifies the need for effective health education for DM risk reduction among pharmacists, nurses and other health care practitioners. As a result, continuing diabetes education is pivotal in improving the performance of these professionals and thus providing better health care services.
Objective
Our goal was to develop an e-learning course on the management of Diabetes mellitus for community pharmacists, primary care nurses and other primary care healthcare professionals and assessing its efficacy, effectiveness, and user satisfaction.
Methodology
This was a self-paced distance learning course on Diabetes Management for pharmacists and other healthcare professionals was developed and evaluated for its efficacy, effectiveness, and satisfaction. We performed a stratified randomized controlled trial with these healthcare professionals which have at least 1 year working experience, using pre- and post-knowledge tests, and satisfaction questionnaires. We wanted to identify the possible improvement in test results (percentage of correct answers), using intention-to-treat and per-protocol analysis.
Results
A total of 72 participants were assigned to the intervention (22 nurses, 42 pharmacists, 8 GPs) with 65 participants in the control group (20 nurses $+$39 pharmacists, 6 GPs). The intervention was completed by 60 participants (17 nurses$+$39 pharmacists $+$4 GPs), with 4 (2 nurses$+$2 pharmacists) discontinued interventions, and 8 (3 nurses$+$3 pharmacists $+$2 GPs) lost to follow-up. Substantial differences were found between intervention and control: 21 versus 4 percentage points (pp) in the primary outcome results.
Discussion and conclusions
This e-learning course is effective, especially for community pharmacists and primary care nurses, which highlights the need for continuing education in Diabetes Management.
Keywords: diabetes mellitus, continuing education, distance learning, evaluation studies, community pharmacists, primary care

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P196

Type 1 diabetic patients with more than five years of disease have increased global methylation levels

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Background and aims
Type 1 diabetes mellitus (T1DM) results from a severe autoimmune destruction of pancreatic beta cells, which renders patients insulin-dependent for life. The triggering of autoimmunity against beta cells is caused by a complex interaction

between environmental, genetic and epigenetic risk factors. Although significant progress has been made in elucidating the genetic factors associated with T1DM, the non-genetic components have remained poorly understood. Recent evidence has suggested that epigenetic regulation is a key mechanism by which environmental factors interact with genetic factors to trigger T1DM. DNA methylation is an epigenetic modification that results in the addition of methyl groups to the cytosine residues of CpG dinucleotides, leading to repression of gene expression. Even though some studies have suggested that T1DM patients have global alterations in DNA methylation levels, little is known about the contribution of methylation to the etiology of T1DM. Therefore, the aim of this study was to investigate the global DNA methylation levels in T1DM patients and non-diabetic subjects from Southern Brazil.
Material and methods
This case-control study was carried out in 55 T1DM patients (cases) and 55 non-diabetic subjects (controls). Subjects were divided into two groups: Group 1: 39 patients with >5 years of T1DM paired to 39 controls, and Group 2: 16 patients with ≤ 5 years of T1DM paired to 16 controls. Case and control subjects from both groups were paired according to body mass index, age and sex. DNA was extracted from peripheral leukocytes, and global DNA methylation levels were quantified using a colorimetric kit (MDQ1, Imprint Methylated DNA Quantification Kit, Sigma-Aldrich). Percentages of global methylation were compared between paired case and control groups using generalized estimating Default (GEE), and are shown as estimated means (95% confidence interval).
Results
Global DNA methylation levels were higher in T1DM cases compared to non-diabetic controls from Group 1: 117.2% (95.9–138.5) vs 74.7% (65.3–84.1); $P=0.001$. In contrast, in Group 2, global methylation levels did not differ between cases and controls 93.7% (57.9–129.5) vs 99.6% (85.2–113.9); $P=0.753$). Moreover, glycated hemoglobin levels were positively correlated with methylation levels in cases and controls from Group 1 ($r=0.369$; $P=0{,}001$), but not Group 2 ($r=-0.335$; $P=0.065$).
Conclusion
Our results indicate that global DNA methylation levels are associated with T1DM, which is dependent on the duration of this disease.

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P197

Results of application intensive weight management program in overweight (obese) patients with type 2 diabetes in real clinical practice

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Aim
To estimate the efficacy of structured lifestyle modification program on clinical and metabolic status in overweight/obese patients with type 2 diabetes (T2DM).
Materials and methods
The program was implemented in 2 centers (Moscow, Kazan) and 130 participants were recruited (100-active group, 30-control group). The patients' characteristics in active group: mean age was 54.6 ± 10.2 years, diabetes duration 6.6 ± 5.6 years, BMI 34.4 ± 3.5 kg/m^2, HbA_{1C} 7.4 ± 1.7%. The patients' characteristics in control group: mean age was 60.6 ± 8.9 years, diabetes duration 11.2 ± 8.5 years, BMI 33.5 ± 3.5 kg/m^2, HbA_{1C} 7.8 ± 1.9%. This program consisted of five components: dietary intervention; individualized exercise intervention; specific model of psychotherapeutic intervention (team coaching); group education and antidiabetic drug adjustment. Before the program patients underwent a comprehensive evaluation. Patients of active group attended the clinic once weekly for 3 hours (12 weeks). Group sessions were conducted each week by the endocrinologist, dietitian, psychologist and exercise physiologist (EP). The exercise plan included weekly 60-minute exercise session (in the 1-st month 30-minute) of aerobic, resistance and flexibility exercises under the supervision of EP. The components of team coaching were: goal setting, self-monitoring, stimulus control, attributive style modification, stress management and relapse prevention. During another 9 months, medical monitoring was carried out monthly. Medical parameters were measured at baseline, after 3 and 12 months.
Results
90 participants of active group and 29 participants of control group completed the study. After 1 year 50% of active group and 13.3% of control group achieved the primary goal ≥ 5% of weight reduction from baseline (OR 6.54 (95% CI [2.01; 21.33], $P=0.002$). The weight loss ≥ 10% was achieved in 26 patients of active group and in two patients of control group (OR 12.09 (95% CI [1.41; 103.39], $P=0.023$). Mean weight loss was 5.6 kg (95% CI [-6.7; -4.4]) and 0.8 kg (95% CI [-2.1; 0.4]) in the active and control groups respectively. The reduction of waist-hip ratio (WHR) was 0.016 (95% CI [-0.023; -0.008]) in active group; WHR increased by 0.017 (95% CI [0.0076; 0.026]) in control group. HbA_{1C} decreased by 0.8% (95% CI [-1.1; -0.5]) and by 0.1% (95% CI [-0.5; 0.2]) in active and control groups respectively. 58.3% of active group achieved HbA_{1C} ≤ 7%. The mean difference of patients' achieved HbA_{1C} ≤ 7% between groups was 58.3% (95% CI [30.2;80.6], $P<0.001$).
Conclusion
Structured weight management program in overweight/obese patients with T2DM showed high effectiveness in both the weight reduction and the improvement of glycemic control.

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P198

Structural changes of bone tissue in patients with type 1 diabetes mellitus

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Objective
The aim of this study is to evaluate the bone mineral density, hip geometry parameters and bone quality, measured by trabecular bone score (TBS) in patients with type 1 diabetes mellitus (T1DM).
Materials and methods
We examined 97 patients with T1DM (28 males, 69 females, age: 31 (24.9 – 37.7) yrs., duration of DM: 11 (7 – 19.5) yrs., HbA1c: 8.6 (7.1 – 10) %, BMI: 23.1 (21.9 – 25.7) kg/m^2). The control group consisted of 77 health age- and BMI-matched persons (20 males, 57 females). Bone mineral density (BMD) and the TBS were measured with dual X-ray absorptiometry. Geometric parameters were determined using Advanced Hip Analysis program including hip axis length (HAL), cross-sectional moment of inertia (CSMI) and cross-sectional area CSA.
Results
T1DM patients had lower BMD both at spine (T1DM: $-0.4(-1.6$–$0.4)$ vs. controls: $0.3(-0.7$–$0.8)$, $P=0.001$, respectively) and at femoral neck (T1DM: $-0.6(-1.5$–$0)$ vs. controls: $0.1(-0.5$–$0.7)$, $P<0.001$, respectively), higher frequency of fragility Fx (T1D: $n=21$ vs controls: $n=6$, $P=0.012$, respectively), lower level of osteocalcin (T1D: 15.14(11.8–24.2) vs controls: 24.5(22.2–28.2) pg/ml, $P<0.001$, respectively) compared with controls. T1D patients had shorter hip axis length (HAL) than in control group (T1D: HAL 107(102–113) vs. controls: 109(106–116) mm, $P=0.010$, respectively). T1D patients had lower CSA (T1D: 145(127–166) vs. controls: 160(139–178) mm^2, $P=0.002$, respectively) and TBS L1–L4 (T1D: 1.382(1.277–1.414) vs. controls: 1.428(1.368–1.470) $P=0.016$, respectively) compared with controls.
Conclusions
BMD, TBS and CSA in patients with type 1 DM were lower in comparison to the control group. Structural changes of bone tissue may indicate the poor bone quality and might potentially predispose to higher fracture risk in T1DM patients.

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P199

Early morphofunctional changes in the myocardium in young people with type 1 diabetes can be detected by magnetic resonance imaging

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Aim
To study the morphofunctional state of the myocardium in young people with diabetes mellitus 1 using magnetic resonance imaging (MRI) technology.
Material and methods
38 patients (14 men, 24 women), aged 18–36 years old, with an experience of type 1 diabetes from 5 to 16 years old were underwent contrastive mri of the heart. The exclusion criteria were: pronounced electrolyte disorders in the blood, dysproteinemia, chronic liver and kidney failure – glomerular filtration rate (EPI) −60 ml/min/1.73 m^2, thyroid dysfunction, obesity (body mass index −30 kg/m^2), diagnosed cardiovascular diseases, contraindications for mri. The indicators of functional changes in the left ventricle (circular strain, strain relaxation index – SRI), peak early diastolic strain (PSRDS) were obtained and the accumulation of the contrast agent in the delayed period were assessed.
Results
The obtained results of strain, SRI, PSRDS do not allow to exclude the presence of functional changes in the myocardium of the left ventricle. In 42.11%, zones of accumulation of the contrast agent were visualized in the delayed period (insignificant – 28.95% and moderate accumulation – 13.16%), mainly by the endocardium of the cardiac apparatus (mitral and tricuspid), and in one observation (2.9%) – in combination with unexpressed diffuse heterogeneity of the myocardium of the left ventricle.
Conclusion
MRI of the heart is a promising direction in the assessment of early morphofunctional changes in the structure of the myocardium, which will probably make it possible to predict life-threatening changes in the heart muscle in young patients with type 1 diabetes.

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P200

PCSK9 inhibitors effects after 2 years in real life

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Introduction
Recently, PCSK9 inhibitors have been approved in our country for familial hypercholesterolemia and for patients with cardiovascular diseases. They are still scarce data in real life patients effects.
Objective
Analyse the features of first patients treated with PCSK9 inhibitors in a specific unit of familial dyslipidemia and the effect on lipid profile and other clinical variables.
Material and methods
Data from patients with familial hypercholesterolemia treated with PCSK9 inhibitors were collected. Clinical data, physical examination and blood test data were collected at baseline, 3 months, 1 and 2 years.
Results
Data were obtained from 35 patients, 50% male. Mean age: 49.5 years (26–74). Mean follow-up: 12 years. Diagnosis: 11.4% combined familial hyperlipemia and 82.9% heterocigous familial hypercholesterolemia, 43% cases with mutation detected in LDL-R. 71% had a family history of premature CVD, 28.6% with obesity, diabetes 19.2%, smokers 2.9%, HTA 43,8%, 71.4% with high lipoprotein(a), 42.4% with early CVD (71% AMI). 69.6% treated with statins (54.3% rosuvastatin, 2.9% atorvastatin, 5.7% Fluvastatina), 66.7% ezetimibe, 20% resincolestiramina. 23% had elevated transaminases with at least two statins and 54.3% did not tolerate adequate dose of statin/ezetimibe because of secondary effects. The mean pre and postreatment levels (3–6 months) were: TC: 246.5 ± 51.6 vs 147.5 ± 39.4 mg/dl (*P* 0.001), LDL-C: 160.2 ± 42.5 vs 70.3 ± 28.6 (*P* 0.001), 60% achieved therapeutic objective, HDL-C: 55.4 ± 17.9 vs 51.1 ± 14.5 (*P* 0.16), non HDL-C:194.3 ± 31.5 vs 97.8 ± 30.7 (*P* 0.001), TG:158.1 ± 46.2 vs 128 ± 56.8 (*P* 0.25), Apo B 135.8 ± 22.9 vs 78.3 ± 17.7 (*P* 0.01), lipoprotein (a) 98.2 ± 54.9 vs 77.5 ± 40.1 (*P* 0.006). There were no significant changes in: Blood pressure, heart rate, HbA1c, thyroid hormones, cortisol, Vitamin D, creatinine, transaminases and cell blood counts. Weight was 75.4 ± 14.2 vs 73.6 ± 13.4 (*P* 0.039) and testosterone 5.06 ± 0.93 vs 4.2 ± 1.1 (0.043) After 2 years of treatment: mean TC was 149.5 ± 49.4, LDL: 75.3 ± 34.6, HDL 54.1 ± 17.5, nonHDL 96.3 ± 38.2, TG 118.1 ± 41.1, Apo B:47 ± 10.6, Lipoprotein (a): 85.8 ± 59.09 (non stadistical differences with effects at 3–6 months) There were no stadistical differences between alirocumab and evolocumab effects. Only four patients had mild side effect: 3 patients with pseudogripal syndrome and another patient with injection site reaction.
Conclusion
PCSK9 inhibitors were well tolerated and significantly reduced levels of TC, LDL-C, ApoB, non-HDL C and lipoprotein (a) after 2 years of treatment, with 60% of patients achieving therapeutic goals on LDL.

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P201

Acquired generalized lipodystrophy: a new cause of Anti-PD-1 immune-related diabetes

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Context
Anti-programmed cell death-1 (Anti-PD-1) antibodies have revolutionized advanced cancer therapy. Anti-PD1 therapy is responsible for immune-related adverse events, with frequent endocrine manifestations. Acquired generalized lipodystrophy (AGL), is a rare disease, thought to be immune-mediated, characterized by loss of adipose tissue and insulin resistance-associated complications. We describe the first case of AGL induced by immune checkpoint therapy.
Case description
A 62-year-old woman is treated with nivolumab for metastatic melanoma. After 18 months of treatment (34 courses), the patient developed a severe and rapidly progressive weight loss. The computed tomography revealed a major liver steatosis hitherto unknown, which was associated with hepatic cytolysis. Autoimmune and viral hepatitis were ruled out, and the liver biopsy showed a nonalcoholic steatohepatitis. One month later, the patient presented with a severe nonketotic hyperglycemia (24.9 mmol/L) and HbA1c 11.4% (97 mmol/mol). Aniti-GAD, IA2 and ZNT8 autoantibodies were negative although the patient exhibited a DR4 haplotype for class II HLA genes (DRB1*04 DQA1*03 DQB1*03:02) conferring a high risk of type 1 diabetes. Her pancreas was morphologically normal at abdominal CT and serum lipases were in a normal range. Fasting plasma insulin and HOMA-IR were strongly increased (40 mUI/L and 44.5, respectively). Diabetes was associated with severe insulin resistance and undetectable plasma leptin. She had presented with a rapidly progressive generalized loss of subcutaneous adipose tissue. The search for serum autoantibodies against insulin and insulin receptor was negative. The pathogenic variant in 23 genes of associated with lipodystrophy was absent. The complement system was unaffected and non-organ-specific autoantibodies were negative. The initiated treatment was composed with high-dose basal-bolus insulin regimen (1.6 U/kg/d) and metformin. Subcutaneous biopsy showed that atrophic adipose tissue was extensively infiltrated with cytotoxic CD8+T lymphocytes and fibrosis.
Conclusions
AGL should be added to the list of immune-related adverse events associated with anti-PD-1 treatment for malignancies. It is associated to a new pathophysiological mechanism of anti-PD-1 related diabetes that should be suspected from recent modification of body appearance with unusual fat loss. The benefit/risk ratio of leptin replacement on metabolic improvement, tumor progression and responsiveness to immunotherapy, needs to be evaluated in that setting.

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P202

Necrotizing external otitis: a severe form of otitis in diabetic patients

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Introduction
Necrotizing external otitis (NEO) is a serious life-threatening infection of the external ear and skull base condition. The precise etiology of this condition is unknown. Diabetes mellitus is well known to be one of the most tightly associated characteristics seen in NEO patients. It is documented that diabetes causes endarteritis and microangiopathy, leading to poor microcirculation and impaired polymorphonuclear cell function.
Patients and methods
A retrospective chart review was performed in the ENT Department and neck surgery of Farhat Hached hospital Tunisia between 2000 and 2018. 94 patients with a diagnosis of NEO were identified in the medical records within this period.
Results
Seventy-seven patients were diabetic within the period of study, which represent 82% of cases. The average duration of diabetes follow up was 8 years. The mean age was of 67 years and the male:female ratio was of 43:33. Four patients had associated chronic renal failure. All patients have received oral and local antibiotics before hospitalization. Symptoms were made of otalgia in all patients, otorrhea in 48 patients. Headache and temporo-mandibular joint pain were reported in six cases. Fever was observed in three patients. Four patients noted ipsilateral facial palsy. Stenosis of external auditory canal was observed in all patients. On admission, the fasting blood sugars levels ranged between 1.8 and 4.8 g/l. The erythrocyte *sedimentation rate* ranged from 33 to 110 mm/h. Computed tomography confirmed the NEO in all cases. Pseudomonas aeruginosa was the most commonly isolated organism in 84% of cases. Patients have primary received intravenous anti-pseudomonal medications. Antifungual therapy was conducted in 16% of cases. Diabetic control worsened with the onset of invasive external otitis in all cases. One patient received hyperbaric oxygen therapy as adjuvant treatment. A regression of symptoms was observed in 88% of cases. Patients were discharged after a mean duration of hospitalization of 34 days.
Conclusion
Successful management of NEO frequently requires a multidisciplinary approach with treatment discussed with an endocrinologist, radiologist, and infectious disease specialist. Adequate control of diabetes, the correction of electrolyte imbalance must be instituted at the earliest opportunity in association with antibiotic therapy. A quick and proper diagnosis is needed to start treatment and reduce morbidity and mortality.

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P203

Does osteocalcin have a role in Turkish gestational diabetes mellitus and its subgroups

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Background
Osteocalcin (Ost) is an osteoblast derived protein locally acting on bone formation. Ost could also have a role in regulation of glucose and fat metabolism. It has been shown that Ost can directly stimulate proliferation of β cells and have effect on secreting insulin, and can act on insulin sensitivity by cytokines. It was not fully investigated in gestational diabetes mellitus. The aim of our study was to investigate osteocalcin in Turkish gestational diabetes mellitus and its subgroups.
Methods
We performed a case–control cross sectional study and evaluated all the demographic and anthropometric parameters of 80, age and body mass indices similar pregnant women, half of them having normal glucose metabolism (NGT) and the other half having gestational diabetes mellitus (GDM). We classified the women according to age, parity, body mass index, and vitamin D levels and compared Ost levels, calcium metabolism, glucose, lipid and insulin resistance parameters and correlation of all the parameters in NGT, GDM and in GDM subgroups.
Results
Osteocalcin levels were high, but not-significant, in gestational diabetes group and also in old, multiparous, having low Vitamin D and high BMI gestational diabetes subgroups. There was a positive correlation between Osteocalcin and C peptide in GDM and GDM subgroups having age >30, multiparous, Vitamin D >20 ng/ml, BMI >30 kg/m^2 ($r=0.424$, $P<0.01$; $r=0.466$, $P<0.05$; $r=0.408$, $P<0.05$; $r=0.520$, $P<0.05$; $r=0.603$, $P<0.01$; respectively) and a negative correlation between Osteocalcin and HDL-Cholesterol in GDM subgroups having multiparous, Vitamin D >20 ng/ml and BMI <30 kg/m^2 ($r=-0.334$, $P<0.05$; $r=-0.352$, $P<0.05$; $r=-0.430$, $P<0.05$; $r=-0.442$, $P<0.05$; respectively).
Conclusion
We concluded that Ost may play a role in Turkish GDM and it increases in order to cope with beta cell dysfunction and insulin resistance which are important in GDM etiopathogenesis. Although we could not demonstrate statistically significant high levels of Ost in our GDM patients and in all subgroups, probably due to our relatively small group and subgroup sizes we think that multiparity, high BMI, low Vitamin D levels provide negative conditions for especially insulin resistance was concerned.

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P204

False memory is very common by elderly diabetics and could be a big problem in patients education and diabetes outcome

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Introduction
False memory, that is, remembering events, prohibitions and recommendations that did not happen. This phenomenon has long been known in forensics as it seems to be much more recognized in everyday life. This also applies to patients who could significantly interfere with communication with the doctor and education opportunities. In the face of surprisingly few papers on this subject regarding diabetes, we would like to present our observation.
Method
Participation in the study was proposed to subsequent patients hospitalized in the internal ward, whose condition allowed them to complete the questionnaire. False memory was investigated according DRM paradigm.
Results
In a group of 159 patients, aged >60 years, [[x +/−]y hospitalised in our internal ward 61 patients were diagnosed with diabetes. Fa; False memory wa every frequent both in the group of patients with diabetes 89% and hospitalised for another reason 90%. We could not find a relationship between the risk of false memory and gender, age, and the results of scales and tests like ADL IADL, GDS TYM MMSEi, Barthel, Berg Tinetti.
Conclusion
False memory is almost common among older patients. The presence of diabetes does not increase the risk of its occurrence. Practical importance for diabetes education and diabetes outcome requires further research.

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P205

GLP-1 secretion after oral glucose load is greater as eGFR is lower

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Background
Glucagon-like peptide-1 (GLP-1) is secreted from L cell at a small intestine and decreases blood glucose by stimulating insulin secretion. Therefore, GLP-1 receptor antagonists (GLP1-RA) is used to treat type 2 diabetes mellitus. In addition to the hypoglycemic effect, GLP-1 has been reported to reduce heart disease and renal dysfunctions. GLP-1 action on the kidneys is a natriuretic effect. Therefore, it may have a renoprotection effect. However, it is unknown whether

there is any correlation between kidney function and GLP-1 secretion. Long oral glucose tolerance test (OGTT) can detects glucose metabolism (i.e.: reactive hypoglycemia) more precisely than 2-h OGTT. In this study, we investigated the relationship between GLP-1 levels and estimated glomerular filtration rate (eGFR) in patients with heart disease, using long OGTT.
Methods
In this prospective observational study, we enrolled 30 non-diabetic patients (age 69 ± 10 years, 70% males, HbA1c 43 mmol/mol). A 4-h OGTT was performed, and glucose, insulin, glucagon (radioimmunoassay [RIA] and sandwich ELISA [S-W] methods) and active GLP-1 were evaluated during 4-h. We compared these factors and eGFR.
Results
HbA1c and area under the curve (AUC) of the glucose, insulin and glucagon during long OGTT are not correlated with eGFR. Although fasting activated GLP-1 is not correlated with eGFR, AUC of the activate GLP-1 after long OGTT is significantly negatively correlated with eGFR ($R = -0.385$ $P = 0.043$). Divided into 3 tertials, although HbA1c (Lowest eGFR group: 42 ± 4 vs. the other eGFR group: 43 ± 3 mmol·min/l, $P = 0.43$), fasting active GLP-1 (Lowest eGFR group: 2.00 [2.00–2.00] vs. the other eGFR group: 2.00 [2.00–2.40] pmol·min/l, $P = 0.59$) and AUC of the glucose (Lowest eGFR group: 1789.2 ± 261.0 vs. the other eGFR group: 1864.4 ± 353.5 mmol·min/l, $P = 0.57$), insulin and glucagon after long OGTT were not different, AUC of the active GLP-1 after long OGTT was significantly greater in the lowest eGFR group (38 ± 10 ml/min/1.73 m^2), than that in the other group (70 ± 12 ml/min/1.73 m^2) (Lowest eGFR group: 1773.0 [1000.5–2958.0] vs. the other group: 982.5 [825.8–1551.0] pmol·min/l, $P \leq 0.05$).
Conclusion
In non-diabetes patients with heart disease, fasting GLP-1 secretion and other glucometabolic factors were not correlated with eGRF. However, GLP-1 secretion after oral glucose load was negatively correlated with eGFR. Greater GLP-1 secretion was observed as eGFR was lower. These data suggest that GLP-1is assumed have renoprotective effect besides glycemic control.

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P206

Lessons from studying the characteristics of type 1 diabetes mellitus patients in a tertiary hospital in Singapore

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Background
To identify areas of improvement in the management of Type 1 Diabetes Mellitus patients by analysing their clinical data.
Methods
Computer records of 333 T1DM patients on follow-up at Tan Tock Seng Hospital from May to October 2017 were reviewed and analysed retrospectively.
Results
The average age of diagnosis is 29.75 years-old, and average BMI was 22.59 kg/m^2. 18% of patients had concomitant thyroid disease. 44.7% of patients had positive anti-GAD and 9.9% had positive serum ICAb. 20.7% of patients were misdiagnosed as having T2DM initially. Complications: 39.9% had DKA, 15.9% had hypoglycemia, 39.3% had microvascular and 13.8% had macrovascular complications. 52% of patients achieved the LDL target of 2.6 mmol/l and below. However, only 15.3% of patients have an established insulin-carbohydrate ratio and insulin correction factor that they use when administering their prandial insulin. While patients with established ICR/ICF do not have lower rates of DKA, (31.4% vs 41.5%, $P = 0.175$), they experienced significantly lower rates of microvascular (42.2% vs 23.5%, $P = 0.012$) and macrovascular (15.6% vs 3.9%, $P = 0.026$) complications. It is also observed that patients going for DM classes experienced significantly lower rates of DKA (18.2% vs 44.2% $P < 0.001$), and experienced lower rates of microvascular (20% vs 43.2%, $P = 0.001$) and macrovascular (5.5% vs 15.5%, $P = 0.049$) complications. Only 2.4% of patients are recorded to have been administered influenza or pneumococcus vaccines.
Discussion
There is little variation from the general population statistics in distribution of gender and ethnicity. However, it is noted that the average age of diagnosis is older, with average BMI that nears the upper limit of normal in Asians, rather than a lower BMI. As 18% of patients had thyroid disease, it is worthwhile screening patients for thyroid disease, even if they are asymptomatic, especially if serum antibodies are positive. Although it could be due to a lack of records, vaccination against common infections is still an important aspect of management which must be reinforced to physicians managing T1DM patients.
Conclusion
These findings break the preconceived notions that T1DM is a disease of only the young and/or lean. Vaccinations for common infections need to be encouraged, thyroid function should be screened regularly, and above all, patient education should be the forefront of management to reduce complication rates. These new insights may pave the way to a more holistic and effective management of T1 diabetic patients.

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P207

An assessment of physician reasons for prescribing insulin lispro 200 units/ml in a prefilled pen in Germany

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Background
Insulin Lispro 200 units/ml is a concentrated rapid-acting mealtime insulin (MTI) available as a prefilled, disposable pen (IL200) indicated for adults who require >20 units/day of prandial insulin. In comparison with Insulin Lispro 100 unit/ml prefilled pen, IL200 permits the delivery of an insulin dose in half the injection volume [1] and a lower glide force [2]. This study aims to understand physicians' reasons to prescribe IL200, as well as characterize patients treated with IL200 in Germany.
Methods
Physicians surveyed were diabetologists, endocrinologists or internal medicine specialists selected through screener questions from IQVIA's Primary Intelligence platform. Only physicians treating at least 20 patients per month with IL200 were invited to participate to gain experienced and specialized physicians. The physician survey comprised questions related to physician rationale for prescribing IL200 and patient characteristics.
Results
A total of 98 physicians were included in the survey. The majority were men (75.5%), above 50 years (51.0%), with a mean 18.1 years (SD:7.0) experience treating patients with diabetes (PwD), and mainly working in an office setting (65.3%). Responders reported that an average of 227 PwD were consulted per month, 39.8% of PwD consulted were treated with MTI therapy, and out of these, 52.0% were prescribed IL200. On average, physicians reported that, for patients treated with IL200, 78.6% had Type 2 diabetes, 50.0% were female, 51.9% were aged 21–64 years old at diagnosis, and 45.1% had a BMI above or equal 30.0 kg/m^2. Physicians reported that 77.9% of patients received an IL200 total daily dose higher than 20 units/day, and 48.3% of patients had an A1c level >7.5%. When asked the rationale for prescribing IL200, physicians rated as 'very' or 'absolutely important' the following objective clinical factors: insulin dose (88.8%); pattern of self-measured glucose levels (80.6%); and A1c level (80.6%). Regarding patient behaviour, the most important reasons for prescribing IL200 were the following patient characteristics: adherence behaviour (88.8%); knowledge about hypoglycaemia (88.8%); motivation to improve lifestyle (80.6%); and desire to reduce insulin injection volume (72.4%).
Conclusions
Physicians are mainly prescribing IL200 to people with T2D that are using more than 20 units of MTI/day. The top reasons of the physicians to prescribe IL200 were the required daily insulin dose, the ability to self-monitor glucose levels, and the desire to achieve better glucose control.

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P208

Lipoprotein apheresis during pregnancy in severe familial hypercholesterolemia – How and when should we switch treatment in the era of PCSK9 monoclonal antibodies?

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Introduction
Familial hypercholesterolemia (FH) is a genetic condition associated with elevated cholesterol levels and increased risk of atherosclerotic cardiovascular

diseases. Lipid-lowering drugs, i.e. statins, ezetimibe and PCSK9 inhibitors (PCSK9inh) are most often combined for effective treatment of FH. While statins may be continued during pregnancy if deemed necessary, other lipid-lowering drugs lack safety data leaving little pharmacological therapeutic options in pregnancies with FH. Thus, guidelines recommend withdrawing lipid-lowering drugs, ideally pre-conception, followed by lipid apheresis.
Clinical case
A 28-year old female patient was diagnosed with FH in the face of total cholesterol level of 17.0 mmol/L (657 mg/dL), HDL-cholesterol 2.6 mmol/L (101 mg/dL), triglycerides 1.2 mmol/L (106 mg/dL) and LDL-cholesterol 14.6 mmol/L (14.6 mg/dL). The three-vessel coronary heart disease was treated by coronary artery bypass graft (CABG) and drug-eluting stents, with a sequential introduction of rosuvastatin, ezetimibe and alirocumab at maximal dosage. Genetic testing confirmed compound heterozygous *LDLR*mutation, in addition to elevated Lp(a) at 1150 mg/L. While the patient was planning a future pregnancy, she was advised to use contraceptives for at least 12 months post-CABG. Pre-conception drug withdrawal was planned, followed by a bridge to lipid apheresis, such as the Direct Adsorption of Lipoproteins (DALI) technique. Meanwhile, an unplanned pregnancy led us to stop all medications abruptly at 6 gestational weeks, except for aspirin. DALI allowed the control of LDL-cholesterol in the range of 4.9–7.9 mmol/L (189–305 mg/dL, before DALI session) to 1.2–3.2 mmol/L (46–124 mg/dL, after DALI session). This first required weekly sessions, then the frequency was increased to twice weekly for the third trimester. The regular pregnancy ultrasounds highlighted an isolated agenesis of the corpus callosum with a normal CGH array and confirmed by fetal magnetic resonance imaging. No first trimester exposure to PCSK9inh has been reported so far. At the time of the ECE meeting, we will be able to report the outcome of the pregnancy, the DALI efficacy and the first neonatal evaluation of this at-risk pregnancy, with an assessment of the accountability of the reported treatment in the observed malformation.
Discussion
Lipid apheresis should be discussed with all female patients of childbearing age with FH. Guidelines do not specifically recommend preconception measures to optimize the fetal development and lower maternal risks. Pharmacovigilance in the era of PCSK9inh for FH requires more data on their potential fetal effects in humans.

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P209

Insulin sensitivity and counter regulatory responses following hypoglycemia in healthy and type 1 diabetes patients

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Background and aim
Insulin resistance is associated with type 2 diabetes and obesity but recent studies suggest that it may also be associated with type 1 diabetes (T1D), which may affect glycemic control. Hypoglycemia is a dreaded condition among patients with T1D and may also limit optimal glycemic management. We aimed to investigate insulin sensitivity and metabolic adaptions in healthy control subjects and T1D subjects.
Material and methods
We used a randomized crossover design to investigate nine normal weight men with T1D and nine age, BMI and gender comparable healthy control subjects. All subjects were investigated on two separate occasions only differing in regards to the intervention: 1) one episode of hypoglycemia (Single hypo-day) and 2) two consecutive episodes of hypoglycaemia (Dual hypo-day). Both study days included ahyperinsulinemic euglycemic glucose clamp and blood samples were obtained consecutively throughout the day.
Results
Glucose infusion rate (GIR) was significantly ($P=0.001$) lower in the T1D subjects ($\approx$ 5.7 mg/kg per min) compared to the control subjects ($\approx$ 7.6 mg/kg per min) with no significant effect of single/dual hypoglycemia events ($P>0.05$). During hypoglycemia, plasma glucose levels reached a comparable nadir of $\sim$2.55 mmol/L within interventions and groups. The T1D subjects had lower increments in glucagon and adrenaline compared with healthy controls ($P<0.05$) without any difference as regards to the interventions ($P>0.05$).
Conclusion
Subjects with T1D were more insulin resistant and had inferior increments in counter regulatory hormones during hypoglycemia compared with control subjects. A preceding hypoglycemic event the day before did not affect these findings. These results indicate that insulin resistance in present in normal weight T1D subjects and confirm that T1D subjects have defective counter regulatory response to hypoglycemia

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P210

Cardiovascular complications in metabolic syndrome in the Chernobyl NPP accident clean-up workers of in a late period upon exposure to ionizing radiation

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Objective
Evaluation of the role of collagen I type turnover in presentation of metabolic syndrome (MS) key components among the Chernobyl nuclear power plant (ChNPP) accident survivors three decades upon.
Results
The study involved 100 clean-up workers of the ChNPP accident of the with MS divided into 2 subgroups: 50 patients with acute radiation sickness (ARS) exposed to doses over 1.0 Gy, 50 patients exposed to doses 0.3–0.9 Sv; 37 patients with MS in the control group not exposed to ionizing radiation. Serum amino-terminal propeptide (PINP) and carboxy-terminal telopeptide of collagen type I (ICTP) levels were greater in exposed patients with ARS having doses over 1.0 Gy than in those with no radiation exposure in a history ($F=3.28$, $P=0.043$ and $F=3.65$, $P=0.041$). Linear dependence was found between the radiation dose and serum PINP and ICTP level in a first subgroup ($R=0.338$, $P=0.041$ and $R=0.689$, $P=0.0001$). This observation may help explain the complex changes in extracellular matrix after radiation impact and may suggest the new ways for diagnostic and therapeutic interventions. Systematic Coronary Risk Evaluation (SCORE) was elevated in the ChNPP accident clean-up workers having a left ventricular hypertrophy (LVH) and correlated with PINP in ARS patients having a concentric LVH ($F=5.46$, $P=0.001$ and $R=0.445$, $P=0.015$).
Conclusions
These findings suggest that abnormalities of collagen I type turnover in exposed persons having metabolic syndrome may be involved in the enhancement of myocardial fibrosis that accompanies the development of systematic coronary risk.

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P211

Pattern of C-peptide response to oral glucose tolerance test: interest and reference values

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Introduction
Oral glucose tolerance test (OGTT) allows classification of subjects in 3 groups, depending on glycaemia 120 minutes after 75 g glucose ingestion: normal (glycaemia $<$ 1.4 g/L), glucose intolerant (1.4–2 g/L) and diabetic ($>$2 g/L). Five insulin profiles associated with different incidence rates of diabetes over 10 years of follow-up have also previously been described. Insulin measurement is very sensible to hemolysis and can advantageously be replaced by C-peptide determination. However, little is known about C-peptide response to OGTT.
Material and methods
128 patients were included to evaluate glyceamia (COBASE801® ROCHE Diagnostics, France), insulin and C-peptide (LiaisonXL®, Diasorin, France) responses to OGTT.
Results
According to Hitashi classification, 23 (18%) patients of the whole cohort harbored a physiological insulin response corresponding to profile I (peak of insulin during OGTT at 30 min and higher insulin level at 60 vs 120 min), 14 (11%) patients were classified in profile II (peak of insulin at 30 min and lower or equal insulin level at 60 vs 120 min), 56 (44%) in profile III (peak of insulin at 60 min), 26 (20%) in profile IV (peak of insulin at 120 min and lower insulin level at 30 vs 60 min), and finally 9 (7%) in profile V (peak of insulin at 120 min and

higher or equal insulin level at 30 vs 60 min). Only 4 different mean C-peptide profiles emerged from the 5 subgroups previously defined by insulin profile, mean C-peptide profile being globally similar to mean insulin profile. The only difference relied on a similar C-peptide profile corresponding to a growing curve from T0 to T120 in both patients with insulin profile IV and V. Mean and 95% confidence interval of C-peptide value at the different times of OGTT were also calculated in the subgroup of patients with both normal glycemic and insulin (pattern I) responses to propose reference values: respectively T0: 0.53 (0.26–0.77); T30: 2.2 (1.24–3.29); T60: 2.26 (1.36–3.68); T120: 1.88 (0.84–2.62) nmol/L.
Conclusion
C-peptide response to OGTT profile seems to give globally the same information as insulin profile and should therefore also be predictive of the risk type 2 diabetes. The slight differences observed between the 2 parameters can be explained by different metabolism kinetics. This work also allows us to propose for the first time reference values for C-peptide at the different times of OGTT using Liaison XL® (Diasorin, France).

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P212

Microalbuminuria and its relation to other factors of cardiovascular risk in type 2 diabetic patients

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Background
Microalbuminuria was originally established as a predictor of renal failure in patients with diabetes mellitus and an indipendent risk factor for cardiovascular disease. The aim of our study is to assess the relationship between microalbuminuria and the other risk factors in diabetics and their prevalence.
Methods
120 patients with type 2 diabetes, were hospitalized at the Internal Medicine in the University Hospital Center 'Mother Teresa' in Tirana. Patients were divided in two groups: with and without microalbuminuria and for each group we evaluated cardiovascular risk factors such as: left ventricular mass index (LVMI), body mass index (BMI), glycosylated hemoglobin (HbA1C), lipidic profile, intima media thickness (IMT).
Results
Prevalence of microalbuminuria in our study is 32.3%. Prevalence of microalbuminuria among males was 37.5% and among females 62.5%. The microalbuminuric patients were older and had a longer duration of diabetes compared with normoalbuminuric patients ($P=0.01$). The microalbuminuric patients had significantly increased LVMI compared with normoalbuminuric group ($P=0.02$). Prevalence of obesity (BMI >30 kg/m^2) in type 2 diabetics patients was high. In our study this prevalence is 44.6%. In microalbuminuric group the mean value of BMI (30.13) was higher than the other group (28.00) ($P=0.04$). Presence of retinopathy was significantly higher in patients with microalbuminuri. (33.3% vs 14.6%) ($P=0.05$). In patients with microalbuminuria the mean value of IMT was higher than the other group (1.28 vs 1.09) ($P=0.03$)
Conclusion
The prevalence of microalbuminuria in patients with diabetes is high. In microalbuminuric group LVMI, IMT, BMI, duration of diabetes is significantly higher than normoalbuminuric group.

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P213

Pecularites of psychoemotional state at diabetes mellitus

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We have interviewed 246 people aged 18–55 years: 126 with DM type 2 with a duration of more than 5 years; 120 – without DM. The median body mass index (BMI) was 28.81 (23.51; 32.65) kg/m^2: at DM – 29.12 (24.48; 33.35); without DM – 27.92 (22.85; 31.26). The presence of DM didn't show any differences in eating behavior (DEBQ questionnaire) in contrast to BMI and gender. The emotiogenic style has become the leading one, the incentive for food intake is not hunger, but emotional discomfort in people with BMI $\geq$ 25 kg/m^2 – 48.6%; in women, in contrast to men ($\chi^2=16.71$; $P<0.0001$). The results of HADS scales indicate the same frequency of occurrence of depression in individuals with and without DM, in contrast to the manifestations of anxiety, which are more often recorded in diabetes ($\chi^2=3.96$; $P<0.05$). We have determined a direct correlation between the frequency of occurrence of clinically significant anxiety with the emotiogenic type of eating behavior in women with overweight or obesity (rS $=0.49$; $P<0.05$) Also there has been determined the absence of correlation between the psychoemotional status of men and types of eating behavior according to BMI and presence of DM type 2. Both individuals with DM (84.62%) and without DM (83.17%) demonstrated high stress tolerance (scales of assessment of social adaptation by T. Holmes, R. Reich), but more often it was noted in individuals with DM ($\chi^2=4.20$; $P=0.04$), which indicates psycho-emotional stress and difficulties in overcoming negative psychological situations. The non-alexithymic type of personality (Toronto alexithymia scale) was noted in 81.58% of cases in persons without DM and in 79.23% with DM ($P>0.05$). The alexitimic personality type was more often noted at BMI $\geq$ 25 kg/m^2 ($\chi^2=6.28$; $P=0.01$) and showed a direct correlation with the clinical manifestations of anxiety (rS $=0.34$; $P<0.042$). The study demonstrated that overweight people, even without DM, are in a state of disadaptation and psychoemotional stress, which may be a risk factor for the development of psychosomatic diseases and DM.

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P214

Peroxisome proliferator activated receptor gamma mutation responsible for partial lipodystrophy with end stage renal disease: pharmacokinetics of metreleptine during hemodialysis: Clinical case report

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Lipodystrophy is a rare disorder characterised by loss of adipose tissue, severe insulin resistance, diabetes, hypertriglyceridemia, hepatic steatosis with hypoleptinemia. Renal complications are also present but end stage renal disease is less frequent in partial lipodystrophy. We report efficacy and pharmacokinetics of metreleptine during hemodialysis in one case of partial lipodystrophy. A caucasian female presented with acute pancreatitis, major hypertriglyceridemia (25 g/l), and diabetes at the age of 21 years. She was non- obese (body mass index BMI:26) but has hirsutism, acanthosis nigricans, muscle hypertrophy and absence of subcutaneous fat on the limbs with facial sparing. She has severe hypertension, hepatosplenomegaly and renal failure (creatinin clearance 25 ml/min). 15 years later, patient developped proteinuria (10 g/l) with end stage renal disease requiring hemodialysis. She was treated by insulin delivered by external pump (300 ui/day). Diagnosis of partial lipodystrophy was made: plasma leptine level (immunoassay ELISA) was 6.89 µg/l. (for BMI 27, Normal: 37.5) A mutation of peroxisome proliferator activated receptor was identified (G 211E). Metreleptine was started at the dose of 0.04 mg/kg three time per week, after every hemodialysis achievement. Leptin plasma level were mesured at time 0 before injection of metreleptine and +1h, +2h, +3h, +4h, +5h, +6h, +8h, +10h, +12h, +24h+36 hafter. Result showed a rise with normalisation of leptine and return to baseline values by 36 h after the injection. Although, the regimen of metreleptine was increased at 0.08 mg/kg three times per week then plasma leptine level stayed in the normal range during 48 h. In addition patient developped for the first time hypoglycemias and the regimen of insulin was dramatically reduced to 90 ui/day, triglycerides were 3.6 g/l and proteinuria g/l (urinary sample).
This case report confirm the efficacy of metreleptine in partial lipodystrophy. We agree that in case of renal failure, plasma leptine level are modified.We analysed for the first time phamacokinetic profils of metreleptine in case of end renal stage disease and after hemodialysis: our results show a prolonged half life of metreleptine. We suggest in this condition, the delivrance of metreleptine at normal regimen but only three time/week after hemodialysis achievement.

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P215

Lipodistrophy, a rare disease: 'If you don't think about it, you doesn't diagnose it'

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Introduction
In the geographical area of southern Spain, in the province of Huelva, we have detected prevalent cases of Dunnigan's partial hereditary lipodystrophy. The genealogy, the suspicion phenotype and the coordination with the Genetics Service and Reference center, have borne fruit, and more and more families are detected in Our Area. The lipodystrophies, in general, are rare diseases that affect the adipose tissue, disappearance of it in different parts of the body together with metabolic alterations: Insulin resistance and hypertriglyceridemia. Traditionally they have been classified as congenital and acquired. We present a clinical case, in which the suspicion of acquired lipodystrophy in relation to AIDS and TARGA therapy coincides, to which is added the clinical suspicion of genetic lipodystrophy. We request genetic study.
Clinical case
62 year old woman HIV infection stage 2 in virological response, on antiretroviral treatment. DM2 bad control of 20 years of evolution. Severe diabetic retinopathy. Ischemic cardiopathy revascularized. Referred to Endocrinology, for treatment optimization, after family history and confirm the inspection, lipodystrophic phenotype, not located on the face and nasolabial fold, loss of the adipose panniculus in MMII, with increase of the adipose panniculus neck and cervical region, and increase of the abdominal perimeter. In treatment with Insulin in basal bolus pattern very poorly controlled Hba10%, Triglycerides> 600, HDL 15. LDL <100. After intensification with insulin therapy Degludec and Rapid Analogs (DTI 220), high potency statins and fibrates in association, the parameters at present Hba1c 7.5%. LDL 30, Tg 223, with stability of their underlying disease and maintenance of their TARGA therapy. Mutation C.1444> T (p.Arg 482 Trp) LMNA gene (Laminin A), compatible with Dunningan lipodystrophy, is confirmed.
Conclusion
The family history, the phenotype and the serious metabolic alterations should make us think about secondary etiologies, suspicion of pathology of less prevalent diseases. We have not found any association of LPD acquired by HAART therapy and basic genetic lipodystrophy, the coincidences exist, we must reflect: 'not everything is what it seems.'

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P216

Please Don't Sugarcoat it: An avoidable case of Euglycaemic DKA in the setting of a SGLT-2 Inhibitor

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Intro
Diabetic Ketoacidosis (DKA) is a medical emergency characterised by hyperglycemia, ketosis and acidosis. If left untreated it can lead to cerebral oedema, acute kidney injury, Adult Respiratory Distress Syndrome andeven death. Euglycaemic DKA (EuDKA) without hyperglycaemia is rare but increasing cases of EuDKAbeing reported in patients taking SGLT2 inhibitors.
Case report
A 53 year old, Type 2 Diabetic was admitted for an elective cholecystecomy. He had a background history of Oesphageal cancer, previous trans-hiatel oesphagecomy, hypertension, and high cholesterol. His diabetic medications included Metformin 1 g BD, Linagliptan 5 mg OD and Empagliflozin 25 mg OD PO. He Smoked 20 cigarettes a day, drank 10 units per week. He was a retired chef and lived with his wife and daughter. He had no family history of type 1 or 2 diabetes. The patient successfully had his gallbladder removed however he had still not recovered on day 3 post-op. He reported to his surgical team that since the surgery he was very Nauseous and was 'feeling dreadful'. He had not been eating or drinking but had still taking all his medications. His surgical site looked clean and he had a CT Abdomen, which was normal. The patient was then seen by the Medical Registrar who did a Venous Blood Gas which showed a severe metabolic acidosis (Ph: 7.04, HCO3: 4.3, pCO2: 2.16, Lactate: 1.93) with a raised anion gap of 18. His Blood Glucose was only 13mmol/lhowever his blood ketones were 4.5. The patient was promptly diagnosed as having a severe euDKA and started urgently on the DKA treatment protocol, his SGLT-2 inhibitor was held and he was transferred to a High Dependency Unit for close monitoring. The patient made a full recovery and was discharged a week later.
Conclusions
SGLT-2 Inhibitors are very popular and effective drugs for use in Type 2 Diabetics. They promote HbA1c reductions, weight loss as well as improved cardiovascular and renal outcomes. There are an increasingly wide range of SGLT-2 Inhibitors available. This case demonstrates the dangers posed by poor education about these drugs among our Diabetic patientsand non-diabetologist colleagues. Poor education aboutthe importance of stopping SGLT-2 Inbibitors when patients are unwell, fasting or going for surgery can lead to repeat hospitals admissions, prolonged hospital stays and potential morbidity and mortality.

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P217

Metabolic health is strongly predicted by free Testosterone and SHBG levels in non-obese postmenopausal women

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Introduction
Ovarian senescence and fluctuating levels of sex hormones is associated with metabolic derangement and central obesity. The aim of this study was to explore the association between serum levels of sex hormones and metabolic health in non-obese postmenopausal women.
Patients and methods
This cross-sectional study included a total of 457 non-obese postmenopausal (BMI $<30\ kg/m^2$) women, retrieved from the Menopause Clinic of Aretaieio Hospital, Medical School, National and Kapodistrian University of Athens. Participating women were classified into metabolically obese, if they fulfilled at least 3 diagnostic criteria of the International Diabetes Federation, used for the definition of Metabolic Syndrome (MONW), while women with less than 3 criteria were defined as metabolically healthy (MHNW).
Results
The prevalence of metabolic health was evident in 80.8% of non-obese women, while metabolic obesity was evident in 19.2% of women. We observed a significant difference in levels of sex hormones between obesity phenotypes (MONW vs MHNW: SHBG 55.8 ± 30.4 vs. 76.7 ± 32.8, P-value <0.001; FAI 3.14 ± 1.82 vs 2.29 ± 1.54, P-value <0.001; FEI 0.157 ± 0.153 vs 0.119 ± 0.127, P-value $=0.036$; E2 17.9 ± 13.7 vs 27.8 ± 44.4, P-value $=0.047$). Levels of testosterone were not associated with phenotypes of metabolic health. Multivariate logistic regression analysis showed significant predictors of the MONW phenotype, in models adjusted for age and YSM (years since menopause): i) SHBG levels (OR 0.979, 95% CI: 0.967 to 0.990); ii) FAI levels (OR 1.339, 95% CI: 1.121 to 1.599, P-value $=0.001$). The multivariate analysis showed that the association between FEI, E2 and the MONW phenotype was lost following adjustment for age and YSM.
Conclusions
This study provided evidence that metabolic obesity is associated with higher levels of free testosterone and lower levels of SHBG, irrespectively of age and time since menopause, in non-obese postmenopausal women.

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P218

The presence of polymorphic variant A1298C of the MTHFR (methylenetetrahydrofolate reductase) gene is associated with lower body mass index in girls with anorexia nervosa

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Introduction
Single nucleotide polymorphic variants of the methylenetetrahydrofolate reductase (MTHFR) gene have been related with a tendency to gain weight according to recent studies. The aetiology of atypical anorexia nervosa remains under investigation and might be associated with the genetic background. The aim of this study was to evaluate the association between the presence of A1298C or C677T polymorphisms of the MTHFR gene and weight status in a sample of adolescent girls diagnosed with anorexia nervosa.
Patients and methods
This cross-sectional study evaluated a total of 40 adolescent girls diagnosed with anorexia nervosa aged 13–19 years. We recorded anthropometric parameters and calculated BMI z-scores adjusted for age, as well as duration of amenorrhea. Blood samples were obtained for genotyping and hormonal assessment.
Results
Mean values of BMI were 16.25 ± 1.41 kg/m^2, while the mean BMI adjusted for age was -2.10 ± 1.31. The prevalence of the MTHFR A1298C polymorphic variant differed, almost significantly, between quartiles of BMI z-scores (CA + CC vs AA genotype, Q1 vs Q2 vs Q3 vs Q4: 70% vs 50% vs 25% vs 20%, Chi-square P-value = 0.092). Multivariate regression analysis showed that girls with BMI z-scores within the top quartile had significantly lower risk of carrying the MTHFR A1298C polymorphic variant compared to the lowest quartile (CA + CC genotype vs AA genotype: OR 0.047, P-value = 0.032), adjusted for age, estrogen levels and duration of amenorrhea. The prevalence of MTHFR C677T polymorphic variant or the combined prevalence of either MTHFR polymorphic variant (C677T or A1298C) did not differ between quartiles of BMI z-score adjusted for age.
Conclusions
We observed a significantly lower prevalence of the polymorphic variant A1298C of the MTHFR gene in adolescent girls with BMI z-score in the highest quartile compared to the lowest quartile, indicating a possible association between the presence of MTHFR wild type genotype and the tendency to lose weight.

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P219

The inverted U-shaped curvilinear effect of fat mass on bone mineral density in Korean adolescent teenagers

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Background
Higher body weight is associated with greater bone mineral density (BMD). Lean mass (LM) is positively related with bone parameters in adolescence. However, a number of controversial studies have suggested that fat mass (FM) has beneficial effect or has detrimental effect on BMD in adolescence. These contradictory results of FM on bone parameters might be developed by the non-linear relationship in the adolescent population.
Objective
We evaluated the effect of FM on BMD in Korean adolescent teenagers according to gender and menarcheal status in female.
Methods
We analyzed the data of 2,060 Korean adolescent teenagers (male = 1,114; female = 946) aged 10 to 19 years from the Korea National Health and Nutrition Examination Survey (2008–2011).The whole body bone mineral content (BMC), bone area (BA), and soft tissue composition (LM and FM) excluding head (total body less head) were measured by dual-energy X-ray absorptiometry. Bone parameters were compared among groups according to age-specific quartiles of total body FM. The effect of FM on BMD was evaluated by multiple regression models (age, menarcheal status, LM, and FM) with second-order polynomial terms for FM.
Results
Bone parameters (BMC, BA, and BMD) were greater in the group of higher quartiles of FM than that of lower quartiles. In a multiple regression result, FM was negatively related to BMD in male adolescents. Furthermore, in a model with second-order polynomial terms for FM, it was in an inverted U-shaped curvilinear relationship with BMD in female adolescents, especially in premenarcheal state.
Conclusions
Our study shows that the relationship between BMD and FM is depended on gender and menarcheal state. The relationship is an inverted U-shaped curve in Korean premenarcheal adolescent teenagers and negative in male adolescents. FM may be beneficial in premenarcheal adolescent. However, FM might have a detrimental effect on BMD in adolescent period with excess FM.

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P220

The effect of dapagliflozin add on to triple combination therapy in Type 2 diabetes

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Before releasing of SGLT-2 inhibitor, triple combination of metformin, DPP-4 inhibitor and TZD except sulfonylurea was commonly used in our center because it could be best option for delaying progression of diabetes by improving both insulin resistance and secretory dysfunction. SGLT-2 inhibitor is commonly used and recommended as initial combination with metformin in most guidelines because of cardiovascular risk and weight reduction, but theoretically add on to above combination can be more effective because of less pancreatic beta cell reserve and relatively high risk of cardiovascular event in long duration of diabetes. But there are few studies about multiple combination therapy with SGLT-2 inhibitor. And triple combination therapy of metfomin, SGLT-2 inhibitor with DPP-4 inhibitor or TZD is not covered by insurance in this country, so we tried to know the effect of that. We recruited 36 patients of triple combination therapy with metformin, DPP-4 inhibitor and TZD and dapagliflozin was added without changing previous dose of triple combination. The difference in HbA1c was compared between mean of 3 months and just before and mean of 3 and 6 months after add on. Weight change was also assessed after 6 months. The mean age was 53.3 years old and duration of diabetes was 11.6 years. 69% of patients have dyslipidemia and 52% have hypertension or proteinuria. The initial mean HbA1c before add on was 8.28 ± 0.76 and it was decreased to 7.33 ± 0.55. The mean decrement was 0.95 ± 0.69. The initial BMI was 26.2 ± 4.2 and body weight was decreased by 2.10 ± 2.28 kg. Add on therapy of dapagliflozin to previous anti-diabetic medication with triple combination therapy was effective both in both glucose control and weight reduction, so it could be more effective than initial combination with metformin in longer duration of diabetes with relatively high cardiovascular risk.

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P221

The correlation between overweight and beta-cell function in a healthy young population: a cross-sectional study in Korea

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Aims
The introduction of Western diet has changed the prevalence of overweight and obesity in Korean young population. The aim of this study was to evaluate the obesity status and its effect on β-cell function and insulin resistance in a healthy young population in Korea.
Methods
This was a large-scale, community-based study conducted from January 2007 to December 2010. A total of 2,587 subjects (1,066 men and 1,521 women) aged 19–29 years who showed normal fasting glucose were enrolled. BMI was categorized into underweight (<18.5), normal weight (18.5–22.9), overweight (23.0–24.9), and obese (≥ 25.0 kg/m^2) according to Asian-specific WHO criteria.
Results
Overweight and obese subjects were 22% and 28% in men, and 13% and 13% in women, respectively. HOMA-β was increased in obese men (189.4 ± 97.6 vs. 152.8 ± 84.4, $P < 0.001$), and overweight and obese women (183.9 ± 90.4 and

212.5±112.2 vs. 161.3±77.1, respectively, P <0.001), compared to normal-weight subjects. HOMA-IR was increased in overweight and obese men (2.25±0.91 and 2.76±1.40 vs. 1.92±0.75, respectively, P <0.001), and overweight and obese women (2.38±1.03 and 3.00±1.42 vs. 2.01±0.85, P <0.001), compared to normal-weight subjects. HOMA-β and HOMA-IR were significantly correlated with BMI in men (r=0.246 and 0.400, respectively, P <0.001), and women (r=0.245 and 0.395, respectively, P <0.001).

Conclusion

Not only obesity, but also overweight was significantly correlated with hyperinsulinemia and insulin resistance, even if in cases of normoglycemic young adults. Overweight should be taken more attention in a healthy young population.

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P222

Vitamin B12 deficiency prevalence and associated biomarkers in type 2 Diabetes (T2DM) treated with metformin: biochemical assessment in a series of 106 patients

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Introduction

Increased B12 deficiency among T2DM patients using metformin has been reported. Holotranscobalamin (HoloTc), the bioactive form of B12, is proposed as a specific and sensitive marker of B12 deficiency. Methods to evaluate vitamin B12 deficiency in these patients remain controversial.

Methods

First, we studied the prevalence of vitamin B12 deficiency in a group of 106 T2DM patients treated by Metformin, not supplemented by B12. Antacids were taken by 29/106 patients. Second, we assessed associated biomarkers of vitamin B12 supply. All venous blood samples were analyzed for total VB12, HTc and Hcy on Abbott Architect. MMA was measured with a LCMS/MS method with the Chromsystems kit. Cut-off values defining VB12 deficiency were total VB12 < 200 ng/l, HoloTc < 35 pmol/l, Hcy > 15 µmol/l and MMA >300 nmol/l.

Results

Metformin dose ranged from 425 to 3400 mg/day (1 to 21 years). Mean age of the cohort was 60.9 years (range: 36–90). Patients under antacid presented lower B12, HTc, MMA and Hcy concentrations (P=0.007, P=0.0008, P<0.0001 and P<0.0001). A total of 18/106 patients (17%) were considered as deficient with total B12 assay but only 9/106 patients (8.5%) with HTc, 29/106 (27%) with Hcy and 21.6% with MMA. Four patients presented B12 <200 ng/l and HTc <35 pmol/l. The mean B12 values observed in patients with HTc <35 pmol/l was 208±83 pmol/l whereas the mean HTc in patients with B12<200 ng/l was 46.0±15.5 pmol/l. 33.3 vs. 55.5% of the patients with B12<200 and HTc <35 had HcY levels >15 µmol/l whereas they were 35% vs. 75% to have MMA>300 nmol/l, respectively (P=0.06). There was a significant correlation (P<0.0001) between B12 and HTC and HCy and between HTC and B12, MMA and HCY. For B12, multiple regression analysis using BMI, age, creatinine, folate, MMA, Hcy, antacid consumption and metformin intakes per day did not show any interrelated variable. Using Htc, as dependent variable and the same independent factors showed that creatinine (P<0.0001), MMA (P=0.0008) and Hcy (P=0.0010) were significantly associated.

Conclusions

The 2018 ADA Clinical Practice Recommendations endorse screening Metformin users for vitamin B12 deficiency. In our series, diabetic patients treated by metformin had B12 deficiency in 17% of cases (total B12) and only in 8.5% (HTC). HTC seems more specific than total B12 to assess vitamin B12 deficiency. Antacids seem to have an impact of vitamin B12 absorption.

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P223

The association between serum cystatin C and carotid artery intima-media thickness in Korean type 2 diabetic patients

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Background

There are several markers of renal function such as estimated glomerular filtration rate (GFR) calculated by serum creatinine and cystatin C and urinary albumin-creatinine excretion ratio (ACR). Recently, a few studies showed relationships between markers of renal function and carotid arterty intima-media thickness (IMT), but the results were inconsistent. The aim of this study is to compare serum cystatin C as risk factors for atherosclerosis in Korean type 2 diabetic patients.

Methods

This study was performed in 450 type 2 diabetic patients, who were evaluated by serum cystatin C, urinary ACR (both divided into tertiles) and carotid artery IMT. Estimated GFR was calculated using the modification of diet in renal disease (MDRD) equation. The carotid artery IMT was assessed by B-mode ultrasonography.

Results

There were no differences in the proportion of gender, obesity, smoking status and dyslipidemia according to serum cystatin C tertiles. Higher level of serum cystatin C was associated with older age, longer duration of diabetes, lower HDL-cholesterol level and increased carotid artery mean IMT (P for trend <0.05, respectively). In multivariate analyses adjusted for traditional atherosclerotic risk factors, carotid artery mean IMT was strongly associated with urinary ACR and serum cystatin C (P for trend 0.025 and 0.032, respectively), but not with estimated GFR (P=0.954).

Conclusion

The level of serum cystatin C beyond traditional risk factors was related with carotid atherosclerotic burden in Korean type 2 diabetic patients. Measurement of these renal parameters might be important for early detection of atherosclerosis as well as renal insufficiency in type 2 diabetic patients.

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P224

Prevalence of psychiatric comorbidities in diabetic patients who are candidates for therapy with SGLT2 inhibitors: clinical and metabolic characteristics

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Introduction

Depression, anxiety and eating disorders appear more frequently in patients with type 2 diabetes and are associated with worse metabolic control and higher risk of developing micro and macrovascular complications. The aim of this study was to determine the prevalence of psychiatric comorbidities in diabetic patients, candidates for therapy with SGLT2 inhibitors (SGLT2i) and to evaluate their clinical profile and degree of metabolic control before beginning the treatment.

Methods

225 diabetic patients included in a therapy protocol with SGLT2i were evaluated analyzing clinical characteristics, biochemical parameters, lifestyle and pharmacological therapy. The analysis was performed separating patients in two groups according to the presence of psychiatric comorbidity. Quantitative variables are expressed by mean (standard deviations). Qualitative variables are expressed by frequencies and percentages. We consider significant P<0.05.

Results

55 patients (24.4%) of the total, 25 (54.5%) women, mean age 63 (S.D. 10.5), had psychiatric comorbidities and the most frequent diagnoses were anxiety (34.5%), depression (32.7%) and anxiety-depressive syndrome (16.4%); time of evolution of diabetes 11.1 years (S.D. 9.4), BMI 35 kg/m^2 (S.D. 6.2), systolic blood pressure 146.3 mmHg (S.D. 18.9), plasma glucose 173.3 mg/dl (S.D. 50.5), glycated hemoglobin (HbA1c) 8.2% (S.D. 1.02) cholesterol 186 mg/dl (S.D. 45.3), low-density lipoprotein cholesterol (LDL-C) 106 mg/dl (S.D. 40), high-density lipoprotein cholesterol (HDL-C) 48.9 mg/dl (S.D. 15.5), triglycerides 189.2 mg/dl (S.D. 89.2); 9.8% smoked; 41.8% met dietary recommendations; 34.5% performed physical exercise; 9% did not receive antihyperglycemic drugs; 16.4% received one, 47.3% two and 27.3% triple therapy; 41.8% of patients were treated with Insulin; 76.4% took lipid-lowering drugs; 36.4% had presented a cardiovascular event (ischemic cardiopathy, stroke, peripheral vasculopathy). The HDL-C was significantly higher in patients with psychiatric comorbidity (P=0.007), but there were no significant differences neither in the prescription of lipid-lowering drugs nor in the rest of parameters evaluated compared with diabetics without psychiatric pathology.

Conclusions

The prevalence of psychiatric comorbidities in diabetic patients included in this study agrees with that described in literature. However, we found no association with a higher BMI, lower adherence to changes in lifestyle, worse metabolic control, a greater prescription of antihyperglycemic drugs and Insulin or a higher prevalence of cardiovascular events compared with diabetics without psychiatric

pathology. According to some authors, this could be due to depression and anxiety oriented treatment.

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P225

Efficacy and safety of multimodal therapy in the management of aggresive prolactinoma

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Background
Aggressive prolactinomas are rare neoplasms that are characterized by rapid growth and usually large tumor size, invasion of adjacent structures, an aggressive clinical behavior with little response to conventional treatment, high rate of recurrence, and elevated morbidity and mortality.
Case Report
48-year-old woman diagnosed with life-threatening aggressive prolactinoma was referred to us for evaluation of complementary therapy after therapeutic failure to dopamine agonists (DA), several surgical interventions and radiotherapy. A clinical assessment by our multidisciplinary team recommended completing treatment with palliative surgery, DA, somatostatin analogues (SSA), temozolomide (TMZ), and re-irradiation. Two years after the last surgery the patient was well, without headaches showing postoperative changes in pituitary MRI, with normoprolactinemia and a partially empty sella without signs of tumor recurrence.
Conclusion
The present case demonstrates how multimodal treatment is effective and safe in the management of life-threatening aggressive prolactinoma.

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P226

Metabolic fingerprint of acromegaly and its potential usefulness in clinical practice

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Background
Acromegaly is a rare chronic and debilitating disease. More than half of patients are not well controlled and most of them require chronic surveillance. Although IGF1 and GH circulating levels are the main targets, they are not in close relationship with the behaviour of the tumour, the clinical course of the disease, the therapy response and the associated comorbidities. Metabolomics is an emergent research tool that we have used to examine in a massive manner the metabolic fingerprint of the chronic exposure to GH and its change after receiving treatment.
Objective
1) To identify metabolites and pathways which could be used as biomarkers of the disease. 2) To explore whether metabolomics could be useful to identify those patients with active disease form those under control by using pharmacological treatment or already cured.
Methods
We compared the serum metabolic fingerprint of 30 patients with acromegaly (16 males and 14 females) and 30 controls matched by age, gender, body mass index (BMI) and smoking habit. Regarding the status of the disease, 5 presented active disease defined by elevated IGF-1 and, 25 had IGF1 concentrations within the specific age-adjusted normal values (14 under medical treatment and 11 in remission or cured).
Results
Patients with acromegaly presented less BCAAs, valine and isoleucine, compared to the control group (valine: 4.50 ± 0.21 AU vs 5.26 ± 0.17 AU, $P < 0.05$; isoleucine: 2.48 ± 0.02 AU vs. 2.80 ± 0.08 AU, $P < 0.05$). BCAAs were lower in those patients with active disease in comparison with patients with normal serum IGF-1 (valine 4.35 ± 0.23 AU vs. 5.01 ± 0.12 AU; isoleucine 5.10 0.32 vs 5.62 ± 0.28 AU; respectively, $P < 0.05$).
Conclusions
The main metabolic fingerprint of acromegaly is a decrease in BCAAs (i.e. valine and isoleucine). The metabolic abnormalities could help to identify active disease and to monitoring the response to several therapeutic strategies. These findings could also open up a new research area in adjuvant nutritional support in patients with active acromegaly. However, further studies to confirm this preliminary results are needed.

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P227

NCKX3 knockout mice showed abnormal motor function and social behavior

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NCKX3 (Sodium/potassium/calcium exchanger 3), a novel member of the family of K^+-dependent Na^+/Ca^{2+} exchangers, is an important component of intracellular Ca^{2+} homeostasis. Ca^{2+} homeostasis has been extensively studied in various cell systems. Dysregulation of Ca^{2+} homeostasis can induce the excitotoxic and neurodegeneration in central nervous system. NCKX3 gene is highly expressed in thalamic nuclei, in hippocampal CA1 neurons, and in layer IV of the cerebral cortex in the mouse brain. Here, we examined the effects of NCKX3 deletion in mice. NCKX3 knockout (KO) mice at 6 week-age were used for behavior assays. NCKX3 KO mice show increased moving distances in the open field test. In the sociability test, NCKX3 KO mice have reduced time spent on general sniffing, anogenital sniffing, and following behavior but increased in fighting. Additionally, the rotarod test revealed motor learning defects in NCKX3 KO mice. However, NCKX3 KO mice showed no change in recognition memory in the novel object recognition test. During acquisition phase in the Morris water maze test, there was no different in escape latency time between wild-type and NCKX3 KO mice. This indicated NCKX3 mutation did not impair to spatial learning in mice. These results suggest that NCKX3 mutation causes abnormal motor functions and social behaviors in mice.

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P228

Long terms effects of cranial irradiation for nasopharyngeal carcinoma on hypothalamic-pituitary function – a 5-years longitudinal study

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Introduction
Pituitary insufficiency is a late-onset sequel of cranial irradiation for nasopharyngeal tumors. In a Cancer Survivor Study, 43% of patients treated for nasopharyngeal tumors had one or more endocrinopathies. We aim to characterize the pituitary-related outcomes following cranial radiotherapy for nasopharyngeal tumors over a period of 5 years.
Material and methods
The effects of cranial irradiation on hypothalamic-pituitary function were studied first after a mean time post-radiation of 3.66 ± 2.91 years than controlled after 3-year period in 13 patients (7 men and 5 women) with nasopharyngeal carcinoma of a mean age 31.08 ± 14.40 yo. No preradiation endocrinopathies were noted. The estimated radiotherapy doses were 68.91 ± 7.26 Gray. The diagnosis of pituitary hormone dysfunction was based on standard criteria. Specifically, GH

deficiency if a peak stimulated GH level was <10 ng/ml after the sequential administration of 2 secretagogues. Central hypothyroidism was diagnosed if the patient had a low free thyroxine value in the setting of a normal level of thyroid-stimulating hormone (TSH). Central adrenal insufficiency was diagnosed if a patient had a peak stimulated cortisol level of <18 µg/dl after low-dose (1 µg) adrenocorticotropic hormone (ACTH) stimulation testing. Hypogonadotropic hypogonadism was diagnosed if patients had absence of puberty by age 13 years in girls and age 14 years in boys with low serum gonadotropin levels. Data are reported as means $\pm$ S.D.

Results

Of the 13 patients who had received radiation therapy after 3.66 ± 2.91 years of radiotherapy treatment, 38.46% have at least one central endocrinological impairment. Significant impairment in the secretion of growth hormone (23.07%), gonadotrophins (15.38%), corticotrophin (7.6%) and thyrotropin (7.6%) were evident and 30.7% of patients developed hyperprolactinemia. Growth hormone deficiency was the earliest endocrine dysfunction observed. The cumulative probability of endocrine dysfunction was estimated to be 62% after a mean of 5 years with deficiencies in growth hormone, gonadotrophins, corticotrophin and thyrotropin found in 84.6%, 61.53%, 53.8%, and 38.46% of patients. Hyperprolactinemia was uncommon in the male patients (23.07%) but occurred significantly more in four of five women within 5 years of cranial irradiation.

Conclusion

Thus, in these patients with no pre-existing disease in the hypothalamic-pituitary region, progressive impairment in hypothalamic pituitary function leading to endocrine dysfunction requiring treatment occurs in 62 per cent of patients 5 years after cranial irradiation. Regular endocrine assessment should be performed in all patients following cranial irradiation.

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P229

A rare case of recurrent granulomatous hypophysitis treated with a trial of oral glucocorticoids

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Background

Granulomatous hypophysitis is an extremely rare condition, therefore, a number of these cases were initially diagnosed as adenoma and inappropriately underwent surgery. Definitive management is not yet established for granulomatous hypophysitis however improvement and resolution of symptoms were noted using oral glucocorticoids.

Clinical case

A 70 year old, Filipino, female, a diagnosed case granulomatous hypophysitis in 2012. At that time she was initially managed as a case non-functioning pituitary macroadenoma (cortisol 13.4 ug/dL (6.2–19.4 ug/dL), prolactin 11.265 ng/ml (3.6–18.9 ng/ml), TSH 0.665 uIU/ml (0.27–3.75 uIU/ml), FT4 12.900 pmol/l (8.8–33 pmol/l), LH 1.876 mIu/ml (5–20 mIU/ml), FSH 15.144 mIu/ml (5–20 mIU/ml)), until the patient underwent transphenoidal surgery and histopathological results showed presence of chronic, non-caseating granulomatous inflammation of the pituitary gland. Tests for the presence of Mycobacterium tuberculosis such as AFB stain, Mycobacterium Tuberculosis PCR/nucleic acid amplification and Silver Methenamine stain were all negative. Patient does not require hormonal therapy and was lost to follow up due to resolution of symptoms. Five years after the surgery, the patient complained recurrent headaches. Cranial MRI, showed presence of an enhancing left sellar nodule measuring $1.2 \times 1.3 \times 1.5$ cm which is superiorly deviating the pituitary infundibulum to the right and abutting the optic chiasm. No visual field defects were noted. Hormonal tests only showed central hypothyroidism and low LH and FSH. The patient was started on oral glucocorticoids (prednisone 30 mg per day and was tapered accordingly). Symptoms completely disappeared after the medication was started. After three months of steroid therapy, cranial MRI showed complete resolution of the sellar mass.

Conclusion

Granulomatous hyophysistis is a rare chronic inflammatory disorder of the pituitary that usually imitates pituitary adenoma. Diagnosis can only be made histopathologically after biopsy or surgery. Glucocorticoids in tapering doses in this case showed complete resolution of the symptoms and the pituitary lesion as well.

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P230

The role of interleukin-1 in the dynamics of exercise-induced copeptin

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Background

The goal of this project was to identify non-osmotic stimuli of arginine vasopressin (AVP) release during exercise. Non-osmotic AVP release can lead to severe hyponatremia in otherwise healthy marathon runners.Interleukin-1 (IL-1) increases during exercise and was shown to induce AVP in animal models. We here therefore investigated whether copeptin (a surrogate marker for AVP) increases upon exercise in young and healthy males, and whether this increase is regulated by IL-1. The effect of the IL-1 receptor antagonist anakinra on exercise-induced copeptin was assessed.

Methods

Data from a randomized, placebo-controlled, double-blind crossover trial were analyzed where 17 healthy male volunteers exercised for one hour at 75% of VO_{2max} and were not allowed to drink/eat 6 hours before and during the study. Participants received either 100 mg of anakinra or placebo one hour before exercise. Blood was drawn at certain time intervals before, during, and after exercise. Statistical analysis: To test for change in copeptin levels over time and for differences between the placebo and the anakinra group, linear mixed-effects models were fit. Fixed-effect explanatory variables were time of measurement (0, 60, 120 min), treatment allocation, and sodium levels. Furthermore, differences in the area under the curve (AUC) for the anakinra and placebo group were analyzed using a Wilcoxon signed rank test.

Findings

In both groups, copeptin levels were induced by 2.5-fold upon exercise ($P<0.001$), from 4.5–10.6 pmol/l in the placebo, and 4.3–11.3 pmol/l in the anakinra group, with no difference between the groups ($P=0.4$). One hour after exercise, copeptin levels dropped to 7.7 and 7.9 pmol/l in the placebo and anakinra group, respectively ($P=0.6$). The increase of copeptin levels was not explained by sodium concentrations ($P=0.1$). The AUCs of copeptin values for the time during and after exercise were not significantly different when participants were treated either with placebo or anakinra ($P=0.7$).

Interpretation

Exercise induces a continuous rise of plasma copeptin levels in healthy male volunteers independently of sodium levels and fluid intake. This increase is not regulated by the IL-1 pathway.

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P231

Growth hormone deficiency, which etiologies?

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Introduction

Growth hormone deficiency is a rare cause of stunting; its diagnosis is often delayed by severe growth retardation; confirmed by non-response to GH stimulation tests (insulin and glucagon-propranolol test). The absence of early diagnosis and treatment can lead to severe growth retardation. We propose to determine the prevalence of different etiologies of growth hormone deficiency in patients followed for a saturo-weight delay at the Arrazi Hospital, Medical University Hospital VI of Marrakech.

Materials and methods

A prospective study was conducted over a period of 4 years [January 2013-January 2017]. 65 files were identified. The clinical symptomatology was varied, ranging from signs of hypopituitarism, polymalformative syndrome to intracranial hypertension. Biological exploration was oriented by clinical symptomatology, based on stimulation tests and reinforced by radiological exploration (hypothalamic-pituitary MRI).

Results

The average age of these patients is 15.6 years with a H-F sex ratio of 3.7. Severe growth retardation was observed in 89.3% of cases. Of the 65 cases with a GHG deficiency, 38 cases of congenital deficiency were found. 58.4% of cases (26.2% of which were due to malformation of the hypothalamic-pituitary area), 13 cases of acquired deficit -tumors- (20%) and 14 cases integrating into polymalformative syndromes (21.6% of cases). Ante-pituitary deficits were associated: 33.9% of cases of gonadotropic deficiency, 23.8% of thyrotropic cases and 8.4% of adrenocorticotropic cases.

Discussion
The plasma IGF-1 assay allows in the majority of cases to detect the severe deficits in growth hormone. Confirmed by the couple, dynamic stimulation tests and hypothalamic-pituitary MRI. Some are currently based on IGF-1 and IGFBP3 assays in combination with imaging of the pituitary region, given the very poor reliability and reproducibility of the tests.
Conclusion
The staggered delay can be the gateway to a large number of serious diseases of the child and that the diagnostic priority is not to ignore a tumor: cranipharyngioma, glioma.

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P232

Mammosomatotropic adenoma and acromegaly: about 3 cases

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Introduction
Somatotropic adenomas are clinically expressed either by acromegaly or by gigantism according to age of onset. Several histological types are involved. Immunohistochemistry provides conclusive evidence that significant diversity exists between growth hormone secreting (GH) tumors in excess. We report three observations of a particular histological type: mammosomatotropic adenoma.
Observation 1
Mrs. M.H., aged 56, hypertensive for 10 years, followed for acromegaly with a pituitary macro-adenoma for 4 years, operated 3 times. The interrogation found a dysmorphic acromegaloid syndrome evolving for 11 years. The patient was put on cabergoline for 3 years. The hypothalamic-pituitary MRI of control is in favor of a sellar arachnoidocele without visible adenoma, the anatomopathological study speaks of aspect in favor of a mixed pituitary adenoma and immunohistochemistry, an aspect in favor of an adenoma mammosomatotrope.
Observation 2
Mrs. L.F., aged 45 years, hypertensive for 1 year, who presents for a dysmorphic acromegaloid syndrome noted for 5 months. The MRI showed a pituitary macro-adenoma, a surgical procedure was performed and the patient was put on cabergoline. The anatomopathological and immunohistochemical studies have objectified an aspect in favor of a mammosomatotropic adenoma.
Observation 3
Mrs. L.B, aged 43, presenting for an acromegaloid dysmorphic syndrome observed for 7 years. The MRI showed a pituitary macro-adenoma, a surgical procedure was performed and the patient was put on cabergoline. The anatomopathological and immunohistochemical studies have objectified an aspect in favor of a mammosomatotropic adenoma.
Discussion
Mammosomatotropic adenoma is characterized by intense immunohistochemistry antiGH and immunopositivity antiprolactin less, but within the same cell. Electron microscopy confirms this granular colocalization of the two hormones. The diagnosis of multi-hormonal somatotropic adenomas requires the routine practice of immunohistochemical tests because there is no specific clinical presentation.

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P233

Silent somatotropic adenoma: about a case

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Introduction
Somatotropic adenomas are classically a source of hypersecretion of GH and consequently of IGF1 responsible for the clinical signs of acromegaly. Rarely, these adenomas remain 'silent', without any obvious clinical manifestation. They can then be detected on the basis of a routine determination of growth hormone under oral glucose tolerance test (GH/OGTT) and insulin growth factor 1 (IGF1) or be diagnosed only to immunohistochemical study as is the case of a patient we report.
Observation
Patient of 33-year-old, consult for secondary amenorrhea with galactorrhea. Clinical examination did not indicate a dysmorphic syndrome. A pituitogram was performed showing the presence of thyrotropic and corticotropic insufficiency, with a prolactin level of 153 ng/ml. The somatotropic axis has not been explored. A pituitary MRI revealed a hypophysary macroadenoma treated as prolactinoma by cabergoline with substitution of both deficits. The evolution at one year was marked by the increase (by 17%) of the tumor volume with a prolactin control at 0, 22 ng/with an altered visual field. An echo-heart was requested, revealing the presence of an average tricuspid insufficiency, the surgical indication was raised. Immunohistochemical analysis favors a somatotropic adenoma. A postoperative 3-month postoperative pituitary MRI showed constant tumor volume with some necrosis areas with IGF1 at 131 ug/l (112–300).
Discussion
Somatotropic adenomas are often identified because of their clinical consequences (dysmorphism); some cases of subclinical adenomas have been described in the literature, where only histopathological examination reveals a positive immuno-marking for GH. Their frequency is poorly studied: in the absence of an immunohistochemical study, a non-functional adenoma is concluded and IGF1 is not carried out as part of the follow-up; all this leads to a diagnostic delay giving later dysmorphism with the various complications of hypersecretion of GH. Treatment of this type of adenoma is initially based on surgery, then somatostatin analogues and lastly time on temozolamide and radiotherapy if signs of aggression.
Conclusion
Silent somatotropic adenoma is a distinct entity with respect to the usual cases of acromegaly, as it may be an onset of the disease, or a benign aspect of the disease?

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P234

Posterior pituitary spindle-cell oncocytoma: case presentation and literature review

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Introduction
Spindle cell oncocytoma (SCO), pituicytoma, granular cell tumor, and sellar ependymoma are rare TTF-1 positive posterior pituitary tumors classified as WHO Grade I, indicating low proliferative potential and high rates of surgical cure.
Aims
To report a case of SCO and review the pertinent literature.
Methods
English and non-English literature was searched, clinical, data were retrieved and summarized.
Results
A 39 years old male presented with complaints of headaches. MRI identified a suprasellar tumor that was initially followed conservatively. Vision and pituitary function were preserved. Symptom exacerbation and evidence of tumor growth led to transsphenoidal surgery. Tumor resection was compromised by profuse bleeding. He developed post-surgical pan-hypopituitarism. 42 publications describing 54 cases of SCO were identified (median age 60 y, 57% males). Presenting symptoms were mostly secondary to mass effect. 67% of tumors were sellar with suprasellar extension, 23% and 9.6% were exclusively intra or suprasellar respectively. All patients underwent surgery, 83% of which was transsphenoidal. Mean Ki-67 was 3.4%. Gross total resection was achieved in only 47.8% of cases, with recurrence-free survival time of 116 months (95% CI, 65–167). After partial resection, event-free survival time was 23 months (95% CI, 12–34). Nine patients received radiation therapy with mixed results.
Conclusions
Surgical resection of these rare tumors is challenging; surgical cure is infrequent and recurrence rates are high. Based on this literature review, we suggest that WHO classification of these tumors as grade 1 is not accurate, and that a revision should be considered.

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P235

No central adrenal insufficiency found in adults with prader-willi syndrome tested by multiple dose metyrapone test

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Introduction
Individuals with Prader-Willi syndrome (PWS) have hypothalamic dysfunction, with deficiencies of several hypothalamic-pituitary axes. Prevalence of central hypogonadism, hypothyroidism and growth hormone deficiency are increased in comparison with non-PWS individuals. Central adrenal insufficiency (CAI) has also been reported in PWS. Several studies, using different testing modalities, have reported strikingly differing prevalences of CAI in PWS, ranging from 0% to 60%. It is speculated that CAI may be responsible, in part, for high mortality (3%) in patients with PWS. If CAI is present, timely diagnosis and treatment is needed in order to prevent avoidable mortality. Due to the lack of consensus, there are no guidelines or recommendations on the appropriate evaluation and management of CAI in the adult PWS population. Many adults patients with PWS receive standard hydrocortisone (HC) stress dose during physical and/or psychological stress. Frequent administration of HC increases the risk of obesity, hypertension, osteoporosis and diabetes, already a major problem in adults with PWS. It is therefore of utmost importance to assess the prevalence of CAI in order to prevent overtreatment with HC.
Methods
We screened medical histories of all patients for symptoms of CAI. We performed multiple dose metyrapone (MTP) test in 47 adults with genetically confirmed PWS. At day one, oral MTP 750 mg (Laboratoire HRA Pharma, Paris, France) was administered orally every 4 hours, starting from 0800 h. At 0800 h on day two, blood was drawn for determining 11-deoxycortisol (11-DOC) levels. At both days, blood was drawn after 8 hours fasting. Levels of 11-DOC greater than 7.6 g/dl (230 nmol/l) were classified as adrenal sufficiency.
Results
Median (IQR) age of participants was 28.8 (22.8–35.5). Twenty were using GH treatment since childhood. Male/female ratio was 28/19. Revision of medical histories revealed that a substantial part of patients had undergone operations or had infections without receiving HC stress dose, without any negative consequences. All 47 patients had 11-DOC greater than 7.6 g/dl during MTP test and therefore CAI was excluded in all patients. MTP test was tolerated well by all individuals.
Conclusion
Central adrenal insufficiency was absent in 47 adults with Prader-Willi syndrome assessed by a multiple dose metyrapone test. This indicates that CAI is rare, or even absent, in adults with PWS. Based on these results, we recommend to perform MTP test instead of routinely prescribing HC stress dose in adults with PWS.

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P236

Serum aryl hydrocarbon receptor-interacting protein (AIP) levels are independent of serum GH levels both at baseline and in dynamic tests of GH stimulation and suppression

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Background and aim
Aryl hydrocarbon receptor-interacting protein (AIP) is evolutionary conserved and widely distributed throughout organism. Broad interest for AIP comes from involvement of loss-of-function AIP mutations in pituitary adenoma pathogenesis. The role of AIP in normal pituitary function is largely unknown. AIP is co-localized with GH in somatotroph secretory vesicles. Serum AIP protein was proteomically identified. We aimed at investigating whether AIP and GH are co-secreted by measuring serum AIP and GH levels at baseline and after GH stimulation and suppression tests using *in vivo* human models of normal GH secretion, patients with GH deficiency (GHD) and patients with GH hypersecretion - acromegaly.
Subjects and methods
ITT was performed in GHD patients ($n=13$) and age-BMI-matched non-GHD controls ($n=31$). OGTT was performed in patients with active acromegaly ($n=26$) and age-BMI-matched controls ($n=18$) with normal GH suppressibility. In-house immunometric AIP assay was developed and employed.
Results
Serum AIP was independent of gender, age or BMI. Baseline AIP levels did not differ in GHD and non-GHD subjects nor did AIPmax, AIP-AUC or AIP-Delta in ITT. AIP levels did not correlate with GH, PRL or cortisol levels in ITT. Baseline AIP, AIPmax, AIP-AUC or AIP-Delta did not differ between patients with active acromegaly versus control subjects at baseline and during GH suppression test (OGTT). Serum AIP values did not significantly change during ITT or OGTT.
Conclusions
A novel immunometric assay was employed for the first time to assess human circulating serum AIP in vivo. Serum AIP levels were independent of age, sex or BMI, and were unaffected by hypoglycemia or hyperglycemia. Contrary to expectations based on secretory vesicles co-localization of AIP and GH, no correlation was found between serum AIP and GH secretion at baseline nor during GH stimulation (ITT) and GH suppression tests (OGTT). A platform of reliable serum AIP measurement is established for further research of the circulatory source, role and impact for this highly conserved protein essential for survival.

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P237

Some risk factors of re-growth of non-functional pituitary adenomas in patients with growth hormone deficiency

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Aim
The aim of investigation to determine clinical aggressiveness diagnostic markers in patients with non-functional pituitary adenomas (NFPA), and growth hormone deficiency (GHD) in the formation of gravity neuroendocrine disease symptoms.
Material and methods
We observed in 87 patients (including man – 44 women – 43) of which have a verified diagnosis of NFPA after surgery – 31 which were subjected transnasal adenomectomy of the pituiatary (TAG). Further analysis was performed on these patients, who were followed from 1 to 3 years.
Results
After the analysis of the frequency of remission and relapse NFPA data selectively in patients we studied the correlation between various parameters and the frequency of relapses. NFPA developed the scale of aggressiveness allowed to identify the risk factors of markers on the 3rd degrees, allowing to create a set of measures of tumor growth relapse prevention.
Conclusions
Comparative analysis of the results of our research showed that there was a direct correlation with these markers of aggressiveness flow NFPA as the young age of the patient, the first symptoms of a manifest disease, large tumor size, asymmetry, and the pituitary gland deformation, signs of tumor invasion into surrounding tissue/artery/cavernous sinus, the presence of small-cell and/or dark cell chromophobe adenomas panhypopituitarism.

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P238

The frequency of growth retardation among children and adolescents from orphanages in Tashkent city

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The aim of investigation to study the frequency of growth retardation in children and adolescents from orphanages in Tashkent city.

Material and methods

We observed 595 children and adolescents (including boys – 342, girls – 253) as part of the special program 'You are not alone' from November 12 to November 17, 2018 in the admission department of the clinic of the Tashkent Pediatric Medical Institute. During the week, children and teenagers from 6 orphanages were examined. The patients were examined by all specialists – endocrinologists, pediatricians, neurologists, urologists, orthopedic surgeons, ophthalmologists, etc. Patients were measured height, weight, considered a lack of growth, weight, performed a palpation of the thyroid gland and an objective examination of sexual development's stages by Tanner. If necessary, performed ultrasound investigation of endocrine organs.

Results

It was established that growth retardation occurred in 36 (6%) patients examined, in 1 (0.16%) case - dwarfism, in 2 (0.32%) cases - puberty delay, in 1 (0.16%) case – varicocele and 1(0.16%) -cryptorchidism. After the analysis of the frequency of growth retardation among 595 children and adolescents we found that in 3 (0.5%) cases patients with growth retardation have diffuse goiter. Total diffuse goiter 1 degree was found in 164 (27.5%) examined.

Conclusions

Comparative analysis of the results of our research showed that there was growth retardation in 36 (6%) patients.

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P239

Supraselar tumor as cause of amaurosis – the unusual suspects-case series

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Background

Most common tumors in the suprasellar region are adenomas of the pituitary gland, craniopharyngiomas, cystic lesions (Rathke's cleft cysts). Supraselar meningiomas are rare and slow-growing tumors that usually arise from the tuberculum sellae or the chiasmatic sulcus. These tumors frequently invade the sella turcica because that they are mistaken for a pituitary tumor.

Methods

A case series

Results

We present a two cases of patients complaning about one side vision loss. First case is a 40 years old female, that was sent to endocrinologist because of infertility. She was diagnosed with PCOS and glucose intolernce. Due to losing eye sight and PCOS we ordered MR of pituirary gland and full hormonal blood work. Her leverls of prolactin, TSH, fT4, FSH, LH, ACTH, GH and IgF 1 were within normal range. MR of showed expansive mass in left supraselar region that compresses optical chiasma and left optic nerv. Surgical treatment was preformed and patohystological examination of tumor showed Meningeoma transitionale WHO gradus I. After surgery vision was restored with preserved pituitary function. Second case is 61 years old male, that was send to endocirnologist due to acute blury sight on right eye and headache. Full hormonal blood work up was done and was withing normal range. On the MR of pituitary gland showed meningeoma in supraselar region. Patient is scheduled for surgical treatment.

Conclusion

Supraselar meningiomas are rare and can be hard to differentiate from pituitary adenomas, and they are often sent to endocrinologist for that reason. It is really important to diferentiate appropriated surgical approach. Follow ups reqiered because of recurrence of the meningeoma.

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P240

Pituitary stalk interruption syndrome: an uncommon presentation

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Pituitary stalk interruption syndrome (PSIS) is a rare clinical entity characterised by an absent or thin pituitary stalk, hypoplasia of the anterior pituitary gland, and ectopic location of the posterior pituitary on magnetic resonance imaging (MRI). Presentation is on early childhood or puberty and the most common hormonal deficiencies are growth hormone (GH) and gonadotropines. We present the case of a 28-year-old female patient who consulted after 2 years in secondary amenorrhea with menarche at 13 years old and previous regular menses; her family doctor prescribed oral contraceptives (restoring regular menses) and patient was referred to endocrinology consultation. She was as well in treatment with Levetiracetam for epilepsy. She didnt have any other familiar or personal pathological antecedents. The anamnesis showed 6–7 liter/day polidipsia, polyuria and nighttime thirst in the last 3 years, with no other symptoms. At physical exploration, her weight was 58.6 kg, height 160 cm (mid parental height: 158 cm) and had a Tanner stage V phenotype; she didnt have any midline craniofacial malformation. One month after contraceptives withdrawal, analysis revealed: glucose 86 mg/dl, creatinine 0.72 mg/dl, sodium 140 mmol/L, potassium 4.6 mmol/L, serum osmolality 290 mOsm/kg (N 275–295), thyrotropin 1.9 μUI/mL (N 0.4–4.2), free T4 0.91 ng/dl (N 0.93–1.7), GH 3.29 ng/mL (N 0.3–9.8), IGF-1 171 ng/ml (N 100–310), prolactin 7.65 ng/Ml (N 6–30), follistatin 3.6 mUI/mL, luteinizing hormone 0.47 mUI/mL, progesterone 0.05 ng/mL, estradiol 37 pg/mL, total testosterone 0.08 ng/mL, corticotropin 13.9 pg/mL, basal cortisol 14.6 μg/dL. Urine test: 6000 ml diuresis, urine osmolality 137 mOsm/kg. Water deprivation test: serum osmolality 273 mOsm/kg and urine osmolality 281 mOsm/kg, after 11 hours of fluid deprivation. Urine osmolality 719 and 756 mOsm/kg, before and after 1 subcutaneous μg desmopressin respectively. Synacthen test: cortisol basal levels 17.1 μg/dl, at 30 minutes 21.1 μg/dl and 25.3 μg/dl at 60 minutes. Propanolol-exercise provocative test: basal GH 4.91 ng/ml, 4.4 ng/ml at 30 minutes. MRI was performed: hypoplastic adenohypophysis (image). Patient was diagnosis with partial central diabetes insipidus (CDI), hypothyroidism, GH deficit and hypogonadism. Nowadays our patient is receiving treatment with 100 μg/day levothyroxine, 0.1 mg/24 hours oral desmopressin and contraceptives. Our case is uncommon due to SPIS presentation at adult age, normal sexual development and initial normal somatotropic axis, as well as partial CDI.

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P241

Long-term results of bilateral adrenalectomy in a patient with cyclic Cushing's syndrome

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Introduction

Cyclic Cushing's Syndrome (CCS) is a rare disorder in which rhythmic fluctuations in the secretion of ACTH trigger cyclic variations in the production of adrenal steroids and an extremely variable clinical presentation. It should be considered when clinical hypercortisolism coexists with normal cortisol levels and a paradoxical response to the dexamethasone test, and when selective transsphenoidal adenomectomy fails after an uncomplicated intervention.

Clinical case

A 34-year-old woman was evaluated from 2000 to 2005 in another hospital and diagnosed with cyclic Cushing's syndrome without evidence of primary adrenal pathology or ectopic ACTH production. In December 2004 and February 2005 hypercortisolism was confirmed, but previous studies were not conclusive because the hormonal determinations were normal in most cases although the patient presented Cushingoid features, and dexamethasone suppression tests were starting from practically normal values of cortisol. Pituitary magnetic resonance (MR), performed in 2000, revealed a possible microadenoma in the left half of the pituitary, not confirmed in subsequent studies. Computed tomography thoracoabdominal and catecholamines, 5-OH-indole acetic acid, histamine in 24-hour urine were normal. For years she followed therapy with ketoconazole, suspended in January 2004 for inoperability. In 2006 the patient was sent to our hospital to perform petrosal sinus catheterization with stimulation of CRH showing these

results: central/peripheral ACTH ratio <2:1 (basal) and >3:1 after stimulation. Further tests included: basal ACTH (with hypercortisolism): 32.9 pg/ml; In-111 Octreoscan and all the biochemical tests repeatedly performed did not show significant alterations; bone densitometry showed very mild osteopenia in the spine; adrenal MR bilateral hypertrophy without nodular images and pituitary MR repletion defects inside the adenohypophysis, of right and left location, in possible relation to microadenomas. Given the impossibility of controlling the episodes of hypercortisolism with cabergoline and ketoconazole, in March 2010 a bilateral adrenalectomy was performed. Histopathological diagnosis corresponded to a combined bilateral adrenal cortical hyperplasia, diffuse and micronodular with several nodules, the largest one being 1 cm, in the right adrenal. Clinical and biochemical hypercortisolism disappeared in the postoperative period and is still the case >8 years later. In September 2018, basal ACTH was 376 pg/ml (0–46). In control pituitary MR a pituitary gland with normal characteristics is observed.
Discussion
The high degree of recurrence of CCS after pituitary surgery often conditions new interventions and/or combined pharmacological therapy. Despite the risk of developing Nelson syndrome, bilateral adrenalectomy could be the best initial surgical option

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P242

Pituitary tumors diagnosed in octogenarians – clinical implications

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Introduction
The aging population brought new challenges in several diseases. Pituitary tumors are usually not related with elderly, although the rise in life expectancy has allowed its diagnosis in unusual age groups.
Aim
To describe the pituitary tumors diagnosed in patients with age $\geq$ 80 years
Methods
Retrospective observational study which included 23 patients with pituitary tumors with age $\geq$ 80 years observed in consultation between October of 2017 and October of 2018. Data were collected from clinical registry.
Results
57% were female ($n=13$), with a mean age at diagnosis of 83.3 ± 2.2 years. 78% were considered incidentalomas ($n=18$) and the clinical diagnosis were: 78% clinically non-functional tumors (CNFT) ($n=18$), 17% prolactinomas (PRLoma) ($n=4$), 4% acromegaly (ACRO) ($n=1$). 91% were macroadenomas ($n=21$) with mean length of 2.7 ± 1.1 cm, 95% with suprasselar extension, 45% with extension to cavernous sinus and 15% with infrasselar extension. 60% of patients presented neurological symptoms, 50% ophthalmological symptoms and 10% endocrinological symptoms. 70% of patients were diagnosed with some degree of hypopituitarism, wherein 13% presented panhypopituitarism ($n=3$). Visual field evaluation was performed in only 44% of patients due to limitations related with age and, in these, visual field defects were observed in 90% of patients ($n=9$). Transsphenoidal surgery was performed in four patients (13%) with CNFT and the immunochemistry was consistent with gonadotroph adenomas. Three patients presented improvement of visual evaluation and no improvement was seen in endocrinological function. Thirteen patients (57%) were treated with dopamine agonists (8 CNFT, 4 PRLomas, 1 ACRO), 54% with bromocriptine with a mean dose of 2.5 mg/day and 46% with cabergoline with a mean dose of 1mg/week, with improvement of hypogonadism in two patients (1 PRLoma, 1 CNFT). Acromegaly patient was also treated with lanreotide. During follow-up two patients developed corticotroph insufficiency and four patients deceased.
Conclusion
These data show that majority of pituitary tumors diagnosed in octogenarians were clinically non-functional macroadenomas, identified in imaging exams performed due to other clinical reasons. Despite the incidental diagnosis, 80% of patients presented some kind of neurological, ophthalmological or endocrinological symptoms. Just five patients (22%) had clinically functional tumors (4 prolactinomas and 1 acromegaly) and no Cushing disease was diagnosed. The presence of non-specific symptoms and its difficult appreciation associated with high prevalence of some degree of hypopituitarism shows the relevance of the diagnosis of pituitary tumors in this age group to do the prompt start of substitutive treatment in order to avoid potentially fatal outcomes.

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P243

Papillary thyroid carcinoma in acromegalic patient diagnosed with McCune Albright syndrome (MAS)

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Introduction
McCune Albright syndrome (MAS) is a rare, sporadic disease that affects the skin, skeleton and several endocrine systems, caused by an activating mutation in the GNAS gene that leads to endocrine cell hyperfunction and increased cell proliferation. The development of thyroid carcinoma in MAS is considered an uncommon event and, on the other hand, it is well established that acromegaly is associated with an increased prevalence of malignant tumors including thyroid cancer.
Clínical case
A 53-year-old female without family history of endocrine disease, surgically treated for facial asymmetry, was diagnosed in 1992 with polyostotic fibrous dysplasia, GH/prolactin producing pituitary macroadenoma and toxic multinodular goiter. Hyperprolactinemia and hyperthyroidism were controlled from the diagnosis with dopamine agonists and methimazole, but acromegaly remained active until 1999 because the patient refused treatment with subcutaneous octreotide. In January 2000 intramuscular Sandostatin LAR 30 mg/month was included in the treatment. In 2007 Sandostatin was replaced by subcutaneous GH receptor antagonist Pegvisomant, 20 mg/day because the control objective for IGF-1 was not achieved. Later, after confirming a significant increase in the size of the pituitary adenoma in magnetic resonance, we opted for combined therapy with Sandostatin LAR and Pegvisomant. Since then, the macroadenoma remains stable and IGF-1, PRL, and thyroid function are normal. In the follow-up thyroid ultrasonography (US) performed in 2017, several nodules in the left lobe thyroid suspected of papillary carcinoma were described and fine-needle aspiration (FNA) of the larger nodule was compatible with papillary thyroid carcinoma (PTC). In June 2017, total thyroidectomy was performed and the histopathological report confirmed the presence of a bilateral multifocal papillary carcinoma with extension to the extrathyroidal tissue adjacent to the left thyroid lobe, associated with nodular hyperplasia and chronic lymphocytic thyroiditis. Radioactive iodine ablation was performed 1 month later and the total body scan performed after treatment did not show evidence of metastasis. Serum thyroglobulin remains undetectable.
Discussion
Several studies report a high frequency of PTC in acromegalic patients, especially in those with prolonged periods of uncontrolled acromegaly, although the controversy remains regarding its BRAF mutation dependence. Previous data suggest relative aggressiveness of these tumours but the outcome seems good after surgery and I-131 therapy. In this patient, the sustained exposure to an overactive GH/IGF axis may have played a dominant role in the development of PTC. Acromegalic patients should be routinely screened by thyroid US and undergo FNA according to current criteria.

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P244

Effects of octreotide on hallmarks of autophagy and on parameters related to cell viability and metabolic activity in rat pituitary tumor cells

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We investigated the direct effects of the somatostatin analog octreotide on hallmarks of autophagy and of cell viability and metabolic activity in rat pituitary tumor cells (GH1 and GH3 cells). The Western blot analysis of cell lysates suggested that octreotide (100 nM) treatment could induce changes in hallmarks related to autophagy activation (increased LC3-I protein lipidation) and to enhanced autophagic flux (SQSTM1/p62 protein downregulation) in pituitary tumor cells in different experimental conditions which included incubation in

Hank's balanced salt solution (HBSS), in Ham's F10 medium without serum and in the same medium supplemented with serum. Actually, these effects of octreotide were observed after short treatments (up to 4-h long) whereas they were not seen after 20-h long treatment. The primary antibodies were from Cell Signalling. In the same experimental conditions, we analyzed the MTT reduction activity as an index of cell metabolic activity and cell viability. Our results did not suggest any decrease in redox activity of the cells following to their treatment with octreotide in all the experimental conditions tested. On the other hand, in GH3 cells incubated in HBSS for short time (2-h), the addition of octreotide to HBSS tended to enhance the MTT reduction activity (112% ± 6% vs vehicle, $N=4$) and to increase the ATP levels in cell lysates (112% ± 8% vs vehicle, $N=4$), as measured by ATPlite kit (PerkinElmer). Finally, an increase of the pyruvate dehydrogenase (PDH) complex activity (PDH Enzyme Activity Microplate Assay Kit, Abcam) in lysates from GH3 cells treated with octreotide for 2-h, was observed compared to control cells (111% ± 4% vs vehicle, $N=3$). Actually, this effect was not related to any change in the phosphorylation of the regulatory subunit E1alpha (ser-293 in PDHE1-alpha), as assessed by Western blot (primary antibody from Abcam). In conclusion, we provided evidence that octreotide can affect autophagy in pituitary tumor cells. The observed effects of octreotide were not related to decreased cell viability and metabolic activity. Finally, the induction of autophagy was either short-lived or overshadowed by other factors in the long term and this limit does not help clarifying their real impact on the pharmacological activity of somatostatin analogs.

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P245

Effects of body mass index and estimated glomerular filtration rate on pituitary function in patients with non-functioning pituitary tumor

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Introduction
Hypothalamus or pituitary disorders frequently cause hypopituitarism. Diagnosing deficits of anterior pituitary hormones is important to manage metabolic impairments induced by hypopituitarism. Provocative tests including TRH, LHRH, CRH and GHRP-2 to diagnose hypopituitarism are recommended in Japan, however, the cut-off values in those tests are not adjusted for age, body mass index (BMI) or estimated glomerular filtration rate (eGFR). We retrospectively evaluated effects of age, obesity and renal function on the results of pituitary function tests in patients with hypothalamus or pituitary disorders.
Methods
In this retrospective study, patients with non-functioning pituitary tumor without history of pituitary surgery who admitted and received GHRP-2 test from 2013 until 2016. We evaluated an effect of age, BMI and eGFR on their pituitary functions. To evaluate pituitary function, TRH, LHRH and CRH combination test and GHRP-2 test were performed.
Results
We identified 116 patients who received GHRP-2 test, of which 90 (78%) were non-functioning pituitary adenoma and 17 (15%) were Rathke's cyst. Of the patients, 111 (96%) received TRH and LHRH test, and 112 (97%) received CRH test in addition to GHRP-2 test. Logarithm of peak serum GH level after GHRP-2 was significantly correlated with BMI ($r=-0.37$, $P<0.001$). Serum IGF-1 level was significantly correlated with age ($r=-0.518$, $P<0.001$) and eGFR ($r=0.19$, $P=0.037$). In multiple regression analysis, age was the only independent variable predicting serum IGF-1 level. Not serum free T4 but free T3 level was significantly correlated with age ($r=-0.20$, $P=0.031$) and eGFR ($r=0.33$, $P<0.001$). In multiple regression analysis, eGFR was the only independent variable predicting serum free T3 level. Serum TSH level was significantly correlated with age ($r=0.19$, $P=0.041$) and eGFR ($r=-0.21$, $P=0.024$). In multiple regression analysis, eGFR was the only independent variable predicting serum TSH level. In only men, serum LH level significantly correlated with eGFR ($r=-0.34$, $P=0.009$). Plasma ACTH and cortisol levels and their peak levels after CRH were not significantly correlated with age, BMI or eGFR, respectively.
Conclusion
When we diagnose hypopituitarism, we have to recognize that thyroid and gonadal functions might be altered by renal insufficiency and GH response to GHRP-2 might be altered by obesity.

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P246

Salivary carcinoma of the pituitary gland: an exceptional localization never described

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Introduction
Epithelial-myoepithelial carcinoma is a rare, we report the case of a patient admitted for pituitary macroadenoma whose anatomopathological study was in favor of an epithelial-myoepithelial carcinoma at the level of the pituitary gland knowing that this is the first case described in Literature.
Clinical case
A 50-year-old man, admitted in July 2018 for pituitary macroadenoma with severe headache and blurry vision associated with polydipsia syndrome and asthenia. Magnetic resonance imaging showed a pituitary macroadenoma with compression of the optic chiasm. A tumor biopsy was performed whose pathological study showed a morphological and immunohistochemical profile of a secondary localization of epithelial-myoepithelial carcinoma probably developed on embryonic salivary parenchymal rests or secondary to primitive salivary tumor. The clinical examination as well as the MRI of the salivary glands is normal and thus we retain the diagnosis of salivary gland carcinoma developed on embryonic rests. The occurrence of these salivary gland rests in the pituitary gland is explained by direct transfer of intact seromucinous glands from the oral cavity, derivation from Rathke pouch remnants, or induction of pituitary epithelium by salivary gland mesenchyme. After discussing the case at the Multidisciplinary Care Teams, we decided to treat the patient by radiosurgery. Our observation is an exceptional case that is never described in the literature.

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P247

MRI follow-up is not useful in patients with GH-secreting pituitary adenomas primarily treated and responsive to long-acting somatostatin analogs (SMSa)

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Introduction
Primary SMSa treatment can be associated with hormonal remission and tumor shrinkage in patients with GH-secreting pituitary adenomas. In the 2014 Endocrine Society guideline for Acromegaly, there is no specific mention of MRI follow-up during long-term SMSa treatment. The aim of this study was to evaluate any change of GH-secreting adenoma size during primary SMSa treatment and whether regular MRI follow-up was necessary in acromegalic patients treated with first generation long-acting SMSa.
Patients and Methods
In this retrospective and monocentric study we included patients with GH/IGF-1 hypersecretion and GH-secreting pituitary adenomas with normal visual field, primarily treated with first generation long-acting SMSa between 1995 and 2015, and regularly followed (clinical evaluation, GH/IGF-1 levels, pituitary MRI) during at least 3 years. To assess meaningful adenoma change during SMSa therapy, maximal height of the adenoma under the optic chiasm, on coronal T2-weighted MRI, was manually measured by the same radiologist blinded to clinical history, at baseline and at last pituitary MRI of each patient.
Results
We included 83 patients (32 men and 51 women, mean age at diagnosis 50 ± 12 years) with mean GH = 19.3 ± 25.6 ng/ml, IGF-1 = 284 ± 110% ULN and pituitary adenoma height = 12.9 ± 4.7 mm. Patients were primarily treated with long-acting lanreotide Autogel ($n=67$) or octreotide LAR ($n=16$), and mean follow-up was 8.9 ± 4.9 years in 36 controlled patients (GH < 2.5 ng/ml, normalized IGF-1 for age and sex) and 2.0 ± 1.6 years in 47 partially responders (decrease of IGF-1 > 10%) to SMSa alone, before association with dopamine agonists/pegvisomant or pituitary surgery. During primary SMSa treatment, no increase of pituitary adenoma height was observed. Pituitary adenoma height decreased significantly in controlled patients (diagnosis: 11.9 ± 4.8 mm, SMSa: 9.6 ± 3.3 mm, $P < 0.001$), and in partially responders (diagnosis: 13.6 ± 4.5 mm, SMSa: 11.5 ± 4.5 mm, $P < 0.001$). Controlled patients were older ($P < 0.05$), had lower mean GH ($P < 0.05$) or IGF-1 ($P = 0.05$) concentrations, and smaller pituitary adenoma ($P < 0.05$) at diagnosis.

Conclusion
During long-term treatment with first generation SMSa, no increase of GH-secreting adenoma size was observed. Primary SMSa treatment was associated with a significantly decrease of adenoma height in controlled and in partially responder patients. Therefore MRI follow-up does not seem useful in acromegalic patients responsive to SMSa treatment.

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P248

Study of relationship between levels of kisspeptin and neurokinin B and markers of calcium-phosphate metabolism and water-electrolyte balance in patients with neuroendocrine disorders

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Objective
To study the effect of neurohormones kisspeptin and neurokinin B on the indices of calcium-phosphate and electrolyte metabolism in patients with neuroendocrine pathology.
Material and Methods
Eighty-two female patients were included in this pilot study divided into 2 groups: 'Cushing's disease' group ($n=51$) and 'Acromegaly' group ($n=31$). Median age was 33 years [27; 38] in 'Cushing's disease' group and 39 years [32; 45] in 'Acromegaly' group. Kisspeptin levels were measured using an ELISA test-system 'Kisspeptin-54 S-1308' (Peninsula Laboratories International, Inc., USA) on a Luminometer Photometer LMA01 (Beckman Coulter, Czech Republic). Extraction of peptide from plasma was performed according to the manufacturer's protocol. Measurement of the level of neurokinin B was carried out by the ELISA method on Cobas 6000 Module e601 analyzer (Roche, Switzerland), set 'Neurokinin B S-1271' (Peninsula Laboratories International, Inc., USA).
Results
The median serum levels of kisspeptin in the 'Cushing's disease' and 'Acromegaly' groups were 10.8 [3.0; 13.5] and 7.9 [0.14; 11.7] ng/ml, neurokinin B – 0.11 [0.08; 0.13] and 0.07 [0.06; 0.1] ng/ml, sodium - 142 [140; 143] and 140 [139; 141] mmol/l, potassium – 4.4 [4.2; 4.8] and 4.6 [4.2; 5.0] mmol/l, chlorides - 106 [105; 108] and 107 [105; 109] mmol/l, total calcium – 2.39 [2.28; 2.46] and 2.38 [2.31; 2.45] mmol/l, phosphate – 1.14 [1.07; 1.26] and 1.34 [1.24; 1.53] mmol/l respectively. We observed statistically significant difference in kisspeptin, sodium and phosphate levels between groups ($P<0.05$). In the correlation analysis, no significant dependencies were obtained between neuropeptides and sodium, potassium and chloride blood levels. Negative correlation was observed between kisspeptin and neurokinin B in 'Cushing's disease' group ($r=-0.55$, $P<0.05$), between kisspeptin and serum phosphate in 'Acromegaly' group ($r=-0.45$, $P<0.05$).
Conclusion
In a pilot study assessing the impact of new neuroendocrine hormones, there is no correlation between kisspeptin, neurokinin B and sodium, potassium, chloride levels, which negates their significant role in the control of water and electrolyte parameters of blood. Relationship between the studied neuroendocrine hormones and calcium-phosphate metabolism is not clearly understood and may be the subject of further research.

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P249

Spontaneous pregnancy obtained in persistent Cushing Disease treated with Cabergoline: Report of two cases

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Introduction
Pregnancy is rare in patients with Cushing Disease (CD) owing to ovulatory dysfunction. When surgery is not curative, medical treatment is usually considered. Ketoconazole and mitotane, commonly used medical therapies, have questionable teratogenicity and are not often options in pregnancy. Cabergoline was found to be effective in reducing hypercortisolism in Cushing's disease. Observational studies suggested that low dose cabergoline treatment at the time of conception and during early pregnancy is not likely to induce an increase in the risk of miscarriage or of fetal malformation.
Aim
To describe two patients who achieved pregnancy after treated with low-dose cabergoline (CAB) for persistent CD.
Case description 1
We report a 33-year-old woman diagnosed with CD at the age of 23. She underwent trans-sphenoidal resection of pituitary ACTH-secreting microadenoma on January 2005. 18 months after surgery, CD persisted and she underwent Gamma Knife radiosurgery (GKRS). Following GKRS, her cortisol levels remained elevated despite no evidence of visible tumour on pituitary MRI. Adjuvant medical therapy was commenced with low ketoconazole doses with successful control of hypercortisolism for the subsequent 9 years. As she was keen for pregnancy, medical treatment was changed to CAB 0.5 mg twice weekly from July 2015, to avoid the potential teratogenic side effects of ketoconazole. The patient subsequently conceived spontaneously in October 2015.
Case description 2
We report a 30-year-old woman diagnosed with CD at the age of 28, with no visible adenoma on magnetic resonance imaging (MRI). Bilateral inferior petrosal sinus sampling (BIPPS) was done and showed a higher IPS/periphery ACTH ratio on the left side as compared to right. A left hemi-hypophysectomy was performed on February 2018, based on BIPSS findings. Surgery was not curative. As she expressed desire to become pregnant, medical treatment with CAB was started on April 2018, with a gradual dose titration up to 3 mg per week. Clinical improvement was observed and the patient conceived spontaneously in September 2018.
Conclusion
These cases reports demonstrates that cabergoline may be an effective and safe therapeutic option for the treatment of persistent CD in women who want pregnancy.

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P250

Genetic study of AHR exonic part and GNAS intronic part mutations in some of Iraqi acromegalic patients

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Acromegaly is a rare syndrome categorized by extreme excretion of growth hormone via a pituitary adenoma, happening everywhere in the world also in Iraqi population. Practically all conditions of acromegaly are produced by a benign tumor in the pituitary that creates much growth hormone. In additions, some tumors in the body may yield an element known as growth hormone releasing hormone which lead the pituitary to oversecrion of growth hormone. So this research proposed to observe the frequency of guanine nucleotide binding protein, alpha stimulating (GNAS), and aryl hydrocarbon receptor (AHR) genes mutations. Consequently, this cross sectional biochemical and molecular genetic study was achieved from December 2016 to September 2017, enrolled seventy patients (36 males, and 34 females) with somatotrophic pituitary adenoma continuously attended to the National diabetic center in Baghdad. Their ages were between 20 to 70 years old. Polymerase chain reaction (PCR) was used for the detection of gsp and AHR mutations as a cause of acromegaly, by using specific primers for amplification of partially intronic and exonic 7 of gsp gene on chromosome no.20 and exon 10 of AHR gene on chromosome no.7. Sequencing was applied for PCR products of AHR and gsp genes, six different alterations in AHR gene and two different mutations in GNAS gene have been recognized. Two were recognized in 6/70 (9%) patients which are codon 705 with substitution thymine by adenine (T/A), and codon 410 with substitution of adenine by thymine (A/T) for 817bp fragment. In addition another four recognized alteration were established in (22/70) (31%) which are codon 193 with substitution of cytocine by adenine(C/A), codon 344 with substitution of thymine by adenine(T/A), codon 459 with substitution of guanine by cytocine(G/C), and codon 518 with substitution of adenine by cytocine(A/C) and this for 706bp fragment of AHR exon 10.Two mutations in GNAS gene were recognized in 5/70 (7%) which their codon 91 with substitution cytocine by guanine(C/G), and codon 128 with substitution guanine by adenine(G/A). We concluded the novelties SNP were identified in Iraqi acromegalic patient. Genetic variationspossiblyencouraging functional irregularities of the aryl hydrocarbon receptor (AHR) pathway and guanine nucleotide binding protein, alpha stimulating (GNAS) are connected with a more severe acromegaly increased pituitary tumor mass, and somatostatin analog resistance in patients living in HR areas.

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P251

Primary infundibulohypophysitis in a young man with DI and Hypogonadism

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Primary hypophysitis is a rare inflammatory condition which is mostly encountered in women. It represents 0.2–0.8% of pituitary pathologies and its annual incidence is estimated at 1 case per 9 million inhabitants. We present the case of a 28-year-old male, smoker, with sudden onset decreased libido, polyuria and polydipsia. At presentation he had an epicranial lipoma with and no other suggestive clinical signs. Biochemistry revealed hypernatremia 146 nmol/L, low testosterone level 0.5 ng/mL, low normal FSH and LH, normal prolactin level, normal adrenal and thyroid function. The dehydration test was positive for central diabetes insipidus (test stopped after 4 hours due to high plasma osmolality- 307 mOsm/l while urinary osmolality was lower than 300 mOsm/l and increased to 756 mOsm/l after Desmopressin). Diagnosis of central diabetes insipidus and hypogonadotropic hypogonadism has been made. Pituitary MRI showed thickening of the pituitary stalk close to the chiasm, a homogenous enlarged pituitary gland with loss of posterior bright spot. Serum alpha-fetoprotein and β-HCG were negative both in blood and CSF and scrotal ultrasound was normal excluding germinoma; normal blood angiotensin-converting enzyme, negative tuberculin purified protein derivative test and normal chest CT excluded sarcoidosis, tuberculosis and lung cancer. Also CSFflow cytometry, serum IGG4, c-ANCA, HIV serology were normal. The patient was treated with Desmopressin and Testosterone undecanoate and reevaluated at 3 and 6 months - pituitary IRM showed regression of the pituitary stalk mass, with persistence of DI and hypogonadism. The etiological spectrum of pituitary stalk (PS) lesions is broad, presenting a diagnostic challenge. We will discuss the differential diagnosis and management of this unusual case of primary infundibulohypophysitis. Pituitary stalk biopsy in this case was considered deleterious and not absolutely necessary as repeated MRI at 3 months showed a reduction of the stalk lesion. In cases of suspected lymphocytic hypophysitis, it is reasonable to try a course of high-dose glucocorticoids before proceeding to PS biopsy. However a positive response to glucocorticoids is not specific for hypophysitis, as a temporary relief can be observed also in lymphoma and germinomas. Similarly, in the absence of mass effect symptoms, like in our case it is reasonable to observe a PS lesion ensuring close hormonal and radiological follow-up as spontaneous resolution of PS has been observed.

Conclusion

Primary hypophysitis occurring in a young man is a rare condition with poorly understood pathogenesis and lack of specific markers, thus represents a diagnostic challenge.

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P252

A case of 'micromegaly': need for revision of oral glucose tolerance test (OGTT) cut-offs with modern growth hormone assays in acromegaly

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The OGTT is the gold standard for confirmation or exclusion of acromegaly in treatment-naïve patients as well as after surgery. According to former guidelines, acromegaly is ruled out if the growth hormone (GH) nadir lies below 1.0 µg/l and 0.4 µg/l pre- and postoperatively, respectively. We present the case of a 40-year-old man who presented to the outpatient clinic in 2014 for endocrinological evaluation after an elevated IGF-I concentration had occasionally been detected within the scope of a clinical study. GH and IGF-I were measured using a modern, monoclonal antibody based assay adhering to recent guidelines (IDS iSYS). At that time, a GH nadir of 0.3 µg/l formally ruled out acromegaly. However, due to the clinical presentation and comorbidities (typical physiognomy, sleep apnea, arterial hypertension, impaired glucose tolerance, hypogonadotropic hypogonadism, and obesity) the patient was scheduled for follow-up consultations. IGF-I was persistently elevated (IGF-I SDS between 3.1 and 5), but GH nadir remained below 0.4 µg/l in two repeated OGTTs (0.36 and 0.24 µg/l in 2015 and 2016, respectively). In 2015, MRI revealed a pituitary microadenoma (9×4 mm) but the patient refused surgery. Tumour size was unchanged in annual follow-up MRIs. In November 2018, over 4 years of initial observation of elevated IGF-I, the patient finally agreed to transsphenoidal tumour resection. Neuropathological examination confirmed GH-secreting pituitary adenoma. Postoperatively, IGF-I concentration fell within the gender- and age-specific reference range (SDS 2, 10 weeks after surgery), and GH was suppressible to <0.05 µg/l after oral glucose load. The case also supports our recent observation in a larger cohort of healthy subjects: Using the same modern GH assay, GH nadir concentration fall below 0.4 µg/l in lean (BMI <25 kg/m^2) and below 0.2 µg/l in obese (BMI >25 kg/m^2) subjects. In the present case the BMI was >38 kg/m^2 at all times. This case suggests that mild or early acromegaly might be missed when the commonly used cut-off of 0.4 µg/l is applied for all patients, particularly if modern, highly sensitive and specific GH assays are used.

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P253

What patients with acromegaly have to say about their diagnostic pathway: A qualitative study

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Background

Acromegaly is a rare disease with a long and complex diagnostic pathway leading to a substantial diagnostic delay associated with an increased risk of comorbidities and psychosocial deterioration. Qualitative methods are the gold standard to explore patients' perspectives, focusing on how individuals understand and report what they are experiencing. To the best of our knowledge, no qualitative study has yet examined the diagnostic pathway of subjects with acromegaly. This study aimed to fill this gap.

Methods

Face-to-face unstructured interviews were conducted by experienced qualitative researchers in a third referral Endocrinology center. Participants, purposively selected until data saturation was reached, were patients with acromegaly with various disease durations, types of treatment, or associated comorbidities. The data were examined by thematic analysis.

Results

Twenty patients with acromegaly, 11 women and 9 men, were included. The duration of misdiagnosis and uncertainty resulting in diagnostic delay ranged between 3 and 16 years (mean, 8 years). Our analysis shows four themes; (i) *what happened for patients before the diagnosis,* with the early symptoms the patients perceived, but also the terror they felt not to recognize themselves and the lack of understanding, (ii) *what happened after,* with the tragic ending of the diagnostic assessment and how they look at the damage retrospectively; (iii) *the style or type of doctor involved*, the ones they met before the right diagnosis, at diagnosis and after and (iv) *participants' suggestions for limiting diagnostic delay,* with two suggestions, one concerning directly doctor training and the other involving how society, patients, and others look at people with acromegaly, as well as the need to look more attentively at oneself and at others

Conclusion

Our findings underline the direct associations between diagnostic delay and the doctor-patient encounter, and the truly catastrophic experience of this disease, both before and after the diagnosis. Limiting diagnostic delay requires an active involvement and awareness of any doctor, especially primary care providers. We suggest several practical implications such as the intervention of patient-experts in medical schools or a statement that all physicians can use to address the catastrophic dimension of their patients' experiences and to support them in this process.

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P254

IgG4-releated hypophysitis: A case report

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Introduction
IgG4-dependent disease is a newly defined fibroinflammatory disease. This disease has been shown to affect almost all organs in the body, especially the pancreas, salivary gland, orbital tissue, lymph node, lung and kidney. IgG4 hypophysitis is a rare and inflammatory process that mimics pituitary tumors. The diagnosis of IgG4 releated hypophysitis can be done in many ways. The definitive diagnosis is biopsy; however, it is not necessary in most cases. If the other organs are diagnosed with IgG4-releated disease with biopsy, the appearance of pituitary mass is also diagnostic.
Case
A 28-year-old woman was admitted to our clinic with blurred vision and double vision during her pregnancy. Our patient was receiving replacement therapy due to total hypophyseal insufficiency. In June 2018, pituitary biopsy was performed and the pathology report was revealed as IgG4 pituitary. In November 2018, outward shifting started in the right eye. The patient presented with a Gamma-knife recommendation. TSH: 0.026 (N: 0.27–4.2 IU/ml), freee T4: 0.836 (N: 0.93–1.7 ng/dl), FSH: 1.24 (N: 3.5–12.5 mIU/ml), LH 0.4 (2.5–11.2 IU/ml), E2 (3 pg/ml), Prolactin: 0.466 (N: 4.79–23.3 ng/ml), IgG4: 340 (N: 80–140 mg/dl). Pituitary MRI revealed bilateral cavernous sinus, optic chiasm and infundibulum infiltration, and T2 hypointense hypophysitis. The patient was diagnosed with IgG4-releated hypophysitis and pulse steroid treatment was started, but because there was no clinical and radiological improvement, rituximab1000 mg was given twice daily for 15 days.
Conclusion
There is still no consensus about the treatment of IgG4-releated hypophysitis, and in patients with steroid resistance, rituximab therapy may be required.

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P255

Trunk fat increase is prevented both in patients undergoing long-lasting continuous r-hGH therapy and in those who discontinued r-hGH compared to untreated patients: results from baseline data of the MAGHD study

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Background
Adult growth hormone (GH) deficiency (AGHD) is related with alterations in body composition, increased abdominal and visceral adiposity, adverse change in lipid and carbohydrate metabolism, and reduction of bone mineral density (BMD).
Aim
To compare baseline outcomes concerning body composition and biochemical/hormonal data among adult patients with AGHD referring to a single endocrinological center and grouped according to their history of r-hGH therapy.
Methods
The Management of Adult Growth Hormone Deficiency Study(MAGHD) is a prospective, single-center trial aiming to improve AGHD management through a smartphone app (MAGHD App: Manage AGHD) and a wearable device integrated with a software framework able to merge several kind of patients' daily data with clinical data collected in institutional databases. Up-to-now, a total of 74 subjects (26 Female, 48 Male, mean age: 56.6 + 14.8 years) with AGHD, fulfilling the inclusion criteria, were enrolled in the study. According to r-hGH therapy, they were divided in 3 groups: patients on long-term r-hGH therapy (Group1, $n = 33$), patients previously treated with r-hGH, who had stopped the therapy at any time (Group2, $n = 18$), patients never treated (Group 3, $n = 23$). Each patient has completed the baseline visit, including biochemical and hormonal measurements and data on BMD and body composition obtained by DXA. The nonparametric Kruskal-Wallis test was used for comparison among 3 groups and data are expressed as median. Only baseline data are here shown.
Results
Mean duration of AGHD disease was 121.2 + 105.8 months; it was lower in Group 3 compared to both Group1 and 2 ($P < 0.05$). Waist circumference (Group 1 95 cm; Group 2 96.5 cm; Group 3 109 cm), total fat mass (Group 1 25016g; Group 2 26491g; Group 3 33887g) and trunk fat mass (Group 1 11743g; Group 2 12598g; Group 3 16761g) were significantly higher in Group 3 compared to both Group 2 and 1 ($P < 0.05$), while total fat mass and trunk fat mass did not differ significantly among Group 1 and 2. Serum insulin and total body fat (%) were significantly higher in Group 3 than Group1 ($P < 0.05$). IGF-1 and IGFBP3 were significantly higher in Group 1 compared to both Group 2 and 3 ($P < 0.0001$). BMD, circulating lipids, and fasting glucose did not differ among the 3 groups.
Conclusions
r-hGH therapy seems to confer a long-lasting beneficial effect on body fat, especially trunk fat even after its discontinuation in AGHD patients, but not on metabolic parameters.
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Hyperglycemia and pasireotide lar in acromegaly: a study with continuous glucose monitoring

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Background
Pasireotide LAR is a multireceptor targeted somatostatin analogue that has been shown to obtain a better biochemical control of acromegaly. However, pasireotide LAR could induce hyperglycemia in acromegalic patients with higher baseline glucose values. The devices that can track interstitial glucose levels such as continuous glucose monitoring (CGM) could be a useful for studying the impact of SSA on patients' glucose status.
Aim
We aimed to study the glucose metabolism with CGM in a group of acromegalic patients during first generation SSA treatment before pasireotide LAR start.
Methods
We studied 10 patients with uncontrolled acromegaly (Male 5; median age 58y) in therapy with first generation SSA eligible for the treatment with pasireotide. At pasireotide start (T0) we performed a CGM of 9 days to investigate the glycemic variability (J whole, GRADE, MAGE, CONGA). We also collected endocrinological and metabolic data (GH, IGF 1, fasting plasma glucose -FPG-, HbA1c) at T0 and after at least 3 months of therapy (T1).
Results
Analysis of the data, revealed a significant decrease in GH (T0 2.06 vs T1 1.02 ug/L, P 0.01) and in IGF1 (T0 275.5 vs T1 193.5 ug/L, $p = $NS) after treatment with pasireotide, with a median treatment duration of 9 months. There was also a significant increase in FPG and HbA1c (FPG T0 97 vs T1 124 mg/dL, P 0.01; HbA1c T0 41.5 vs T1 44.5 mmol/mol, P 0.01) At T0, 5 patients (50%) had glycemic alterations: 2 patients had diabetes mellitus (DM) in therapy with metformin and 3 patients had an impaired fasting glucose (IFG). At T1, 5 patients (50%) received antidiabetic medications and among this 60% started antidiabetic treatment after T0. Patients with FPG > 100 mg/dl at T0 showed higher glucose variability for most important CGM-based variability indexes (FPG < 100 vs FPG > 100: J whole 17.3 vs 25,2 $P < 0.03$, GRADE 2 vs 4 $P < 0.03$, MAGE 54.7 vs 96.1 $P < 0.01$, CONGA1h 12.8 vs 28.3 $P < 0,03$).One patient discontinued the drug due to severe hyperglycemia (> 500 mg/dl). At T1 there were no significant correlations between HbA1c/FPG and glycemic indexes.
Conclusions
We confirm the efficacy of pasireotide and the effect on glucose metabolism. For the first time in literature we found higher glycemic variability indexes in acromegalic patients with known alterations of glucose metabolism. Further studies are needed to determine the role of CGM in acromegalic patients on pasireotide treatment.

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P257

Radiation therapy in patients with pituitary somatotropinomas

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Purpose
To assess the effect of radiation therapy (RT) in patients with acromegaly, depending on the age of the patients and the activity of the formation.
Materials and methods
The object of the study was 50 patients (36 women and 14 men) with acromegaly who received gamma-therapy in a total dose of 45-60 Gr. The age of patients ranged from 29 to 77 years. By age, the patients were divided into 3 groups: 1st age group-29–44years old-23patients (46%), 2nd group-45–59years old-16 patients (32%), 3rd group-60-79years old-11patients (22%). All patients underwent hormonal (GH, IGF-I) studies in the dynamics of treatment.
Results
The hormone levels of GH and IGF-1 remain high in group I in 22% of patients, and in group III in 9%. Remissions reached 64% in the III group. The highest levels of GH were in the age range from 45 to 59 years old and amounted to 77.5 ± 9.68 mMe/l, and from 26 to 44 years old was 68.1 ± 6.84 mMe/l. After RT, this indicator in both age groups was almost equally depressed, but not to the norm. At the same time, in the Igroup, a decrease in the level of GH is observed in 10 patients, and in the II age group in 9patients it was 9.99 ± 6.2 mMe/l. As the results of the study showed, the use of RT leads to a significant decrease in the level of GH and IGF-1 in all age periods and a particularly significant decrease was observed in age group III.
Conclusions
Thus, the analysis of the results of studying the relationship between the age of patients and the activity of the process at different periods of observation after RT showed that in all age periods, RT is a fairly effective method of treatment and gives positive results in most cases.

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P258

Anterior pituitary insufficiency in clinically non-functioning pituitary microadenoma

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Background
Systematic exploration for anterior pituitary deficiency in patients harboring pituitary microadenomas is not well defined. So far, little is known on the involvement of pituitary function in clinically non-functioning pituitary microadenomas (CNFPM).
Objective
To evaluate the prevalence of anterior pituitary insufficiency, defined as at least one hormonal deficiency, in patients diagnosed of CNFPM.
Patients and methods
A multicenter retrospective study in patients diagnosed of CNFPM was performed. In every patient, clinical parameters (age at a diagnosis, sex, and main complaint at presentation) and endocrine dysfunction (the presence of hypopituitarism, number of axes involved, and hyperprolactinemia) were recorded.
Results
Of a total of 162 patients with CNFP adenomas, 31 patients (19.1%; mean age 43.6 ± 15.65 yr (range, 14–83); 21 women (67.7%)) with microadenomas (median size 5 mm (IQR, 4–7 mm) were evaluated. In most patients ($n=23$, 74.2%), the finding of the pituitary microadenoma was incidental. In the remaining, the main complain at presentation was galactorrhea ($n=3$), erectile dysfunction ($n=2$), infertility ($n=1$), amenorrhea ($n=1$) and menstrual disorders ($n=1$). Anterior pituitary insufficiency was seen only in 2 patients (6.5%), both of them with only one hormonal deficiency. The first one was a 51-year-old woman who complained of facial pain. Pituitary MRI showed a 5 mm pituitary microadenoma and hormonal evaluation was compatible with ACTH deficiency (low/normal ACTH (13 pg/ml) with low cortisol (3.8 µg/dl)). The second one was a 28-year-old man studied for infertility. Investigations showed hypogonadotropic hypogonadism (low FSH (0.2 mU/ml), low LH (0.4 mU/ml) and low total testosterone (20 ng/dl)). Pituitary MRI showed a 4 mm pituitary adenoma. In both patients serum PRL concentrations were into the normal range.
Conclusion
In our series, the percentage of pituitary hormone deficiencies associated with CNFPM was very low (6.5%). Although the relationship between CNFPM and pituitary hormone deficiency might be coincidental, it would seem appropriate and prudent to rule out pituitary hormonal insufficiency in these patients.

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P259

Neural network for predicting recurrence of the Cushing's disease within three years after neurosurgical treatment

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Introduction
The reccurence rate after successful neurosurgery for patients with Cushing's disease (CD) varies between 10% and 65%. It is shown earlier that some features are associated with the probability of recurrence, yet no rules were elaborated how to analyse the set of variables.
Materials and methods
The retrospective study was based on 219 cases of CD (32 men, 187 women) with a disease duration ranged from 4 months to 22 years, who underwent an endoscopic transsphenoidal adenomectomy in 2007-2014 at the age of 38 ± 12. The duration of a postoperative follow-up was 3 years or more. The 3-years remission persisted in 172 patients, the recurrence developed in 47 patients. Univariate and multivariate analyses were performed.
Results
The univariate analysis did not reveal association between the CD recurrence and sex, age, duration of disease, size of adenoma. At the same time, adrenocorticotropic hormone (ACTH) and cortisol levels in the early post-operative period found out to be statistically significant predictors: patients with ACTH levels less than 7 pg/ml had recurrence about 6 times less than patients with higher levels of ACTH, odds ratio (OR) 0.16, 95% CI [0.06; 0.43]; patients with cortisol levels less than 123 nm/l had recurrence about 5 times less than patients with higher levels of this hormone, OR 0.19 [0.09; 0.39]. However, in 58% of cases the levels of these two hormones are dissociated, so it is not possible to use any of them to predict recurrence. This made multivariate analysis reasonable. No effective logit-regression model was developed, but the highly effective neural network (3-layer perceptron) was obtained. The predictors are sex, age, duration of disease, size of the adenoma, levels of ACTH and cortisol in the blood in the early postoperative period. The correct prediction on randomly generated samples was 94.2% on the training sample ($n=155$), 84.4%, on the control sample ($n=32$), and 87.5% on the test sample ($n=32$). The model has sensitivity 74%, specificity 97%, positive predictive value 85%, negative predictive value 93%.
Conclusion
The developed ANN is an effective tool for predicting recurrence and it will allow to perform personalized approach to the management of patients who underwent neurosurgery, eg. vary frequency of dynamic examinations, prescribing and correcting drug therapy, etc.

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P260

Hyperglycemia in patients with acromegaly treated with pasireotide LAR

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Pasireotide long-acting release (LAR) is a multireceptor-targeted somatostatin receptor ligand approved for treatment of patients with acromegaly. In some clinical reports, pasireotide LAR has been shown to regulate biochemical outcomes more than other somatostatin receptor ligands. However, hyperglycemia was frequently observed in pasireotide LAR treated patients with acromegaly. Three patients were treated with pasireotide LAR to regulated biochemical parameters of acromegaly. They had an elevated levels of insulin-like growth factor 1 (IGF1) and growth hormone (GH) after surgery of pituitary tumor and medication treatment of octreotide LAR. All three had consistently high level of IGF1 and GH for several years. After 3 months of pasireotide LAR treatment, IGF1 level tended to decrease compared to the previous clinical

outcomes. In first case, IGF1 and GH before pasireotide LAR were 369.41 ng/ml and 6.28 ng/ml. After 3 months of pasireotide LAR, IGF1 and GH were decreased to 187.56 ng/ml and 3.41 ng/ml. In second and third cases, levels of those were 409.98 ng/ml, 341.7 ng/ml and 4.48 ng/ml, 5.14 ng/ml to 167.07 ng/ml, 178.18 ng/ml and 2.27 ng/m, 1.00 ng/ml. But levels of fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) increased. FPG and HbA1c were elevated 2-fold from baseline in 2 patients with diabetes mellitus (DM) treated oral hypoglycemic agents (OHAs); FPG 183 mg/mL to 312 mg/mL and HbA1c 6.2% to 11.9% in first case. Another, FPG 110 mg/mL to 265 mg/mL and HbA1c 6.3% to 12.6%. The patient with previously normal glucose tolerance was newly diagnosed DM; FPG 85 mg/mL to 461 mg/mL and HbA1c 6.0% to 12.6%. These clinical cases suggest that the effect and safety of the pasireotide LAR should be considered in patients with acromegaly. Especially, pasireotide LAR-induced hyperglycemia should be carefully observed and treatment of hyperglycemia should be started at an appropriate time.

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P261

Novel insight into ACTH-secreting pituitary tumors biological behavior: somatostatin receptor type 5 (SST5) modulation by ubiquitin specific peptidase 8 (USP8)

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Cushing's Disease (CD) is a rare condition characterized by an overproduction of ACTH by an ACTH-secreting pituitary tumor, resulting in excess of cortisol release by the adrenal glands. Pasireotide is the pituitary-targeted drug approved to treat adult patients. Its mechanism of action seems to rely on the preferential binding to the highly expressed somatostatin receptor in corticotroph tumors, SST5. Recently, somatic mutations in the deubiquitinase *USP8* gene have been reported in 40% of patients affected by CD, resulting in epidermal growth factor receptor (EGFR) signaling hyperactivation and ACTH secretion. Although mutated tumors were found to express significantly higher levels of SSTR5, the interplay between USP8 and SST5 has never been explored so far. The aim of this study is to investigate whether modulation of USP8 activity could affect SST5 physiology. First, by immunoprecipitation experiments we found an enhanced SST5 ubiquitination in murine corticotroph tumor AtT-20/D16v-F2 cells incubated with the chemical inhibitor of USP8, RA-9, compared to basal (2.1 ± 0.4-fold increase vs basal, $P < 0.05$). On the contrary, pasireotide did not significantly modify the ubiquitination status of the receptor. Interestingly, a significant SST5 protein expression levels increase was only observed in cells pre-treated with RA-9 and exposed to 10 nM pasireotide for 72 h ($+36\% \pm 12.1$, % vs basal, $P < 0.01$), this effect being reverted by cycloheximide treatment ($-49.3\% \pm 23$, % vs basal, $P < 0.05$). Accordingly, cells transfection of the catalytically active USP8-C40, followed by pasireotide incubation, resulted in a reduction of SST5 expression level ($-38.7\% \pm 18.4\%$ vs basal, $P < 0.05$). In AtT-20/D16v-F2 cells, similar inhibitory actions on p-ERK1/2 were triggered by pasireotide, RA-9 and by their co-incubation ($-72.1\% \pm 16.1$, $-60.2\% \pm 16.7$, and $-66.4\% \pm 14.6$,% $P < 0.05$ vs basal), whereas RA-9 was able to reduce p-ERK1/2 levels ($-48.5 \pm 9.2\%$ vs basal, $P < 0.05$) in human tumoral corticotroph primary cultures regardless *in vitro* responsiveness to pasireotide. Altogether, our data demonstrate that the expression of agonist-activated SST5 is negatively modulated by USP8 in AtT-20/D16v-F2 and that RA-9 is effective in reducing ERK phosphorylation in mouse and human ACTH-secreting pituitary tumor cells.

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P262

Rare lesions of sellar, parasellar and suprasellar pathologies

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Differential diagnoses of sellar, parasellar and suprasellar pathologies other than tumors such as common adenoma, rathke cleft cysts and meningioma and craniopharyngiomas were presented. This retrospective study was performed including 25 patients who were operated or treated medically in between 2008 and 2019. The patients were analyzed with preoperative/postoperative magnetic resonance imaging (MRI), endocrinological and neuro-ophthalmologic examination results. Pre and post contrast sagittal T1WI, pre and post contrast dynamic coronal T1WI, coronal T2WI were obtained for MRI. Some patients were imaged several times to reach final diagnosis and treatment control. The diagnosis revealed metastatic tumors ($n = 3$), colloid/epidermal/dermoid cysts ($n = 3$), pilocytic astrocytomas ($n = 5$), and one case each of hemangioblastoma, lymphoma, chordoid glioma, meckel cave schwannoma, chordoma, aneurysm, fibrous dysplasia, germ cell tumour. 3 hypophysitis, (lymphocytic/tuberculous granuloma/xanthomatous), 2 developmental chordomatous lesions (fossa navicularis, notochordal remnants), 2 hamartoma. Metastatic tumors demonstrated main growth within destructive remodelling of the dorsum sellae. Big lesions (> 20 mm) showed a significantly worse outcome regarding hormonal and visual deficits. Developmental lesions (developmental chordomatous lesions (fossa navicularis, notochordal remnants), hamartoma were stabile. While some of the lesions were operated some were followed by MRI.

Conclusion

The correlation of the radiological findings with the specific clinical features maybe helpful for the differential diagnosis of rare lesions of the sellar, parasellar and suprasellar pathologies. Interdisciplinary diagnostic and therapeutic procedure for these lesions are very important to control the specific disease.

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P263

Baseline characteristics of adult patients with growth hormone deficiency (GHD) enrolled in NordiNet® International Outcome Study (IOS): are there variations between countries?

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Czech Republic background

NordiNet® IOS (NCT00960128), a non-interventional study (2006–2016), assessed the effectiveness and safety of real-life treatment with Norditropin. From 23 countries, 2,321 adults with GHD were included; 971, GH-naïve at baseline, were included in the effectiveness analysis set (EAS). Baseline characteristics in the six largest contributing countries were evaluated.

Methods

Patient information was entered at routine clinic visits by participating physicians. EAS baseline data are presented (Table 1).

Results

Proportionally more females than males were enrolled in France and Czech Republic versus other countries. Patients were older in Sweden, Germany and UK; males were older than females except in France and Czech Republic. Mean baseline IGF-I SDS was below 0 across all countries. Mean GH peak was lower in males than in females and varied across countries. Mean BMI (kg/m^2) was >25 across all countries. Average baseline GH dose was lowest in Sweden, highest in UK (females) and lowest in Sweden, highest in France (males).

Table 1

	Germany	Sweden	Denmark	France	UK	Czech Republic
N (% of patients enrolled)	389 (40)	199 (20)	151 (16)	72 (7)	41 (4)	37 (4)
Females (%)	44	42	37	65	46	54
Age (years)	48.1 [14.7]: 50.1 [14.8]	49.8 [13.7]: 53.5 [13.6]	43.4[13.9]: 49.6[13.4]	43.3 [11.6]: 38.6 [13.5]	46.6 [14.2]: 52.1 [13.2]	45.4 [9.0]: 42.5 [12.8]
IGF-I SDS	−1.25 [1.54]: −1.32 [1.68]	−1.05 [1.14]: −0.91 [1.29]	−0.55 [1.29]: −0.70 [1.02]	−0.71 [1.62]: −0.75 [2.19]	−1.01 [0.94]: −1.02 [2.91]	−1.09 [1.58]: −0.94 [1.26]
GH peak (ng/mL)	1.83 [3.41]: 1.49 [1.79]	5.07 [8.34]: 2.04 [2.04]	1.52 [1.92] :0.97 [1.34]	3.01 [3.46]: 1.35 [1.55]	4.01 [9.16] :0.58 [0.90]	1.10 [1.87]: 0.74 [0.77]
Waist circumference (cm)	98.16 [16.63]: 103.00 [13.77]	97.32[14.41]: 102.90[12.04]	92.21 [20.64]: 106.5 [13.86]	94.60 [14.51]: 100.70 [14.62]	93.00 [7.78]: 114.00 [11.14]	92.38 [15.95]: 91.30 [9.37]
BMI (kg/m^2)	28.85 [6.63]: 29.47 [5.50]	28.93 [5.84]: 28.51 [4.94]	27.64 [6.77]: 28.79 [4.84]	29.62 [8.16]: 29.65 [5.92]	29.35 [6.85]: 31.90 [5.30]	29.98 [9.86]: 25.62 [4.66]
Average baseline GH dose (mg/kg/day)	0.23 [0.16]: 0.24 [0.15]	0.17 [0.13]: 0.16 [0.12]	0.30 [0.15]: 0.27 [0.21]	0.28 [0.10]: 0.29 [0.15]	0.31 [0.19]: 0.25 [0.07]	0.24 [0.20]: 0.26 [0.21]

Baseline values, mean [SD] for females:males unless shown as N or %.

Conclusions
This report on adult patients enrolled in NordiNet IOS revealed variations in baseline characteristics, suggesting that national diagnostic and clinical characteristics may affect the country-specific profiles of GHD in adults.

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β-arrestin 2 expression is required for dopamine receptor type 2 (DRD2) inhibitory effects on Akt phosphorylation and cell proliferation in PRL-secreting and non functioning pituitary tumors

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Dopamine receptor type 2 (DRD2) agonists (DAs) are the first-choice treatment for PRL-secreting pituitary tumors due to their efficacy in reducing tumor size and hormonal secretion. However, DAs are poorly effective in non-functioning pituitary tumors (NFPTs), despite most of them express DRD2. No correlation between DAs clinical responsiveness and DRD2 expression was found, suggesting post-receptor alterations underlying resistance. DRD2 signaling pathways that control cell proliferation are mostly unknown. In particular, no data are available in pituitary tumor cells about DRD2 effects on Akt activation, a survival and proliferative pathway over-activated in pituitary tumors. In other cell models, a β-arrestin 2-mediated Akt inhibition by DRD2 has been shown. The aim of this study was to investigate the effects of DRD2 activation on Akt phosphorylation (p-Akt) and cell proliferation in human primary cultured NFPT cells and in rat tumoral lactotroph cells MMQ, and to test the involvement of β-arrestin 2. Firstly, Akt inhibitor GSK2110183 reduced cell proliferation in both MMQ ($-88.2\pm3.6\%$, $P<0.001$ vs bas) and NFPTs ($-41.4\pm10.9\%$, $P<0.01$ vs basal). DRD2 specific agonist BIM53097 inhibited p-Akt in MMQ ($-24\pm7\%$, $P<0.001$ vs basal) and in a subset (30%, $n=23$) of NFPTs ($-25\pm7\%$, $P<0.001$ vs basal) (subgroup 1), whereas increased p-Akt ($+1.9\pm1.2$ fold vs basal) in the remaining tumors (subgroup 2). Western blot analysis revealed a striking correlation between DRD2 ability to inhibit Akt and β-arrestin 2 expression, since it was expressed only in MMQ and NFPTs subgroup 1, but not subgroup 2. The mechanism by which DRD2 dephosphorylates Akt is G protein-independent, as demonstrated by pertussis toxin treatment in MMQ and NFPTs, and β-arrestin 2 mediated, since β-arrestin 2 silencing prevented DRD2 effects on p-Akt in MMQ. Accordingly, β-arrestin 2 transfection in subgroup 2 NFPTs conferred to DRD2 agonist the ability to inhibit both p-Akt ($-23\pm8\%$, $P<0.05$ vs bas) and cell proliferation ($-32.1\pm23.8\%$, $P<0.05$ vs bas). In conclusion, these data demonstrate that β-arrestin 2 is required for DRD2 inhibitory effects on Akt phosphorylation and cell proliferation in MMQ cells and NFPTs, paving the way for a potential role of β-arrestin 2 as a biomarker predicting NFPTs responsiveness to treatment with DAs.

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P265

Somatostatin receptor type 2 trafficking through the cytoskeleton: role of scaffolding proteins Filamin A and β-arrestin 2

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The high expression of somatostatin receptor 2 (SST2) in growth hormone (GH)-secreting tumors represents the rationale for the clinical use of somatostatin analogs (SSAs) in acromegaly. However, about one third of patients displays resistance to SSAs and, to date, the responsible molecular mechanisms are still under investigation. Recently, the cytoskeletal protein Filamin A (FLNA) and the scaffolding proteins β-arrestins have emerged as key modulators of the responsiveness of GH-secreting pituitary tumors to SSAs, by regulating SSTR2 signaling and desensitization, respectively. The aim of this study is to further explore FLNA involvement in SST2 intracellular trafficking in somatotroph cells, since alterations in this system might affect the amount of available receptor at the plasma membrane and lead to unresponsive tumor features. By biotinylation assay we first found that FLNA silencing strongly reduces octreotide-mediated SST2 internalization in rat GH-secreting pituitary tumor cell line, GH3 cells, ($26.9\pm2.7\%$ vs $4\pm1.7\%$ SST2 internalization, control vs FLNA SiRNA cells, respectively, $P<0.001$) and in one human GH-secreting primary culture tested (93.2% vs 31.6% SST2 internalization, control vs FLNA SiRNA cells, respectively). Then, co-immunoprecipitation and immunofluorescence experiments performed in GH3 cells showed that FLNA knock down does not prevent the recruitment of β-arrestin2 to cell surface ligand-activated SST2, but rather impairs receptor localization into cytosolic vesicles positive for the early endocytic marker Rab5 (Pearson's coefficient mean 0.29 ± 0.07 vs 0.16 ± 0.03 of SST2-Rab5 colocalization in control vs FLNA SiRNA, $P<0.01$). Furthermore, after octreotide removal, SST2 recycling fate was affected by the loss of FLNA. Conversely to control cells, SST2 failed to accumulate into intracellular recycling vesicles linked to the early recycling marker Rab4, as resulted by Rab4-SST2 colocalizaition analysis (Pearson's coefficient mean 0.24 ± 0.05 vs 0.16 ± 0.04 of SST2-Rab4 colocalization in control vs FLNA SiRNA, $P<0.05$) and could not reach the plasma membrane in wash out experiments. Altogether these data unveil a crucial role of FLNA in the regulation of octreotide-induced SST2 trafficking in GH-secreting cells, suggesting the possibility of targeting FLNA-SST2 complexes for the treatment of pharmacologically resistant GH-secreting pituitary tumors.

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P266

Antitumor effects of growth hormone-releasing hormone (GHRH) antagonists in ACTH and GH-secreting pituitary adenoma cell lines

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Pituitary neuroendocrine tumors (PitNETs) are mostly benign lesions originating from the anterior pituitary and represent 10–15% of all the intracranial neoplasms. PitNETs can be classified in non-secretory, clinically non-functioning pituitary adenomas (NFPAs), and secretory, comprising prolactin (PRL), growth hormone (GH) and adrenocoticotropic hormone (ACTH) PitNETs. Surgical resection is the first line treatment for PitNETs, whereas chemotherapy and radiotherapy are preferred for resistant or metastatic tumors. GH-releasing hormone (GHRH), apart from promoting pituitary GH secretion, exerts many extrapituitary functions, including stimulation of cell proliferation and survival. GHRH, GHRH receptor (GHRH-R) and splice variant 1 (SV1) of GHRH-R, are expressed in different cancer cell types, where they promote cell growth and tumor progression. Conversely, it has been shown that GHRH antagonists inhibit the growth of different tumors *in vitro* and *in vivo*; moreover, previous reports showed that first generation GHRH antagonists reduce the secretion of GH in tumoral rat GH-secreting (GH3) cells. However, to date the role of GHRH antagonists in PitNETs remains largely unknown. Thus, the aim of this study was to evaluate the effects of the novel GHRH antagonists, MIA-602 and MIA-690, on survival, apoptosis and hormone secretion using tumoral murine ACTH-secreting cells (AtT-20/D16v-F2) and tumoral rat PRL- and GH-secreting cells transfected with human GHRH-R (GH3-hGHRHR). Our results show that MIA-602 and MIA-690 dose-dependently reduced cell survival and promoted apoptosis in tumoral ACTH-secreting cells; moreover, we observed an increase in expression of the proapoptotic protein BAX and the tumor suppressor protein P53, paralleled by a reduction of the antiapoptotic protein Bcl-2. MIA-602 and MIA-690 also reduced colony formation and expression of c-Myc oncoprotein, indicating inhibitory activity on migration and proliferation. Furthermore, the combination of MIA-

602 or MIA-690 with Temozolomide (TMZ), the main chemotherapy agent for PitNETs, produced a synergistic effect on inhibition of cell survival in AtT-20 cells. Importantly, ACTH secretion was also attenuated when these cells were treated with the antagonists. Finally, our preliminary results showed that GHRH antagonists reduced cell survival and promoted apoptosis in GH3-hGHRHR. Overall, these results demonstrate GHRH antagonists reduce aggressiveness features in PitNETs, suggesting the putative utility of these drugs as novel therapeutic tool for the treatment of these pathologies.

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Somatostatin receptor type 5 modulation by Filamin A in ACTH-secreting pituitary tumors

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Cushing's disease (CD) is a rare disorder of chronic hypercortisolism due to an adrenocorticotropic hormone (ACTH)-secreting pituitary tumor. Pasireotide, a multireceptor-targeted somatostatin (SST) analog with high binding affinity for the predominant SST receptor in human corticotroph tumors, SST5, has been recently approved to treat adult patients for whom surgery failed or does not represent a suitable option. However, to date, the molecular predictors of antisecretory and antiproliferative favorable responses to the medical therapy with pasireotide, are unclear. The cytoskeletal protein FLNA plays a crucial role in GH-secreting pituitary tumor responsiveness to somatostatin analogs by regulating the physiology of SST2. Aim of the present study was to investigate a possible involvement of FLNA in the modulation of SST5 expression, signaling and pasireotide-mediated downregulation. First, by co-immunoprecipitation experiments, we demonstrated that FLNA binds to SST5 in mouse tumor corticotroph AtT-20/D16v-F2 cells. FLNA genetic silencing led to statistically significant strong decrease of receptor expression in basal condition ($-45.3\pm$ 33.5% and -27 ± 12%, % of basal negative control, $P<0.05$, in AtT-20/D16v-F2 and primary tumoral corticotroph cells). Moreover, downregulation of SST5 was observed in negative control cells incubated with 10nM pasireotide for 72h (-46 ± 25.7%, $P<0.01$, % of basal), whereas no further reduction of SST5 was detected in FLNA silenced cells. Regarding SST5 signaling, FLNA expression knock down caused an impairment of SST5 inhibitory action on ERK 1/2 phosphorylation (-48 ± 25%, $P<0.05$, in negative control cells vs $-22\pm$ 30.3%, $P=$ ns, in FLNA silenced cells). Furthermore, by Western blot, FLNA and SST5 protein expression levels correlates in 8 human ACTH-secreting pituitary tumors tested ($r=0.762$, $P=0.037$). Interestingly, a trend of higher FLNA protein expression levels were observed in the group of primary tumor cultures that responded to pasiretoide (with reduction of p-ERK1/2 levels) compared to the not responding group ($P=0.071$). In conclusion, our study demonstrated that FLNA is implied in SST5 expression modulation and SST5 signal transduction mechanisms. Additional experiments are needed to unveil a possible role of FLNA in the inhibitory effect of SST5 on ACTH secretion.

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The PATRO adults study of Omnitrope® for the treatment of adult patients with growth hormone deficiency: latest safety results

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Introduction
PATRO Adults is an ongoing, longitudinal, noninterventional study assessing the long-term safety and efficacy of Omnitrope® (Sandoz; recombinant human growth hormone [rhGH]), among adults with severe growth hormone deficiency (GHD) treated in routine clinical practice in European countries. Omnitrope® was approved by the European Medicines Agency (EMA) in 2006, representing the first biosimilar approved by the EMA. We report the latest safety data from PATRO Adults, focusing on diabetes risk.
Methods
Adult patients receiving treatment with Omnitrope® and providing informed consent were eligible for inclusion, regardless of prior treatment with another rhGH. This interim analysis was performed using data available as of 30th November 2018.
Results
At the interim analysis timepoint, 1324 patients had been enrolled since 2007, including 1106 (83.5%) with adulthood-onset and 206 (15.6%) with childhood-onset GHD. In total, 665 (50.2%) patients had previously received another rhGH. Mean age at baseline was 49.2 years (standard deviation [SD]: 15.4), with mean BMI of 29.5 kg/m^2 (S.D.: 6.4). Overall, 4287 adverse events (AEs) were reported by 934 (70.5%) patients; 812 of these events (among 400 [30.2%] patients) were serious AEs (SAEs). One hundred and sixty-nine AEs in 102 (7.7%) patients were suspected to be treatment-related, with musculoskeletal/connective tissue disorders (36 patients), general disorders/administration site conditions (27 patients), and nervous system disorders (24 patients) most commonly reported. Twenty-eight SAEs (among 21 patients [1.6%]) were suspected to be treatment-related, resulting in treatment discontinuation in 7 patients. Overall, 349 (26.4%) patients have discontinued the study, 83 (6.3%) due to AEs (31 [2.3%] due to treatment-related AEs). Twenty-eight cases of diabetes have been reported as AEs (24 in combined GHD patients; 27 in adulthood-onset GHD); 14 cases were SAEs, of which 3 were suspected to be treatment-related. These three cases included: diabetes in a 29-year-old male with childhood-onset combined GHD, following ~11 years' GH therapy, in whom Omnitrope® treatment was not changed; diabetes mellitus aggravation in a 45-year-old male with adulthood-onset combined GHD, following 4–6 months' GH therapy, in whom treatment was discontinued; and worsening of diabetes in a 72-year-old male with adulthood-onset combined GHD, following 19 years' GH therapy, in whom treatment was interrupted.
Conclusions
This interim analysis indicates that Omnitrope® is well tolerated in routine clinical practice, including among those previously receiving GH. The ongoing PATRO Adults study will provide further insights into the overall safety and diabetogenic potential of long-term GH.

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P269

Diabetes insipidus and diabetes mellitus type 2 diagnosed at the same time in a male with langerhans cell histiocytosis

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Introduction
Langerhans cell histiocytosis (LCH) is a rare systemic disease. Diabetes insipidus is the most frequent endocrine alteration and occurs mostly after diagnosis. Others are hypogonadism, growth hormone deficiency (GHD) and alterations in glucose metabolism.
Clinical case
A 61-year-old smoker, diagnosed with LCH 9 years ago with pulmonary and hepatic involvement, without treatment, who consulted for asthenia, unquantifiable polyuria, polydipsia and 3 kg of weight loss over a period of 2 weeks. The physical examination showed blood pressure of 128/81 mmHg and dry mucus membranes. The blood test showed hypernatremia, hyperchloraemia, hyperglycemia and elevated glycosylated hemoglobin (HbA1c). It was oriented as type 2 diabetes mellitus (DM2) and treatment with metformin was initiated. The patient did not show improvement and because of the persistence of the same symptoms he went to the emergency department. The blood test showed hypernatremia with high osmolality, hyperglycemia, hypercalcemia and elevated HbA1c. The 24-hour urine test was 10 litres and had decreased osmolality and density. Given these findings, Diabetes insipidus was also diagnosed with DM2. A pituitary magnetic resonance was requested that revealed thickening of the pituitary stalk and absence of posterior pituitary bright spot in the T1 sequence. Treatment was started with sublingual desmopressin with normalization of serum sodium and diuresis. The pituitary hormones were normal, except for an elevation of cortisol and ACTH and a decreased vasopressin. Cortisol after 1 mg dexamethasone suppression test was normal. Positron emission tomography (PET) showed hypermetabolism only in the pituitary gland. The patient was discharged with sublingual desmopressin 60 mcg every 8 hours and metformin 850 mg every 12 hours.

Conclusions
- We have to consider the endocrinological alterations in patients diagnosed with LCH and their referral to Endocrinology consultations
- The importance of quantifying polyuria and assessing the coexistence of two types of diabetes in these patients, as in our case

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Assessment of endocrine function before and after transsphenoidal surgery for Cushing s disease

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It is known that disoaders of the hypothalamic-pituitary-adrenal system and excess glucocorticoids in Cushing's disease (CD) can significantly affect various organs and systems, in particular, the secretion of pituitary hormones. However, in the literature there is practically no work on the assessment of the state of tropic hormones and hormones of the peripheral glands in the early postoperative period after transsphenoidal adenomectomy. The aim of this study was to assess the effect of transsphenoidal adenomectomy on the state of pituitary function before and in the early postoperative period in patients with Cushing's disease. The our study included 434 patients with active stage of Cushing's disease {374 women (age 38.0 (23–55) years) and 60 men (age 32 (19–51) years}. The duration of the observation from 2001 to 2017. The state of pituitary function was analyzed in patients with CD before and directly in the early postoperative period (average follow-up period from 4 to 14 days) on the basis of hormonal parameters in peripheral blood in the morning (GH, prolactin, TTH, fr T_4, LH, FSH, estradiol, testosterone). The content of ACTH and cortisol in the blood was determined two times a day: in the morning and in the evening, and the average daily content of these hormones was calculated. In addition, to confirm the diagnosis of CD, a study of free cortisol levels in saliva (in the evening) and daily urine was conducted. It was shown that the number of patients with simultaneous reduction of all tropic hormones was minimal – only 22 (4.7%). Different combinations of hormone reduction were found in other patients. The most common decrease in blood levels of prolactin (66.2%) and TSH (53.0%). The most rare decrease in gonadotropins: LH-36.7% and FSH – (21.2%). This mosaic in the lower level of tropic hormones, which may be explained by the fact that often the cells of the pituitary tumors have a mixed activity, and most often in conjunction with an ACTH produce prolactin. Thus, the rehabilitation of patients with CD after transnasal adenomectomy is a complex multicomponent process characterized by a complex approach to therapy and requires regular monitoring of all the tropic functions of the pituitary gland.

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Diverticular perforation of colon: a dangerous complication in Cushing's disease

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Exposure to supraphysiologic doses of exogenous glucocorticoids is associated with gastrointestinal (GI) complications such as peptic ulcer disease, gastrointestinal hemorrhage, duodenal ulcer, and colonic diverticular perforation (DP). Patients receiving high dose glucocorticoids, for rheumatological or autoimmune disease are at increased risk for lower gastrointestinal tract abscesses and perforation. However, little is known about GI complications in endogenous hypercortisolism caused by Cushing syndrome (CS). Here we present a case with Cushing Disease (CD) who developed sudden diverticular perforation (DP) that necessitated surgical intervention. 29 years old female patient was first admitted to outpatient clinic with symptoms of weight gain, edema, weakness, easy bruising, wide purplish stria, hirsutism and skin atrophy. There was history of refractory hypertension, diabetes mellitus,heart failure, asthma bronchiale and menstrual irregularity. She was married and had two children. On presentation the patient had a blood pressure of 190/95 mmHg and a potassium level of 2.6 meq/L. Her physical exam was significant for a moon and plethoric face, dorsocervical fat pad, abdominal obesity and skin thinning with several large areas of ecchymosis. Biochemical evaluation confirmed severe hypercortisolism: Cortisole: 25.13 µg/dl, 1 mg dexamethason suppression test (DST): 24.9 µg/dl, 2 day 2 mg DST: 19 µg/dl, ACTH- 210 pg/ml, 24-hour urinary free cortisol (UFC) 690 mg, diurnal rhythm was disturbed midnight 0300 h cortisole: 20 µg/dl. MRI of the pituitary showed an area of 5 mm in the left lobe of the pituitary that had decreased uptake of contrast on early dynamic screening. Transphenoidal hypophysectomy was performed and ACTH secreting adenoma (Kİ67: <%1) was found on pathological examination. While she was being followed with symptoms due to diabetes insipidus and hypokalemia, 15 days following surgery, the patient also developed symptoms of abdominal pain and vomiting. Laparotomy revealed an intra-abdominal abscess and extensive colonic diverticulitis with evidence of perforation at the ascending colon. Right hemicolectomy with colostomy was performed and pathological specimen revealed diverticular disease complicated with supurative inflammation, diverticulitis, multiple intraabdominal abscesses. This case illustrates the potential for fulminant diverticular disease complications in patients with Cushing's disease. Multiple elements contribute to the increased risk of diverticular perforation in association with hypercortisolism. Surgeons and endocrinologists should be aware of this potentially fatal complication when caring for patients with Cushing's disease. When treating such patients, this risk should be eliminated through management of malnutrition, uremia, hypokalemia, constipation, early detection and aggressive management of diverticulitis and DP.

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A retrospective study of 275 cases of pituitary intervention in south great plain region of Hungary

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Objective
Tumors of the pituitary gland and sellar region, called pitiutary adenoma (PA) represent approximatly 10% of all central nervous system tumors. The characteristics of these tumors may vary from population to population.
Aim
The aim of this retrospective study was to investigate and understand the clinicopathological characteristics, the invasiveness, tumor features and clinical symptoms of PA in adult patients at south great plain region of Hungary.
Design and methods
Totally, 275 patients were retrospectively reviewed from 2007 to 2017. At 171 cases the pathological diagnosis was pituitary adenoma. Patients were periodically followed up at the Department of Neurosurgery and 1st Department of Medicine, University of Szeged, Clinical Center. Data of general information, clinical symptoms, invasive behaviors, surgery approaches, adenoma type by immunhistochemistry and adenoma relapses were collected and analyzed. All patients underwent transsphenoidal approach: total of 83 (48.53%) males and 87 females (50.87%) were diagnosed as pituitary adenoma with the mean age of 52.1 and 53.7 years, respectively. The main clinical manifestations were visual defects, headache and hormonal abnormalities such as increased growth hormone (GH), prolactin (PRL) and adrenocorticotropic hormone (ACTH), respectively. Among the patients with firm adenomas 21.63% had hypopituitarism.
Results
Based on the WHO 201 classification of pituitary adenomas, the types of adenoma in the investigated region were the following: 53% non-functioning null cell adenoma. Among the hormonally active adenomas 22% was somatotroph, 9-9% lactotroph and plurihormonal and 7% corticotroph. Interestingly, the adenoma recurrence was observed not in null cell adenomas; 41.6% relapse was detected in ACTH producing type.
Conclusion
Detailed clinical, hormonal and pathological evaluation is essential for better understanding the nature of adenoma growth and its progression. This study is the first at this region which overview the PA from endocrinological, neurosurgical and pathological aspects together. Specialized care and teamwork of endocrinologists, neurosurgeons, pathologists are equally important during treatment planning.

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P273

Differences of efficiency of treatment of isolated growth hormone deficiency and panhypopituitarism in children in real clinical practice

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Introduction
Deficiency of growth hormone (GH) in children is manifested by pronounced stunting (below −2 sigmal abnormalities (SD)), different changes in body composition. Frequency of occurrence varies from 1:4000 to 1:10000 newborns.
Objective
To assess the effectiveness of treatment by comparing the dynamics of growth of those with isolated growth hormone deficiency (IGHD) and of those with panhypopituitarism (PHP).
Materials and methods
Medical History of 47 patients aged from 3 to 18 years diagnosed with IGHD and PHP in 2006–2018 have been analyzed in the Republican Center for Pediatric Endocrinology. Microsoft Excel, SPSS have been used for statistical data analysis.
Findings
Among 47 patients participating in the study (66% girls, 34% boys) eighty-three per cent (83%) is with IGHD and seventeen per cent (17%) with PHP. It was revealed that before treatment, 36 patients had a significantly short stature (from –6 to –2.01 SDS); SDS of 11 patients (2 of them with PHP) was from −1.9 to −1. At the time of diagnosis, the mean height SDS was −2.4 in children with IGHD, after completion of treatment, SDS was −1,4; height SDS was −2.7 before treatment and −0.8 after completion of treatment in children with PHP. The largest values of STH maximum level according to stimulation tests was 6.8 ± 5.2 ng/ml in group with IGHD and 2.56 ± 1.65 ng/ml in group with PHP ($P < 0.05$). IGF-1 was below normal range in 76.6%, after treatment it was below normal range in 46.68% of patients; the IGF-1 level in the group with PHP was lower compared to the IGHD group ($P < 0.05$) and were observed in 87.5%. After treatment completion, IGF-1 remained below reference values in 87.5% of patients with PHP. A lagging of the bone age from the passport in the IGHD group before treatment was 2 years 5 months ±1 year 3 months, after treatment it was 2 years 5 months ±2 years; in the group with PHP it was 2 years 11 months ±1 year 4 months before treatment and 3 year 7 months ±4 year 7 months after treatment ($P < 0.05$). The average dynamics of growth during the entire period of treatment in patients with IGHD is 6.9 ± 1.62 cm/year, while in patients with PHP it is 7.9 ± 4.3 cm/year ($P < 0.05$).
Conclusion
Comparative analysis of the effectiveness of growth hormone treatment showed a significant dynamics of growth, more obvious in patients with panhypopituitarism.

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Functioning gonadotroph adenoma in a 46 years old male

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Introduction
Functioning gonadotroph adenomas (FGA) are adenomas secreting and expressing biologically active gonadotropins and causing distinct clinical manifestations. The vast majority of the immunohistochemically confirmed gonadotroph adenomas are hormonally silent (presenting only with mass effects), clinically FGA's being very rare; whereas their exact prevalence is not known.
Case study
A 46 years old male patient presents to our clinic after being diagnosed with pituitary macroadenoma on MRI scan. The scan was made for elucidating the cause of cluster type of headache, symptom that appeared 4 years prior to the investigation. The contrast MRI scan showed a 37/34/24 mm expansive mass located intra-, supra-, and infrasellar, going in the sphenoidal sinus. General examination revealed symptoms like headache and increased libido, while the signs showed right facial muscle spasm and macro-orchidism (approx. 45 ml). Blood test showed polyglobulia (RBC = $6.70*10^6$/µl, Hb = 17.9 g/dl, Hct = 55.6%) and increased levels of FSH (145.4 mIU/ml), LH (23.2 mIU/ml), Testosterone (>1500 ng/dl), Estradiol (152.8 pg/ml). We recommended surgical intervention for the macroadenoma. Histopathology slides made by hematoxylin and eosin staining revealed a proliferation of cuboidal-columnar and oval cell with a fine chromatin nucleus, eosinophilic cytoplasm, arranged in a trabecular, papillary and perivascular pattern, with the reticulin network disorganized at tumoral level. Immunohistochemical testing found positive result for chromogranin A, FSH and LH with a Ki 67 of 4%. The patient presented 3 months after surgery for postoperative evaluation. On the follow up contrast MRI scan no tumoral rest was detected, the head ache was gone but the facial muscle spasm remained. The patient accused a lack of libido and a decrease in testicular size (in present approx. 30 ml). The CBC returned to normal, the FSH dropped to 1.6 mIU/ml, LH to 1.12 mIU/ml, Testosterone to 23.05 ng/dl and Estradiol to 5 pg/ml. After a Diphereline 0.1 mg (triptorelin) stimulation test FSH and LH levels remained the same at 4- and 24-hour testing. We started testosterone replacement therapy.
Conclusion
This is a rare case of functioning gonadotroph adenoma treated surgically. The 46 years old patient is now suffering gonadotropin insufficiency for which he receives testosterone replacement therapy.

Keywords: functioning gonadotroph adenomas, testosterone
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Acromegaly: ominous cause of hirsutism

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Hirsutism though common in women of reproductive age, is classically associated with polycystic ovarian syndrome (PCOS). It is rarely seen as a prominent feature of acromegaly because of its lack of specificity and occurrence. We report a case of 28-year-old female with 3 year duration of aligoamenorrhea and hirsutism. She was followed by a gynecologist who retains the diagnosis of polycystic ovary syndrome (PCOS). After 5 years the patient complaints of increased hand finger and shoes size. She was referred to endocrine department for suspicion of Acromegaly. Clinical examination revealed acromegaloidism features with mandibular prognathism and moderate macroglossia wic. Biological investigation were significant for elevated insulin-like growth factor 1 (IGF-1) level (774 ng/ml normal: 98–290 ng/ml) and a growth hormone level not suppressed by a glucose challenge test. MRI brain revealed a pituitary macroadenoma (10.7× 14 mm). The patient underwent an uncomplicated trans-sphenoidal resection of a pituitary macroadenoma. Immunohistochemistry demonstrated a GH tumor. The patient subsequently had normalization of growth hormone dynamics and regular menstrual cycles. Our case highlights the importance of a lookout for subtle features of acromegaly in patients with hirsuitism and going for hormonal investigation to make the diagnosis of acromegaly at an earlier stage of the disease.

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Pituitary apoplexy: clinical features, management and outcomes

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Background
Pituitary apoplexy is a rare clinical syndrome due to abrupt hemorrhaging and/or infarction of the pituitary gland, generally within a pituitary adenoma. The outcome of acute apoplexy is variable and difficult to predict. This explains why the optimal management of acute pituitary apoplexy remains controversial. The aim of our study was to investigate the clinical, hormonal and radiological characteristics of pituitary apoplexy and to determine treatment outcomes.
Methods
We performed a retrospective study of pituitary apoplexy managed at the department of endocrinology, National Institute of Nutrition over a 23-year.
Results
A series of 33 patients with a clinical diagnosis of pituitary apoplexy was reviewed. It included 16 men and 17 women aged between 21 to 73 years (mean age: 42 years). A pituitary adenoma was unknown at the time of apoplexy in twenty-eight patients. Pituitary apoplexy occurred in macroadenoma in all the cases. It was observed most frequently in non functioning adenoma,

A precipitating factor was identified in ten cases. Tumor syndrome with headache of sudden was the main complaint: 81.9%, associated with decreased of visual acuity in 57.7% of cases, visual-field impairment with bitemporal hemianopsia in 18.2%. Corticotropic deficiency which is the life threatening complication was noted in 11 patients. Thyrotropic deficiency was the most common endocrine deficiency in our work (36.4%). The diagnosis of pituitary apoplexy has been confirmed by cerebral computed tomography in 6 cases and magnetic resonance imaging in 27 cases. Surgery was indicated in 61% of cases and 39% of patients received conservative medical treatment. The outcomes in terms of visual disturbances were a resolution in 86% after conservative treatment, against 100% improvement after surgery. After conservative treatment, 39% of patients normalized their pituitary function versus 65% in the group that received surgical treatment, but one patient developed diabetes insipidus and 4 patients maintained hypopituitarism with a permanent corticotropic deficiency. Three patients had tumor recurrence after surgery.

Conclusion

Pituitary apoplexy can be difficult to diagnose. It is usually related to a pituitary unknown macroadenoma. A high index of clinical suspicion is essential to diagnose this condition as prompt management may be life and vision saving. It is always used to be treated surgically; nowadays conservative management can be used in selected patients.

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P277

Gross total versus incomplete resection of craniopharyngioma in adults

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Background

Craniopharyngioma is a rare epithelial tumor of the central nervous system, affecting both children and adults and associated with significant morbidity.

Objective

To study the postsurgical evolution of craniopharyngioma in adults after total or incomplete surgical resection.

Material and methods

We performed a retrospective review of craniopharyngioma patients evaluated in the National Institute of Endocrinology in Bucharest between 1998 and 2018.

Results

A total of 60 patients (39.62 ± 15.6 years-old) diagnosed with craniopharyngioma were included. All underwent initial surgery (68.3% transcranial, 31.7% transsphenoidal approach). Gross total resection (GTR) was achieved in 21 cases (35%), in all the others maximal resection was attempted (non-GTR). Surgery led to anosmia (in 2 cases), CSF leak (3 cases), subdural hematoma (2 cases). After surgery 13 cases (21.66%) had cognitive impairment (2 with GTR, 11 with non-GTR), 14 (23.3%) had hypothalamic syndrome (diurnal sleepiness, appetite and memory dysfunction- present in 1 case with GTR, 13 with non-GTR), 27 cases (45%) reported lethargy (7 GTR, 20 non-GTR), 24 (40%) complained of headaches (6 GTR, 18 nonGTR). All these complications were significantly more frequent in cases with incomplete tumor resection compared to those with GTR: $P = 0.000$; 0.000; 0.036 and 0.009, respectively.

Conclusions

Craniopharyngioma is a tumor associated with very significant morbidity. GTR should only be attempted when a low risk of neurologic injury is considered; for the rest of the cases limited tumor resection followed by irradiation of the remnant might be the safest approach.

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P278

When a rare syndrome keeps behaving in rarer manners over and over again!

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Pituitary apoplexy arises when haemorrhage and/or infarction occurs within a pituitary tumour. In Malta, the estimated standardised incidence rate (SIR) of apoplexy is 0.15/100,000/yr. ACTH secreting pituitary adenomas have a SIR of 0.17/100,000/year.

Case Report

A 46 year-old gentleman with a history of poorly controlled diabetes mellitus was referred following the diagnosis of a pituitary adenoma. He had presented with a 1.5 year history of left third cranial neuropathy with complete ptosis. Magnetic resonance imaging (MRI) showed a 3.2×1.5 cm lesion extending into the suprasellar cistern, abutting the optic chiasm and extending into the cavernous sinuses, more pronounced on the left side. Biochemical assessment revealed cortisol of 483 nmol/l, prolactin 31 mIU/l, Testosterone 3.5 nmol/l, LH 1.9 U/l, FSH 4.5 U/l, TSH 2.34 micIU/l and T4 12.27 pmol/l. The patient had an inadequately suppressed cortisol level (149 mmol/l) on a 48-hour low dose dexamethasone suppression test and a high ACTH (102 pg/ml) in keeping with ACTH-dependent Cushing's syndrome. The patient was referred for infra-petrosal sinus sampling, which confirmed an ACTH secreting pituitary macroadenoma. The patient could not undergo surgery at the time in view of an infected diabetic foot ulcer. He was initiated on Metyrapone in an effort to control his hypercortisolaemia. The patient presented two months later with severe headache and new onset visual disturbances. He developed a right III and VI cranial nerve (CN) palsies. Ophthalmological assessment revealed a reduction in visual acuity. Areas of hyperintensity in the pituitary adenoma were noted on unenhanced T1 MRI scan and there was lack of enhancement on a contrast scan, in keeping with apoplexy. Urgent debulking was carried out through a trans-sphenoidal approach. Clinical symptoms and visual disturbances showed improvement post-operatively; the right 3rd and 6th CN palsies improved but he had a persistent right temporal visual field defect. Histology confirmed pituitary apoplexy due to tumour infarction of a functional (ACTH secreting) pituitary macroadenoma.

Conclusion

Presentation of Cushing's Disease can be very varied and the work up is extensive and elaborate with a number of different steps. Cushing's syndrome is associated with multiple comorbidities including increased risk of cardiovascular events, neurological consequences osteoporosis and poor quality of life. Hence, it is imperative that an early diagnosis is made as early as possible so that the condition is appropriately treated. Although apoplexy is rare, this complication needs to be kept in mind as an inherent risk when managing patients with pituitary adenomas.

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Ipilumumab induced hypophysitis

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Introduction

Immunotherapy has advanced significantly over the past years. Immune-related adverse events (IRAEs) are various and include endocrinological complications such as Ipilimumab-induced hypophysitis (IIH). The incidence of this cytotoxic T-lymphocyte antigen 4 antibody ranges from 0 to 17%. Patients usually present with symptoms secondary to hormonal insufficiencies.

Case report

A 73 year-old lady, known case of metastatic melanoma on immunotherapy presented with a 1 week history of pre-syncopal episodes and nausea. She gave a few week history of non-vertiginous dizziness, lethargy and headache. The patient had received her third course of ipilimumab few days prior to presentation. Cortisol level during admission was 23 nmol/l, from a previously normal level of 993 nmol/l few weeks prior. The patient had low T4 and TSH levels (0.080 mIU/ml and 6.7 pmol/l respectively) together with low FSH (2.4 U/l), LH (0.6 U/l) and prolactin levels (59 mIU/l) in keeping with panhypopituitarism. The patient was started on glucocorticoids and thyroxine with rapid improvement of her symptoms.

Imaging

MRI brain at presentation showed a $1.5 \times 1.4 \times 1.2$ cm sellar lesion involving the pituitary gland with mild suprasellar extension. The lesion demonstrated low T1 and mildly hyperintense T2 signal intensity and enhanced avidly following contrast administration, with a central non-enhancing component. The infundibulum was thickened. Repeat MRI after 3 months revealed complete resolution of the sellar and infundibular changes with normalization of the gland confirming the initial hypothesis of hypophysitis.

Discussion

Literature suggests that a high index of suspicion for hypophysitis needs to be kept in mind in patients receiving immunotherapy. It is advised that patients undergo 6 monthly assessment of pituitary function and MR scans should be compared to previous imaging if available to assess for a change in pituitary size. In hypophysitis, the degree of pituitary enlargement should reduce after treatment as was in our case. If this is not observed, alternative diagnoses such as pituitary metastasis should be considered. It is debatable whether patients with IIH should

be administered higher dosages of glucocorticoids in contrast to physiological replacement, since there are concerns that treatment with high dosages of glucocorticoids may affect the antitumor efficacy of Ipilimumab. In our patient, a physiological replacement dose was sufficient for her to improve clinically and have complete resolution of symptoms after 3 months.
Conclusion
Development of IIH can precipitate acute adrenal failure or crisis. Early diagnosis and management are vital to prevent complications including increased morbidity and mortality rates.

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P280

Acute lethargy, the main symptom of macroprolactinoma

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Introduction
The most common pituitary adenoma is a prolactinoma.The most relevant clinical manifestations are amenorrhoea galactorrhoea infertility *gonadal and sexual dysfunction*. Macroprolactinoma are more often in men because they had more difficulty for asking the sintomatology. Initial treatment of macroadenoma wasinitiated with a dopamine agonist with control of PRL concentration and size of tumor
Clinical case
A 52-year-old manpresented at the emergency roomby acute lethargy. He has acongenital blindness, deafness and chronic depression with history of suicide attempt in three times. He had only taken lorazepam. He didn't complain ofdecreased libido, impotence, or infertility.On examination, he had blilater-alasymptomatic ginecomastia. There were no other stigmata of endocrine dysfunction. Pituitary MRI found a pituitary macroadenoma ($27 \times 17 \times 15$ mm) and laboratory evaluations showedhyperprolactinemia(PRL 1998 ng/ml) and central hypogonadism, adrenal insufficiency. The patient was prescribed the dopamine agonist cabergoline (0.5 mg twice a week) hydroaltesone 30 mg. After 4 months of treatment, PRL level decreased to 47.17 ng/ml, normalitation of testosterone and tumor size wasn't suffer any change. After a year of treatment PRL concentration was normal (8.20 ng/ml) and tumor size has been reduced by one third ($10 \times 6 \times 5$ mm)
Conclusion
Our clinical case is an atypical manifestation of pituitary adenoma. The treatment with dopamine agonist allowed restore only gonadal funtion and control size of tumor.

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P281

Pituitary apoplexy: which treatment?

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Introduction
Pituitary apoplexy (PA) is a syndrome caused by acute hemorrhage or infarction of the pituitary gland, generally within a pituitary adenoma. Early diagnosis of PA and a multidisciplinary approach are essential for the timely treatment of pan-hypopituitarism and prevention of severe neurologic complications.
Observation
We report the cases of two men aged 46 and 53 years old with pituitary apoplexy. Apoplexy occurred in one patient with pre-existing pituitary macroadenoma and as a presenting form in the second case. Unilateral ptosis with severe visual acuity loss was the main clinical symptom in one patient and without visual acuity loss in the second one. Hypothalamic-pituitary MRI showed a macro-adenoma with hemorrhagic remodelling in one case and heterogeneous intrasellar processes in T1- and T2-weighted images. Necroticohaemorrhagic areas were observed in the second patient. Surgical treatment was proposed for both patients, after a multidisciplinary meeting. Only one patient underwent transsphenoidal surgery while conservative treatment was the therapeutic option chosen by the second one. The hormonal evaluation revealed an anterior pituitary insufficiency in both cases leading to an appropriate hydrocortisone and levothyroxin substitution.
Conclusion
The treatment of pituitary apoplexy remains controversial. Therefore, its management inside a pituitary referral center should be the rule. But the main issue remains about choosing the best therapeutic option: either surgery or conservative treatment.

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P282

Cushing disease: Clinical presentation

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Objective
Cushing's disease (CD) accounts for approximately 80% of cases of Cushing's syndrome. Its clinic is nonspecific and its diagnosis difficult. The objective of this study is to review the most frequent clinical signs of this disease in our environment and compare it with that described in the literature.
Patients and methods
Retrospective descriptive study of patients with CD. We included all patients diagnosed with CD (2005–2017) treated with transsphenoidal surgery, and whose tumor sample was analyzed in the Department of Cell Biology, Physiology and Immunology of the University From Córdoba. Variables analyzed: age, sex, body mass index (BMI), reason for consultation, clinical presentation and time to diagnosis. The data obtained were compared with those described in the literature. Statistical analysis (SPSS v.18.0 for Windows): t-student for comparison of means and McNemar for comparison of proportions.
Results
Thirty-seven patients with CD. Age 45.03 ± 13.13 years. Women: 94.6% %. Cyclic EC: 10.8%. Time to diagnosis: 40.96 ± 31.91 months. Most frequent reason for consultation: suspected cushing syndrome (24.3%), obesity and overweight (24.3%) and type 2 diabetes (DM-2). BMI: 32.91 ± 7.06 kg/m^2. Clinical presentation: central obesity 90.9%, asthenia 93.1% ($P=0.001$), menstrual disorders 46.2% ($P=0.000$), face of a full moon 93.5%, cutaneous atrophy 85%, cervical lipomatosis 89.3%, muscular atrophy 84.6%, fragile capillary 56.3%, hirsutism 83.3%, raclavicular fat 87.5%, stretch marks 57.1%, acne 63.6% and edema 46.2%. Comorbidities: arterial hypertension 62.2%, osteoporosis 50% (8.3% atypical fracture), dyslipidemia 37.8%, DM-2 43.2% ($P=0.02$), depression 34.6%, infections 8.3% ($P=0.03$), gastric ulcus 14% and stroke 2.7%.
Conclusions
CD is more frequent in women, predominating in the fourth decade. Clinic present in our series is very similar to that described in the literature. Only significant differences were seen with the published series on the appearance of menstrual disorders, diabetes mellitus and infections, which is higher in the literature. The presence of asthenia is greater in our series.

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The Importance of AGR2 Expression in Pituitary Adenoma Tissue Specimens on Tumor Aggressivity

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Purpose
Tumor-associated protein called as anterior gradient 2 (AGR2), which is defined particularly in breast and lung carcinomas, is involved in a variety of cellular functions such as cell migration, differentiation and proliferation. Since the role of AGR2 expression in pituitary adenomas is not well known yet, it was aimed to compare AGR2 expression in normal pituitary tissue and pituitary adenoma specimens in the study.
Material and Method
We included 44 patients' pituitary adenoma specimens (20 female/24 male) who underwent pituitary surgery at the neurosurgery clinic between 2015 and 2017 years and 10 patients' normal pituitary tissues (5 female/5 male) operated for any reason were included as control group. Examples were stored frozen at $-80°C$

until the study. After RNA isolation from adenomas or pituitary tissue specimens, AGR2 gene expression was evaluated by Livak method using real-time PCR method. The results were calculated as multiples of '1' by making calculations according to the control group, and AGR2 expression >1 was considered to be significantly higher than the control group. Those with AGR2 expression <1 and >1 were compared with possible related parameters. Invasiveness of adenomas is described to Hardy classification and Knosp scale.
Results
The mean age at diagnosis was 47 ± 15 (range 20–71) years, the mean maximum tumor diameter was 28 ± 16 (range 4–75) cm. The distribution of adenomas with AGR2 expression >1; 80% (4 of 5) in ACTH secreting adenomas, 93% (13 of 14) in GH secreting adenomas, 77% (2 of 3) in PRL secreting adenomas, 71% (10 of 14) in LH / FSH secreting adenomas, 0% (0 of 1) TSH was in secreting adenomas and 71% (5 of 7) in nonsecretory adenomas ($P>0.05$). The maximum tumor size was larger ($P=0.043$), and the tumors were more invasive ($P=0.01$), the tumors had higher Ki-67 labelling index ($P=0.05$) and in AGR2<1 group when compared with AGR >1. In addition, there was a negative correlation between AGR2 expression levels and Ki-67 labelling index ($r=-0.328$, $P=0.029$).
Conclusion
The results revealed that pituitary adenomas with weak AGR2 expression present with more aggressive behaviour. However, more adenoma tissue specimens are needed to evaluate the relation with hormonal secretion pattern and effects on clinical long term course.

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P284

The assessment of octreotide suppression test, ihc- and mr-structure, mr-signal of gh-producing pituitary adenoma for determining the prognosis of disease and management.

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Introduction
A growth hormone-secreting pituitary adenoma (GH-PA) increases the risk of complications and death. It's management is determined by MRI data and decrease of insulin-like growth factor-1 (IGF-1) during the octreotide suppression test (OST). Currently, there is evidence that MRI-T2-hypointensive somatotropinoma and high expression of somatostatin receptors type 2 (SSTR2) according to immunohistochemical analysis (IHC) predict high efficacy of somatostatin analogues (SSA).
Objective
To study the relationship of the MR-structure, MR-signal intensity, the SSTR1-5, p53 and Ki-67 expression with the sensitivity of GH-PA to octreotide to assess their predictive value.
Materials and methods
This retrospective study included 34 patients. 15 MRI of pituitary gland, 19 IHC, 29 OST were performed. The average values of the signal intensities of the somatotropinomas areas of 2–3 adjacent sections on T2-, pre-contrast T1- (preT1) MRI images relative to white and gray matter were calculated. 17 patients received SSA during the last 3 months. Correlation analysis was performed in the STATISTICA 12 program.
Results
High sensitivity to octreotide is associated with a lower average intensity of T2-hypointense plots of adenomas relative to gray matter ($r=-0.9$) and greater intensities of preT1-hypointensive (relative to gray matter) and preT1-isointensive (relative to white matter) – $r=0.9$ each. However, the combination of preT1-hyperintense plots with preT1-hypointense or T2-iso-intensive zones correlates with reduced suppression of IGF-1 ($r=-0.88$ and -0.79 respectively). Presence of T2-isointensive and preT1-hypo- and preT1-isointensive plots correlates with a higher concentration of GH before OST ($r\geq0.83$ each), which is a predictor of lower sensitivity to octreotide. High intensity of T2-hyperintense plots relative to gray matter is associated with higher SSA doses ($r=0.89$), including the simultaneous presence of the T2-hypointensive area ($r=0.52$). The expression of SSTR2 positively correlates with suppression of IGF-1 after OST ($r=0.56$). The presence of SSTR2 was strongly associated with lower doses of SSA ($r=-0.91$). When comparing participants with suppression of IGF-1$<30\%$ and 30–60%, the latter had higher SSTR2 levels (1.82 ± 1.1 vs 3.00 ± 0.00). p53 expression implies less suppression of IGF-1 ($r=-0.57$) and higher SSA doses ($r=0.77$). Ki-67 has a positive correlation with prolactin level ($r=0.83$). All results are significant ($P<0.05$).
Conclusion
Hypointense adenoma on T2-weighted images and high concentration of SSTR2 are positive predictors of response to SSA therapy. T2-iso- and T2-hyperintensive, as well as preT1-hypo- and preT1-isointensive sites of adenomas suggest the resistance to SSA. Further research is needed to study this results because of a small sample group of this work.

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Precocious puberty in girls in Qazvin, Iran from 2006–2018

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Background
This is associated with important physiological and psychobiological changes for the girl, the family and society. Decreasing the age of puberty has made it difficult to adapt to early sexual activity. Therefore, the diagnosis and management of precocious puberty must be specially considered to ensure the health of future generations. The appearance of secondary sexual characteristics in girls under the age of 8 is considered as precocious puberty (_2.5SD lower than the average age for normal puberty).
Objectives
Determine the prevalence of precocious puberty referred to pediatric endocrine clinic in Qazvin province of Iran from 2006 to 2018.
Materials and methods
In a descriptive epidemiological study, the cases of girls with precocious puberty referred to the endocrine clinic from April 2006 to June 2018 were investigated. Patient's information was extracted with using a questionnaire and then were analyzed using t-test and chi-2 tests, and SPSS 16 software.
Results
From 586 girls, 94.4% had central precocious puberty and 5.6% had peripheral precocious puberty. Among the patients with central precocious puberty, 98.4% had idiopathic form and 1.6% had organic causes of true precocious puberty. Of patients with peripheral precocious puberty 64.9, 13.5, 10.8, 8.1 and 2.7% had hypothyroidism, CAH, ovarian cyst, exogenous estrogen consumption and Mac Cun Albright disease respectively. The average age of onset of puberty was 7.1 years. Most patients were in Tanner stage II of breast development. 13.4% of patients were obese and 11.3% were SGA (birth weight<2500 gr). The relationship between BMI, birth weight, age of onset of puberty with the causes of puberty was not significant.
Conclusion
True precocious puberty was the most common cause of precocious puberty in girls. Hypothyroidism was the most common cause of peripheral precocious puberty in girls.

Keywords: precocious puberty, central precocious puberty, peripheral precocious puberty, girls

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Spinal Epidural Lipomatosis: A rare complication of Cushing's disease

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Background
Spinal Epidural Lipomatosis (SEL) is an excessive fat deposition in the spinal canal which can lead to compression of nervous structures. SEL is a rare but recognised side effect of exogenous steroid excess. There are only six previously reported cases of SEL associated with endogenous steroid excess in the available literature. We present a case of SEL, caused by Cushing's disease, that presented in the immediate post-operative period.
Case
A 17-year old man presented with increasing stretch marks for 1 year, two stone weight gain within 6 months, lower limb weakness, poor mobility, pedal oedema and loss in height. He had a history of bronchial asthma, which was well controlled with beclomethasone inhaler. On examination, he displayed typical Cushingnoid features such as facial plethora, widespread striae covering torso and limbs and proximal myopathy. He was obese and hypertensive. Investigation showed that he had hypokalemia, low testosterone and low gonadotrophins levels. His 24 hour urinary free cortisol was 4411 nmol/l, serum cortisol (overnight dexamethasone suppression test) 696 nmol/l and ACTH 146 ng/l, confirming he had ACTH dependent Cushing's disease. Initial MRI failed to reveal pituitary adenoma. He was then commenced on metyrapone and dexamethasone block and replacement therapy. Subsequent SPGR MRI confirmed 5 mm pituitary microadenoma. IPSS also confirmed that pituitary was the source of excess ACTH secretion. On day 1 post-transphenoidal surgery, he became paraplegic with increased tone, power 2/5 and reduced sensation from T2 level. MRI spine showed increased fat deposition in spinal canal from T2 to T9. A conservative approach for spinal epidural lipomatosis (SEL) was adopted. He was transferred to a rehabilitation facility and has gradually regained his mobility. This case illustrates a rare but serious complication of endogenous steroid excess and an additional cause of leg weakness in Cushing's patients.

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Diagnostic tests in Cushing's disease

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Objective
Cushing's disease (CD) accounts for approximately 80% of cases of Cushing's syndrome. Diagnosis of CD is difficult, it is carried out with a screening test and confirmation test. The aim of this study is to describe the diagnostic results of the different diagnostic tests used in the diagnosis of CD in our environment.
Patients and methods
Retrospective descriptive study of patients with CD. We included all patients diagnosed with CD (2005–2017) treated with transsphenoidal surgery, and whose tumor sample was analyzed in the Department of Cell Biology, Physiology and Immunology of the University From Córdoba. Variables analyzed: age, sex, basal cortisol level, 24-hour urinary cortisol level, midnight plasma cortisol level, midnight salivary cortisol level, low-dose dexamethasone (DST), ACTH level, high-dose DST, MRI pituitary and cavernous sinus sampling with desmopressin stimulation.
Results
Thirty-seven patients with CD. Age 45.03±13.13 years. Women: 94.6%. Biochemical determinations at diagnosis are shown in the table. Patients presented pathological determination: 100% cortisol after 1 mg DST, 77.1% 24-hour urinary cortisol level, 100% nocturnal plasma cortisol, and 100% nocturnal salivary cortisol. Cortisol after DXT 2 mg was pathological in 95.8% and cortisol after DXT 8 mg in 95% of the cases. In all patients, MRI pituitary with contrast was performed, detecting 48.6% macroadenomas (*n*: 18), 43.2% microadenomas (*n*: 16) and 8.1% (*n*: 3) without findings. Size adenoma: 11.66±8.57 mm (me ± RIC: 8±11 mm). Cavernous sinus sampling with desmopressin stimulation was performed in 13 patients (35.1%), indicated when no lesion was detected in the pituitary test or it was less than 6 mm, in all of them ACTH gradient confirmed the diagnosis of CD.
Conclusions
Cortisol after 1 mg DST, nocturnal plasma cortisol and nocturnal salivary cortisol were pathological in all patients. MRI pituitary detected most ACTH-producing adenomas, almost half of the macroadenomas. Cavernous sinus sampling with desmopressin stimulation confirmed the diagnosis in all patients not diagnosed with MRI pituitary.

Diagnostic tests	Mean ± Standard deviation	Median ± Interquartile range
Basal cortisol (μg/dl)	24.27±11.99	22.10±8.13
Cortisol after 1 mg DST (μg/dl)	15.14±8.96	15.50±15.54
Midnight plasma cortisol (μg/dl)	21.54±18.79	15.40±8.69
Midnight salivary cortisol (μg/dl)	1.51±1.34	1.17±1.46
24-hour urinary cortisol (μg/24h)	350.48±334.66	300.00±236.60
Cortisol after 2 mg DST (μg/dl)	13.68±13.41	11.00±11.65
Cortisol after 8 mg DST (μg/dl)	8.80±10.90	4.20±5.7
ACTH (pg/ml)	86.76±60.34	80.00±58.00

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Efficacy and safety of dopamine agonists in psychiatric patients treated with antipsychotics and presenting a macroprolactinoma

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Dopamine agonists (DAs), used as first line therapy in patients with macroprolactinomas, and antipsychotics have opposite effects on dopamine receptors (D2R). In patients with severe psychiatric conditions treated with antipsychotics, the rare occurrence of a macroprolactinoma, particularly with optic chiasm compression, represents a therapeutic challenge. Indeed, on one hand, antipsychotics by their antagonistic effect on D2R, could decrease or even abolish the effects of DAs on prolactinomas; on the other hand, DAs could make antipsychotics ineffective and lead to psychiatric exacerbation. Our retrospective study aimed at evaluating the efficacy and psychiatric safety of DAs prescribed for the treatment of large macroprolactinomas in patients whose underlying psychiatric disorder necessitated antipsychotics. Endocrinological and psychiatric data on 18 patients were obtained from charts from 12 centers in France and Belgium. Results are expressed as median value (interquartile range). Each of the 18 patient received DAs. Nine had also pituitary surgery (most often because of insufficient tumoral response) and two had radiotherapy. The median decrease of PRL levels, under DA, was −94.7 (30.6) % for the 8 patients treated with DAs only [from an initial median level of 1247 (13012) ng/ml to a minimal level of 42 (244) ng/ml, $P=0.008$], −85.5 (16.5) % for the 7 patients treated before surgery [3850 (8831) ng/ml to 141 (1510) ng/ml, $P=0.03$] and −18 (62.75)% for the 6 patients treated after surgery [1664 ng/ml (1473) to 1215 ng/ml (3094), $P=0.56$]. The median decrease of prolactinoma largest diameter was −28 (23.5) % for patients only treated with DAs [from an initial median diameter of 27 (22.5) mm to 24 (11.75) mm after treatment; $P=0.02$] and it almost did not change in the patients who had surgery. Nevertheless, DA treatment allowed optic chiasm decompression in 82% of the patients. Five patients (28%) were admitted for psychiatric relapse while they were receiving DAs (but 3 of them had stopped their antipsychotic treatment at that time). Moreover, 89% of them had a history of one or more psychiatric admissions compared to 11% among those who did not have any relapse ($P=0.0034$). Even if DAs efficacy on PRL levels and tumoral volume in macroprolactinoma patients under antipsychotic drugs is less impressive than that observed usually, it may be considered as satisfactory for half of them, particularly in case of optic chiasm compression. Psychiatric symptoms exacerbation was unusual. DAs may therefore be used as antitumoral treatment of macroprolactinoma in patients receiving antipsychotics.

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Imaging features of children with growth hormone deficiency

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Introduction
Growth hormone deficiency (GHD) is a non-exceptional cause of short stature. Hormonal evaluation and hypothalamic-pituitary MRI are essential to establish the etiological diagnosis. The objective of our study is to assess the different pituitary lesions found in imaging in a group of children with GHD.
Patients and methods
This is a retrospective longitudinal study of 22 cases of GHD who underwent pituitary MRI examination collected in the Endocrinology-Diabetology Department of Mohammed VI University Hospital.
Results
The mean age at diagnosis was 10.9 years with a sex ratio (M/F) of 2.14. Mean height Z-score at time of diagnosis was −4.46 SD. The mean bone age (BA) at the time of diagnosis was 6.23 years. The delay of BA over the chronological age was of 5.37 years on average. The diagnosis of total GHD was found in 77.3% of patients and partial GHD in 22.7% of patients. The isolated deficiency was noted in 31.8% of cases and multiple deficiencies in 68.2% of cases. Magnetic resonance imaging of the hypothalamic-pituitary region was normal in 27.3% of cases. Pituitary stalk interruption was observed in 56.2% of patients, pituitary hypoplasia was observed in 18.8% of patients, an empty sella was observed in 12.5% of patients, and agenesis of anterior pituitary in 12.5% of patients.
Conclusion
The multiplanar capability of MR imaging plays an important role in the assessment of the hypothalamic-pituitary area and in determining the underlying cause of various pituitary disorders in GHD.

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The polyuria-polydipsia syndrome: clinical and etiological profiles

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Introduction
Polyuria-polydipsia syndrome is an uncommon problem in clinical practice defined by the combination of production of 'abnormally' large volumes of urine (>3 L/day in adults and 2 L/m^2 in children) with the persistent intake of abnormally large quantities of fluids. The purpose of this study is to detail the clinical and etiological profile of polyuria-polydipsia syndrome in the Endocrinology-Diabetology Department of Oujda's University Hospital.
Materials and Methods
A retrospective study including 10 patients with polyuria-polydipsia syndrome, excluding patients with diabetes mellitus, hypercalcemia or hypokalemia.
Results
The mean age was 22 years, with a male predominance. History of cranial trauma was noted in one patient, while another patient was treated for pleuro-pericardial tuberculosis. The endocranial syndrome was found in 3 cases and 2 cases had an associated short stature. The mean diuresis was 9.18 l/24h with a maximum of 25 l/24h. Water deprivation test was performed in 5 patients with an average duration of 5 hours. Hormonal testing revealed GH deficiency in 2 cases, thyrotrophin deficiency in 3 cases, corticotrophin deficiency in 2 cases and gonadotrophin deficiency in 2 cases. Magnetic resonance imaging of the hypothalamic-pituitary region was normal in 30% of patients and showed hypophysitis in 3 cases one of which was related to pituitary tuberculosis, germinoma in 1 case, prolactinoma in 1 case, and the posterior pituitary was not visible in 2 patients.
Conclusion
The polyuria-polydipsia syndrome diagnosis is challenging. The water deprivation test is the gold standard to differentiate between diabetes insipidus and primary polydipsia. Pituitary MRI is essential when central diabetes insipidus is suspected. Close clinical follow of idiopathic cases is mandatory to avoid diagnosis delay.

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P291

Syndromic growth retardation: etiological aspects

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Introduction
Growth retardation is a frequent reason for consultation in endocrinology, it is often isolated but it can integrate into a syndromic context. Its management requires a rigorous diagnostic procedure conducted in a specialized environment. The aim of our work is to analyze the epidemiological, clinical and etiological profile of RSP occurring in a syndromic setting.
Materials and methods
This is a retrospective study of 68 cases among 192 patients consulting for growth retardation, conducted in the Endocrinology Diabetology Department of the Mohammed VI university hospital center of Oujda in Morocco. The diagnostic procedure consisted of first-intention exploration followed by a stimulation test of GH secretion.
Results
Mean chronological age at diagnosis was 12.21 ± 6.49 years, sex ratio (W/M): 0.64. Birth weight was low in 25.4% of cases, neonatal suffering in 23.9%, parental consanguinity in 29.9%. The average admission size was – 4 ± 1.45 standard deviations. A dysmorphic syndrome was present in 85.1% of our patients. The etiological profile was dominated by stunting whose exploration has concluded that there is a GH-deficient integrated into a congenital malformation of the hypothalamic-pituitary axis in 26.9% (Pituitary Stalk Interruption with ectopic post-hypophysis in 55.5% of the cases, anterior pituitary atrophy in 44.4%, an empty sella turcica in 11.1% of cases), a constitutional bone disease in 10.4% (50% achondroplasia, 25% pycnodysostosis, 12.5% dyschondrostosis), Turner syndrome in 13.2%, Prader-willi syndrome in 5.9%, 3M syndrome in 4.4%, syndrome Noonan in 2 cases, DMC (Dyggve Melchiore-Clausen Dysplasia) in 2 brothers, Silver syndrome in 2 cases, Ellis VantCreveld syndrome in 1 case, Meier Gorlin syndrome in 1 case, Neurofibromatosis type 1 in 1 case, a statural delay with gonosomal anomaly in 3 cases (Trisomy 9p, partial Trisomie 8, chromosome 15 anomaly, a Robinow syndrome in 1 case, a suspicion of waardenburg syndrome, a suspicion in Gitelman syndrome in 1 case, and growth delays whose genetic diagnosis is not yet labeled in 14.7%.
Conclusion
The causes of growth retardation in a syndromic setting are multiple. An adapted diagnostic procedure helps to guide the diagnosis. Their management requires multidisciplinary expertise conducted in a specialized environment. Treatment with recombinant GH is initiated according to the indication.

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P292

GH deficiency and congenital malformation of the hypothalamic-pituitary axis: experience of the Endocrinology-diabetology Department of the Mohammed VI University Hospital Center of Oujda, Morocco

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Introduction
Growth hormone deficiency (GHD) associated with a congenital malformation of the hypothalamic-pituitary axis is rare. It can be isolated or part of a combined pituitary deficiency. The purpose of our work is to describe the clinical picture in which between GH deficiency in children.
Materials and methods
This is a retrospective study of 18 cases among 192 patients consulting for growth retardation, conducted in the Endocrinology Diabetology Department of the Mohammed VI university hospital center of Oujda in Morocco.
Results
Mean chronological age at the time of diagnosis was 12.07 ± 6.97 years, sex ratio (M/W): 2.6. Birth weight was low in 11.1% of cases, parental consanguinity in 22.2%. The reason for consultation was a growth retardation in all cases. The clinical examination objectified a severe growth retardation in 44.4% with a mean of – 4.2 SD, the mean weight was – 2.8 ± 1.33 SD. A dysmorphic syndrome was present in 77.8% of our patients. A micropenis in 38.4% of boys. A pubertal delay

was noted in 22.2% and diabetes insipidus in 2 patients. Biologically, an isolated deficit of GH was found in 38.8% and an hypopituitarism in 61.11%. The hypothalamic-pituitary MRI showed a pituitary stalk interruption with ectopic post-hypophysis in 55.5% of the cases, anterior pituitary atrophy in 33.3%, an empty sella turcica in 11.1%. The substitution of the corticotropic axis concerned 50% of the cases, and the thyreotropic axis 61.11%. The treatment by recombinant growth hormone concerned 88.9% with an initial dose of 0,035 mg/kg/day and the average statural gain was 0.82 ± 0.24 SD during the first year of treatment.

Discussion and conclusion

Neuroimaging has become a major diagnostic tool, which suggests that such investigation might precede hormonal investigation to confirm GHD[1]. The hormone abnormalities may evolve with time, necessitating frequent evaluation. The risk of progression from isolated GHD to combined PHD in children is highest displayed by children with abnormalities in the Hypothalamo-Pituitary region[2].

References

1. Pierre C *et al*. Growth Hormone & IGF Research 2001, 11, 137–165; doi:10.1054/ghir.2001.0203

2. Manuela Cerbone, Mehul T. Dattani; Progression from isolated growth hormone deficiency to combined pituitary hormone deficiency; doi:10.1016/j.ghir.2017.10.005

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P293

Long-term effects of GH replacement therapy on thyroid function in children with GH deficiency

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Background

Several studies have investigated the effects of GH replacement therapy (GHRT) on thyroid function in children with GH deficiency (GHD) leading to contrasting results. Indeed, GHRT has been reported to affect the peripheral metabolism of thyroid hormones, to alter TSH secretion by pituitary and to unmask secondary hypothyroidism.

Objective

To evaluate long-term effects of GHRT on thyroid function in a large cohort of GHD children.

Methods

Sixty-five children (40 M) aged 9.47 ± 3.73 years with isolated GHD were studied before and during the first three years of GHRT. Clinical parameters (height, weight, BMI and growth velocity) and serum TSH, FT4, FT3 and IGF-1 levels were evaluated at baseline, after 6 months of GHRT and then annually.

Results

At study entry, all GHD children were euthyroid and none became hypothyroid during the follow-up. Six months of GHRT were associated with reduction in FT4 levels ($P < 0.05$) and increase in FT3 levels ($P < 0.05$) even though they were still normal associated with no differences in TSH concentrations. No further modifications were observed in the following years of therapy (Table 1).

Table 1

	Baseline	6 months	1 year	2 years	3 years
Height (SDS)	−2.73 ± 0.82	−2.42 ± 0.73[a]	−2.18 ± 0.72	−1.77 ± 0.78	−1.52 ± 0.85
BMI (SDS)	−0.35 ± 1.21	−0.51 ± 1.20[a]	−0.44 ± 1.13	−0.45 ± 1.16	−0.32 ± 1.20
Growth velocity (SDS)	−2.57 ± 1.45	3.30 ± 2.63[a]	3.09 ± 3.16	2.65 ± 3.21	1.62 ± 2.81
FT4 (ng/dl)	1.20 ± 0.22	1.14 ± 0.20[a]	1.13 ± 0.22	1.14 ± 0.21	1.14 ± 0.21
FT3 (pg/ml)	3.79 ± 0.72	4.01 ± 0.69[a]	4.03 ± 0.71	3.97 ± 0.66	3.99 ± 0.69
FT4/FT3	0.32 ± 0.06	0.28 ± 0.04[a]	0.28 ± 0.04	0.29 ± 0.04	0.28 ± 0.04
TSH (mcU/ml)	2.67 ± 1.28	2.63 ± 1.48	2.71 ± 1.45	2.48 ± 1.15	2.55 ± 1.28
IGF-1 (SDS)	−0.99 ± 1.06	0.22 ± 1.45[a]	0.81 ± 1.69	0.93 ± 1.72	0.58 ± 1.34

[a] $P < 0.05$ vs Baseline

Conclusion

GH replacement treatment in GHD children was associated with a persistent decrease of FT4 concentrations which however remained within reference ranges. No effects on other markers of thyroid function were detected. Whether these mild changes may have a clinical impact should be further investigated with long-term studies.

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P294

Menstrual dysfunction (MD) with ACTH dependent Cushing syndrome

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MD are the most frequent complaint of women with Cushing Syndrome at the time of diagnosis.

Objective

To study the frequency of occurrence of MD in patients with Syndrome Cushing and to characterize their clinical and hormonal parallels. We investigated 34 women (average age of 27 years, variation in age from 18 to 30 years) with a newly identified ACTHA. The patients were divided into 4 groups: (1) the normal cycle is 26–31 days; (2) oligomenorrhea 32–120 days; (3) amenorrhea -more than 120 days, and (4) polymenorrhea- when the cycle was shortened to less than 26 days. The following hormonal studies were carried out: at 9:00 am on an empty stomach, blood was taken to determine the level of LH, FSN, PRL, test, androstenedione, DEAS, SSSG and ACTH. Cortisol blood was determined at 9:00; 18:00; and 24:00. Statistics processing of the results was performed by the package.

Results

Only 6 women (17.6%) had a normal cycle, 9- (26.5%) oligomenorrhea, 12- (35.3) amenorrhea and 7- (20.6%) polymenorrhea. Comparative analysis of clinical and hormonal parameters reveal is the following: in the group of patients with amenorrhea, there is a significant decrease in the level of estradiol 104 nmol/e compared with oligomenorrhea (217 ± 12 pool/l + 0.05) and patients with a normal menstrual cycle (246 ± 22,6 pmol/l $P < 0.05$). The average indices of cortisol level were significantly higher than in the compared groups and accordingly, amounted to 9:00 841 ± 11.2 nmol/l, 701 ± 472 and 560.6 ± 18.2 nmol/l, $P < 0.05$) and at 18:00 (926 ± 31.2 versus 620 ± 18.4, 681.4 ± 18.4 pmol/l $P < 0.05$). The correlation analysis showed an inverse relationship between the level of estradiol and cortisol at 9:00 in the whole group of patients,regardless of the type of MD ($r = -0.40$; $P < 0.01$) and at 18:00 ($r = -0.51$; $P < 0.01$). There was no connection between androgens and estradiol or cortisol.

Conclusion

In our study, 82.4% of patients with ACTG dependent Cushing Syndrome had menstrual dysfunctional that were highly dependent on cortisol and had. Androgenov. Significantly high levels of cortisol contribute to the development of amenorrhea combined with low estradiol levels. We believe that MD in Cushing develop possible due to the inhibition of gonadotropins by hypercortisolemia and not by levels of circulating androgens.

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P295

Silent, isolated ACTH-deficiency in melanoma patients treated with immune checkpoint inhibitors

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Background

The incidence of hypophysitis has increased since the introduction of Immuno-oncologic treatment. Treatment with anti-CTLA-4 (Ipilimumab) and anti-PD-1 has improved the prognosis for patients with malign melanoma drastically, but immune-mediated side effects can occur in any organ, including the thyroid and the pituitary. Headache is considered a key symptom of hypophysitis. Here, we report three cases with silent, isolated ACTH-insufficiency following immunotherapy for malignant melanoma.

Case 1

Female, *1978

- 2015: diagnosed with primary malignant melanoma, stage IV diagnosed in February 2018.
- 17 September 2018: first dose ipilimumab and anti-PD-1.

- 6 December 2018: hyperthyroidism with painful thyroid enlargement, treated with prednisolone 20 mg/d tapered over 10 days. Two days after last prednisolone dose, undetectable morning cortisol. Repeatedly undetectable ACTH and morning cortisol after 6 weeks with low dose cortisone replacement.
- No headache, no other pituitary deficiency detected.

Case 2
Female, *1951:
- 1998: diagnosed and underwent surgery for uveal melanoma.
- 2015: liver metastases detected.
- 25 June 2015: first dose ipilimumab; 4 doses until 27 August 2015.
- 22 September 2015: pseudoprogression; good general condition.
- 8 October 2015: admitted with pyrexia, nausea, vertigo, hyponatremia and hypotension (BP: 85/65 mmHg).
- Cortisol: 106 nmol/l; ACTH 0.5 pmol/l.

Case 3
Male, *1955
- 2016: Diagnosed with primary melanoma on head, stage IV diagnosed autumn 2017.
- 31 October 2017: First dose ipilimumab and anti-PD-1.
- December 2017 - January 2018: immunotherapy induced hyperthyroidism.
- February 2018: follow up for monitoring of thyroid function including routine cortisol levels: increasingly tired, normal thyroid values.
- 6 March 2018: mild hyponatremia, morning cortisol: 36 nmol/l.
- Tired, sleepy, no headache, no other pituitary deficiencies detected.

Discussion
We describe three cases of immunotherapy-associated, isolated ACTH-deficiency without the classical signs of hypophysitis. Hypophysitis occurs in about 4% of patients treated with the CTLA4-immune checkpoint inhibitor Ipilimumab, to a lesser extent in patients treated with PD-1 inhibitor monotherapy and more frequently in combination therapy with ipilimumab plus PD-1 inhibitor. In the presented cases, isolated, immunotherapy-associated ACTH-deficiency was discovered due to routine cortisol assessment or clinical suspicion of cortisol deficiency.
Conclusion
Isolated ACTH-deficiency occurs in immune-oncologic therapy and may be underdiagnosed due to unspecific symptoms of cortisol deficiency. If the correct diagnosis is missed, fatal hypocortisolism can occur. In the follow-up of patients undergoing immune-oncological treatment with CTLA-4 checkpoint inhibitors, we recommend routine assessment of morning cortisol and screening for symptoms of hypocortisolism.

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A Case of Granulomatous Hypophysitis Mimicking Pituitary Macroadenoma

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Idiopathic granulomatoushypophysitis is a rare inflammatory disease which is characterized by inflammation and cellular infiltration of the pituitary gland. The infiltration may cause pituitary insufficiency, compression symptoms due to mass effect and diabetes insipidus. We report the case of a 33-year-old female patient who presenting with weakness, fatigue, amenorrhea and worsening of headaches about 3 months. The patient did not have blurring vision and polyuria-polydipsia. With these complaints, the patient was referred to neurology department and her brain magnetic resonance imaging (MRI) revealed pituitary adenoma and she was referred to neurosurgery and endocrinology departments. Patients' physical examination was normal. Hormonal assessment showed anterior pituitary hormone deficiency and slightly high PRL levels. Pituitary MRI revealed 23x19 mm macrodenoma with suprasellar extention and diffuse homogeneus contrast enhancement. Pituitary mass extending up to optic chiasma but patients' visual field examination was normal. Glucocorticoid and then levothyroxine treatment was started. The patients was performed transsphenoidal surgery for total resection of adenoma with glucocorticoid cover. Histopathological assessment revealed granulomatoushypophysitis. Tests for sarcoidosis, tuberculosis, histiocytosis X and other rare granulomatous diseases were proven negative. And so the patient was diagnosed as idiopathic granulomatoushypophysitis. Pituitary insufficiency persisted after the surgery and glucocorticoid, levothyroxine and estrogen-progestin replacement were continued. Diabetes insipidus did not develop for follow-up period. The last visit was in the portoperative third month, unfortunately the patient had permanent hypopituitarism and and there was an empty sella on the pituitary MRI. As a conclusion, differential diagnosis of hypophysitis from ptiuitary adenomas is very important since their treatment strategies are different. While total resection is recommended in adenoma surgery, biopsy of the pituitary mass and to reduce the compression signs if present are sufficient for hypophysitis. Because, pituitary functions may return to normal with glucocorticoid treatment or spontaneously in hypophysitis. Therefore, true interpretation of MRI findings before surgery is very important.

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Reproductive Endocrinology 1

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The natural course of normal weight women with polycystic ovary syndrome: an insight into metabolic changes of a large Caucasian cohort

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Objective
Polycystic ovary syndrome (PCOS) is hypothesized to originate in foetal life, while its long-term consequences extend beyond menopause. However, the natural course of the disorder has not as yet been elucidated, and recent data suggest differences in the evolution of PCOS according to a woman's weight. We aimed to define the evolution of normal-weight Caucasian women with PCOS through the years.
Design
Cross-sectional case control study
Methods
A total of 763 normal-weight women with PCOS (Rotterdam) and 376 age- and BMI-matched controls were included. The study group was further divided into three age groups, representing women post-adolescence, of reproductive age, and of late reproductive age to menopause. All the subjects were assessed clinically, biochemically, hormonally, and by pelvic ultrasound.
Results
Waist circumference, lipids, androgens and insulin resistance index (HOMA-IR), and ovarian volume were significantly higher in the PCOS group compared to controls. Age subgroup analysis showed that androgens remained significantly higher among PCOS and controls, whereas lipid levels and HOMA-IR were comparable between PCOS and controls in all age groups. A significant negative association of age with waist circumference, androgens, insulin, and HOMA-IR was revealed. Multiple regression analysis disclosed significant negative association of HOMA-IR with age (r: −0.123) and a positive association with BMI (r: 0.105) and DHEAS (r: 0.175).
Conclusions
Lipids, androgens, and insulin resistance are gradually improved in an age-dependent manner in normal weight PCOS women and controls. It seems evident that if PCOS women retain their normal weight over the years, their cardiovascular risk is significantly improved.

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P298

Inhibin-B and FSH are the best predictors of spermatogenesis

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Objective
Sperm cells are produced in the testes by the Sertoli cells. These cells produce Inhibin B too and they are stimulated by FSH. Can Inhibin B be a good marker of spermatogenesis? Should we use other marker (FSH?, testosterone?)
Design
Prospective study.
Patients
We examined 56 patients with infertility.
Methods
Semen analysis and hormonal analysis was performed. Semen analysis was performed according to World Health Organization guidelines (WHO 2010). Hormone analysis include: FSH (follicle stimulating hormone), LH (luteinizing hormone), testosterone, prolactin, TSH and inhibin B. We analysed the dependencies between semen parameters and hormons, especially inhibin B.
Results
The sperm count was significantly and positively correlated with Inhibin B ($r=0.4$, $P<0.0001$). The Inhibin B was negatively correlated with FSH ($r=-0.6$, $P<0.0001$). The lower was the concentration of inhibin B, the lower was the number of sperm in the semen. There was also a relationship between seminogram and FSH - the higher was the FSH, the lower was the number of sperm. There was no relationship between the number of sperm and the concentration of LH, testosterone, TSH, prolactin.
Conclusions
It seems that we can use the value of inhibin B and FSH to assess the intensity of spermatogenesis. The decreased concentration of inhibin B correlates with the number of sperm (the lower the concentration of inhibin B the lower the efficiency of spermatogenesis) and with FSH (the higher FSH, the lower the sperm count). **High levels of FSH and reduced levels of inhibin B clearly indicate impairment of spermatogenic function in addition to the testes. The concentration of testosterone is not good predictor of spermatogenesis.** (Inhibin B and testosterone are produced from different types of cells in the testis). FSH and inhibin-B can be used if the doctor wants to assess spermatogenesis and the patient does not want to perform sperm analysis (in young boys, for example).

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P299

High prevalence of psychopathologies among transgender patients presenting at a large tertiary center: implication for the treating clinicians

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Background and aim of study
Endocrinologists play a central role in the gender affirming process that transgender people chose to undergo, and may be ill-prepared to recognize and manage psychologic difficulties that accompany gender dysphoria. We sought to characterize the patient population currently under our care with respect to their mental health, and to address the question of possible differences between transwomen (TW) and transmen (TM).
Methods
Records of all adult transgender people treated during the last decade at our Transgender Health Clinic in our medical center were reviewed. Social, demographic, and clinical data were recorded. The mandatory psychological assessment provided at the first visit was inspected for any psychiatric diagnosis. All psychoactive medications taken, addictions, and suicidal or non suicidal self-injury attempts were noted.
Results
Altogether 405 subjects were followed for a mean duration of 2.4 ± 0.1 y. The cohort consisted of 221 TW, and 184 TM (TW:TM = 1.2:1). TM were significantly younger 26.1 ± 7.3 vs 31.3 ± 11, and presented at a younger age 23.6 ± 7.2 vs 29.1 ± 10.7 than TW ($P<0.0001$ for both). TW tended to be in a relationship more often than TM (35/221, vs 18/184, $P=0.08$), and to be parents (27/221 vs 9/184, $P=0.03$). There was no significant difference in the level of education, but TM were more frequently employed than TW ($P=0.0002$). TM had generally more family and friends support ($P=0.04$). Despite those differences, TW did not differ from TM in any of the psychopathologies, which were highly prevalent, and well in excess of the rates for the general population. 35% of all subjects had at least one psychiatric diagnosis, and 22% were currently medicated. Major depression was present in 85 subjects (21%), anxiety disorders in 40 (9.9%). 27 subjects had attempted suicide (6.7%), while 10 had self-inflicted non suicidal injuries (2.5%). Smoking was extremely prevalent as 164 subjects smoked (40.5%). Substance abuse and addictions, albeit underreported, were also common and coexisted with smoking in each instance. Alcohol abuse was reported by 2.5%, cannabis by 2.7%, cocaine and heroin abuse by 2.5% each. Assessing the effect of gender reaffirming hormonal therapy on the prevalence or severity of these pathologies was beyond the scope of this study.
Conclusions
Our findings highlight the need to prepare endocrinologists for the high prevalence and severity of psychopathologic conditions in transgender people. A mental health professional should be an essential part of any multidisciplinary team of clinicians treating the transgender population.

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P300

Bardet-Biedl syndrome in two siblings: a rare entity

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Introduction
Bardet–Biedl syndrome (BBS) is a rare genetic ciliopathy with a prevalence of 1 in 160,000 in Europeans and 1 in 13,500 in some Arab populations The primary clinical features of BBS include retinal dystrophy, obesity, postaxial polydactyly, renal dysfunction, learning difficulties, and hypogonadism. Traditionally, BBS is clinically diagnosed when a patient shows 4 primary features
Case report
17 year old male, single, worker, presented to our endocrine clinic complaining of delayed puberty short stature and poor vision, especially at night. He was third of Four siblings born of consanguineous marriage. Childhood details could not be elucidated except for poor mental milestones and scholastic performance. His vision was poor since childhood at the age of 5, and had deteriorated recently especially at night. Tonsillectomy and adenoidectomy at age of 8. Physical examination: Clinical findings included height: 141 cm (upper segment, 60 and lower segment, 80), weight 58.8 kg (body mass index: 29.74 kg/m^2), waist circumference: 92 cm. He had 22 digits with syndactyly of second and third toes bilaterally. Genitalia examination revealed pubic hair: Tanner stage 1, genitalia stage 2; stretched phallic length: 2 cm and testicular volume 6 ml bilaterally. No gynecomastia. Normal Systemic examination. Laboratory work up showed normal complete blood picture, liver enzymes, creatinine,BUN follicle-stimulating hormone: 3 mIU/ml (*N*: 0.7–11.1), Luteinizing hormone: 1.4 mIU/ml (*N*: 0.8–7.6), testosterone 0.5 ng/ml (*N*: 2.5–8.4 mg/ml). Fundus examination showed atypical retinitis pigmentosa with vascular attenuation and salt–pepper type changes in both. Electroretinogram (ERG) showed grossly reduced amplitudes. Suggesting peripheral rod–cone dysfunction. His elder brother 21 years old, obese BMI: 35.95, he had learning difficulties and quit school, diminution of vision since childhood especially at night, polydactyl, evidence of virilization with small penile size (SPL: 8 cm).
Conclusion
BBS demonstrates highly variable expression, even among affected siblings, making the diagnosis difficult and often delayed. There is no definitive treatment method for BBS. Complications related to BBS Should be treated symptomatically. A multidisciplinary management approach may be required in patients with BBS.

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P301

After up to 11 years observation, testosterone undecanoat 1000 mg at 3 months did not increased Prostatic Specific Antigen level (January 2019)

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Aim
Has testosterone undecanoat 1000 mg intramuscular injection (Nebido^{R}; Bayer), 1 at 3month, negative effect on prostate? For this purpose, we appreciate the prostatic volume (see Pisoschi, this congress) and PSA (this study) in hypogonadic patients after testosterone injection up to 11 years.
Material and method
A. PSA (ng/ml) was done in Bucharest accredited laboratories.
B. Patients: PSA analysis was done before treatment and recorded every year from 1 year treatment to 11 years; in some patients PSA was done at 14 days, 3 and 6 months.
C. Statistical analysis: Student test, simple correlation, multiple regression.
Results
A. Patients at onset: 279 men, age: 18–96 years, average: 59,67 years; median: 61.
B. Prostatic volume (cmc): average: 33,74.
C. Average PSA (no patients): before treatment =1,55 (279); [14d=1,73 (59); 3m=2,76 (60); 6m=1,46 (54)]; 1y=1,76 (143); 2y=1,48 (104); 3y=1,48 (72); 4y=1,7 (60); 5y=1,52 (54); 6y=1,75 (42); 7y=1,7 (35); 8y=1,73 (27); 9y=2,1 (16), 10 y=1,28 (9), 11 y=1,81 (5).
D. Statistical difference of averages from 1y to 11 y: nonsignificant for all times: p= between 0,46-0,84.
E. Correlation between age and PSA was *significant* ($P<0,05$) at: T0: $r=0,34$; and 1y: $r=0,19$; and *nonsignificant* at 2 years to 11 years ($r=0.16$–0.68). Significance is depending on group size.
F. Correlation between PSA and prostatic volume was *significant*, both before and after treatment at 1, 2, 3, 4, 8, 9 years (depending on group size, $r=0.2$–0.52).
G. Multiple regression test shows the relationships between PSA before/after treatment, prostatic volume before/after treatment and the impact of testosterone on PSA and prostatic volume. Statistical significance: P values < 0.01 for all years (including 5 data for 11 year treatment: $P=0.015$): $R^2 = 0.32$–0.99, F=3,24–1584.
Comments. Comparing with 2017 (Lisbon Congress) data, patient number increased by 15%.
Conclusions
1. Testosterone undecanoat 1000 mg injectable i.m. at 3 months did not increased PSA level after up to 11 years administrations.
2. Based on multiple regression data, **PSA level post testosterone does not depend on testosterone administration** but on the age and the prostatic volume before treatment and depend on the initial PSA level, i.e. before testosterone administration.

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Analysing by decade, testosterone undecanoat depot injectable does not increases prostate volume: Study during up to 11 years on hypogonadic patients. (January 2019)

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Aim
Re-Analysing (study starting in 2007) the effect of injectable testosterone undecanoat depot (TUD) in hypogonadic patients.
Material-method
A. Patients: at onset 278 men with hypogonadism (median: 61 y).
B. Distribution: by decade (starting with 20y); no =6, 17, 25, 70, 86, 55, 18, 1.
C. TUD (Nebido^{R}-Bayer) 1000 mg injected one/3 months i.m.
D. Prostate volume (PV) appreciated by per-abdominal ultrasound: 3,5-5 MHz probe, elliptical/3D (cm^3).
E. Analysis in time: before starting testosterone (T0=279), after ½ month (T1=279), 3m (T2=220), 6m (T3=170), 1y (T4=143), 2y (T5=104), 3y (T6=72), 4y (T7=60), 5y (T8=54), 6y (T9=42), 7y (T10=35), 8y (T11=27), 9y (T12=16), 10 y (T13=9), 11y (T14=5).
F. Maximum increment from T0 noted **Δ M %**. **Average increment** noted **Δ A %**.
G. Statistical analysis: Student test.
Results
I. A. Mean prostatic volume (cm^3) before testosterone by decade (and significance) increased: 13.17; 16.85 (0.2,NS); 23.96 ($P=0.01$); 29.88 ($P=0.0002$); 36.75 ($P=0.000001$); 41.90 ($P=0.0000001$); 46.97 ($P=0.00001$); 32.00 (ND). B. All average prostatic volume post testosterone by decade and time were tabulated (see pdf).
II. Maximum increment post testosterone (Δ M %) per decade: 45.95; 44.44; 56.41; 56.60; 48.72; 68.18; 54.55; 20.00.
III. The moment of Δ M % - per decade: T4; T5; T8; T6; T3; T7; T5; T2.
IV. Average increment (Δ A %) per decade: +5.43; −11.42; −18.04; −4.54; −10.89; −51.71; +13.64, +12.94.
V. Considering all observations, TUD did not increase PV significantly. A. The average of increment (%) in all patients was negative: −8.08%. B. Per decade (significance): 5.43 ($P>0.05$); −11.42 (decreased); −18.04 (decreased); −4.54 (decreased); −10.89 (decreased); ! −51.71 (decreased); 13.64 ($P>0.05$!); 12.94.
VI. In many patients, especially from 30 to 79 years, TUD could decrease slightly prostatic volume.
Comments. After 1 month, many patients give up treatment. At 1 year, around half patients withdraw. However, comparing with 2017 (Lisbon) data, patient number increased by 15%. 18 patients were operated before starting testosterone, two patients were operated during treatment. 5 patients received the diagnosis of prostatic cancer. To them, TUD was administrated when PSA < 1, usually after 3 years anticancer treatment.
Conclusions
Considering the risk for prostate (in elderly), testosterone undecanoat 1000 mg depot injectable is a safe treatment, even after 11 years of administration. Precautions should be accorded to men over 80 y old, after the 5th year of administration. Under strict control, TUD could be administrated also in prostatic cancer.

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Evidence for preserved ovarian reserve in transgender men receiving testosterone therapy: Anti-mullerian hormone serum levels decrease modestly after one year of treatment

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Background
Although successful pregnancies carried by transgender men have been reported, long-term effects of testosterone therapy on fertility remain unknown.
Aims
To study markers of ovarian reserve during testosterone therapy.
Methods
Prospective open-label study of transgender men prior and during treatment with testosterone. Sampling was conducted at baseline and 12 months after treatment initiation.
Main outcome measures
Anti-Mullerian Hormone (AMH), gonadotropins and sex steroid serum levels; endometrial thickness and antral follicular count determined by pelvic US.
Results
52 subjects (23.4±6.1 y) were recruited, 32% of which were in a stable relationship. 17% expressed desire to have children while 26 (50%) were unsure about future parenthood. Four (7%) have already undergone fertility preservation procedures. Interestingly, 5 participants (9%) that initially were sexually attracted to women became bisexual under testosterone treatment. Complete data is available for 32 subjects. In the course of 12 months of treatment, AMH levels decreased from 5.65±0.52 ng/ml at baseline to 4.89±0.65 ng/ml ($P=0.036$). Antral follicular count (16.9±1.4, 13.9±1.7) and endometrial thickness (6.9±0.7, 5.6±0.5 mm) remained unchanged. As expected, testosterone levels increased (0.84±0.1, 7±0.7 nmol/l; $P<0.0001$) and estradiol levels decreased (90.8±7.9, 55.4±4.6 pmol/l; $P=0.0013$) during therapy, with a concomitant decrease in LH (7.56±0.7, 3.8±0.6 mIU/ml; $P=0.0012$), but not FSH (5.1±0.41, 4±0.3; $P=0.07$ mIU/ml) levels.
Conclusion
AMH levels slightly decrease during testosterone treatment but remain within the normal, 'healthy' range, thus likely indicating well-preserved ovarian reserve. This assumption is corroborated by the unchanged antral follicular count. The significance of these findings on fertility potential remains to be explored.

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P304

Female infertility: etiological factors and management

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Infertility affects milions of couples worldwide. Determining the exact cause represents a real challenge and may require a complex work-up.
Objective
To asses the main etiological factors of female infertility and the best treatment.
Methods
Retrospective study which included 150 women diagnosed with infertility in a Romanian tertiary center. The median age was 30.5 years (20–41), 65.3% ($n=98$) of the patients were diagnosed with primary infertility and 34.4% ($n=52$) of the patients had secondary infertility.
Results
The patients underwent diagnostic laparoscopy and by case therapeutic intervention. The most frequent etiological factors were: polycystic ovaries (20.8%), endometriosis (18.4%), bilateral hydrosalpinx (14.4%), peritoneal adhesions (13.6%). There was an increased frequency of polycystic ovary cases in both primary and secondary infertility. 26 patients with polycystic ovaries underwent ovarian drilling.
Conclusions
In the cases of infertility laparoscopy represents a complementary diagnostic method and can offer diagnosis and treatment in the same time and can identify the discrete lesions that can explain the cases of idiopathic infertility. In our study the most common cases of infertility were: polycystic ovaries, endometriosis and hydrosalponx.

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P305

Assessement of frequency of depression in women of reproductive age with polycystic ovarian syndrome

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Objective
To study the frequency of depression in women of reproductive age with different phenotypes of polycystic ovarian syndrome (PCOS).
Materials and Methods
Sixty-eight women with diagnosed polycystic ovarian syndrome aged 18–44 and 30 practically healthy women of the comparable age. Hospital Anxiety and Depression Scales (HADS) were used to diagnose depression. According to the results of the HADS assessment, the patients were counseled by psychotherapist to confirm the presence of depression and to assess its severity. Patients from the main group were divided into 3 subgroups: patients with PCOS and visceral obesity of varying severity (BMI >25 kg/m^2, WC\TC >0.85); patients with PCOS and gluteal-femoral obesity (BMI >25 kg/m^2, WC\TC <0.85); patients with PCOS and normal body weight (BMI <25 kg/m^2).
Results and Discussion
According to the study results, depression was diagnosed in 28.2% of patients in the main group, of which 14.7% had subclinical depression, and 13.5% had severe form. This indicator significantly exceeds the frequency of depression in the control group - 17.3%, of which subclinical depression is 9.3%, severe depression is 8%. The obtained results show that the frequency of depression in patients with PCOS exceeds the values detected in healthy women ($\chi^2=5.75$, $P=0.01$). When assessing the frequency of depression depending on the phenotype of patients with PCOS, it was found that the frequency of depression in patients with PCOS and visceral obesity was 24.7%, in patients with PCOS and gluteal-femoral obesity it was 12.3%, in patients with PCOS and normal weight - 19.7%. When analyzing the results, a direct correlation was determined between the level of depression according to the HADS scale and age ($r=0.17$; $P<0.05$) in patients with PCOS and visceral obesity, and by the logistic regression method it was confirmed that the development of depression in patients with PCOS and visceral obesity is associated with age over 40 years (OR $=1.06$; $P<0.05$; 95% CI 0.99–1.13).
Conclusion
The obtained results show that the frequency of depression in patients with PCOS exceeds the values detected in healthy women. One of the possible risk factors for the development of depression in patients with PCOS and visceral obesity is an age over 40 years.

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A rare cause of the hypergonadotropic hypogonadism: GAPO sydrome

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GAPO syndrome (OMIM 230740) is a rare, multiple congenital anomalies syndrome characterized by Growth retardation, Alopecia, Pseudoanodontia and Ocular manifestations. Syndrome caused by anthrax toxin receptor 1 (ANTXR1) gene (NM_032208.2) mutation leading to deficiency of an enzyme involved in the metabolism and breakdown of extracellular matrix (ECM). Disease show parental consanguinity, autosomal recessive inheritance and since first description in 1947 a total of 38 patients have been reported to date. Lack of the breakdown result dyshistogenic sequence of the ECM and deposition of those materials in the multiple organs. Affected patients have short stature, distinctive craniofacial features, typical facial appearance, ocular manifestations and maldeveloped teeth. Hypergonadotropic hypogonadism may be seen due to extensive deposition of the extracellular material in the female reproductive organs. In this study; we introduce a young Syrian woman, with typical phenotypic appearance and clinical features of the GAPO syndrome, admitted with primary amenorrhea. Her endocrinological investigations showed hypergonadotropic hypogonadism prominent with elevated FSH, LH and low estradiol and progesterone. Patient had no parental consanguinity and by direct sequencing of the *ANTXR1* gene, we identified a novel homozygous splicing variation (c.152+1G>T in intron 1) in the patient. This variant has not been previously reported in the Human Gene Mutation Database (HGMD; http://www.hgmd.cf.ac.uk/ac/index.php) and in population studies (ExAC: Exome Aggregation Consortium and 1000 Genomes Project). Our findings expand the spectrum of causative mutations and clinical findings in GAPO Syndrome.

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P307

Menstrual disorders in patients with different etiology of hyperprolactinemia

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Introduction
Hyperprolactinemia (HP) is a common disorder in endocrinology. Based on the various etiology, HP could be divided into: physiological, pathological, drug-induced and idiopathic HP. Regardless of its origin, HP usually affects reproductive endocrine axis. The aim of the study was to determine differences in menstrual cycle abnormalities in patients with different causes of hyperprolactinemia.
Patients and methods
The study included 81 patients with HP, divided into the following groups: pathological HP (PTHP, 29 patients), drug-induced HP (DIHP, 27 patients) and idiopathic HP (IHP, 25 patients). Following diagnostic procedures were

performed: clinical examination, detailed drug history, biochemical investigation and radiological imaging. Hormonal testing included prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), progesterone, testosterone, thyroid stimulating hormone (TSH) and free thyroxin (FT4), cortisol and adrenocorticotropic hormone (ACTH).
Results
PRL concentrations were significantly higher in PTHP and DIHP compared to IHP. The youngest patients were with IHP, followed by PTHP and DIHP. Among PTHP majority of the patients had oligomenorrhea (37.9%) followed by polymenorrhea (20.7%). Regular cycle length with absence of ovulation and amenorrhea was verified in the same number of patients (13.8% each). Two women were in menopause (6.9%) and two were with completely regular cycle (6.9%). The highest number of the patients with DIHP had amenorrhea (37%) and oligomenorrhea (22.2%), followed by polymenorrhea and menopause (14.8%, each). Only two patients had regular cycle (7.4%) and one regular cycle without ovulation (3.7%). In the group of patients with IHP, majority had regular cycle (44%) and regular cycle without ovulation (24%), followed by polymenorrhea (16%) and oligomenorrhea (12%). Only one patient had amenorrhea (4%) and none menopause. Normalization of the prolactin concentration after discontinuation of the drugs which caused HP/ or after dopamine agonist treatment, resulted in the significant decrease in menstrual cycle abnormalities in all study groups.
Conclusion
Majority of patients with highest PRL levels (PTHP and DIHP) had oligomenorrhea and amenorrhea, while patients with less increased PRL concentrations (IHP) rarely had this type of abnormalities. Even though different etiology of hyperprolactinemia can cause different menstrual disorders, the main factor which will determine severity of these abnormalities is the level of PRL concentration.

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P308

Reproductive phenotype in 265 men with congenital hypogonadotropic hypogonadism and 531 men with acquired hypogonadotropic hypogonadism: a monocentric comparative study

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Context
Hypogonadotropic hypogonadism (HH), defined by LH and FSH deficiencies, lead to impairment in testicular growth, testicular hormonal secretions and spermatogenesis. HH can have a prenatal (congenital HH, CHH) or post-natal (acquired HH, HHA) onset. Direct comparison of reproductive phenotypes (RP) between CHH and AHH has not been systematically performed in large series representative of these two populations.
Patients and methods
60 normal men, 265 men with CHH (Kallmann syndrome 44%; normosmic CHH 56%) and 531 men with AHH from a single center were included. Causes for AHH included pituitary tumors (74.6%), other intracranial tumors (12.7%, (craniopharyngioma 8.3%)), infiltrative diseases (3.5%) and other causes (9.2%). Testicular volumes (TV), serum gonadotropins, sex steroids (testosterone (T) and estradiol (E2)) and testicular peptides (inhibin B (IB), AMH and INSL3) were measured before therapy.
Results
TV was larger in AHH (16.7 ± 6.0 ml) than in CHH (3.1 ± 1.9 ml; $P<0.0001$). LH, FSH, T and E2 were higher in AHH than in CHH ($P<0.0001$ for all parameters). IB and INSL3 were also higher in AHH than in CHH men, respectively (126 ± 87 vs 59 ± 55 pg/ml, and 566 ± 372 vs 60 ± 40 pg/ml, $P<0.001$). Conversely, serum AMH and SHBG levels were lower in AHH than in CHH (246 ± 234 vs 46 ± 38 pmol/l, and 35 ± 22 vs 26 ± 21 nmol/l, respectively, $P<0.0001$). In the subgroup of AHH patients caused by craniopharyngioma ($n=44$), TVs and T, E2, IB and INSL3 levels were significantly lower than in patients with AHH caused by pituitary adenomas ($P<0.001$).
Conclusions
Our data clearly demonstrate that RP is more impaired in CHH than in AHH. Preservation of the gonadotrope/testicular axis (GTA) activation during the fetal, neonatal and pubertal periods in AHH probably could account for these differences. Severity of GTA impairment in patients with craniopharyngioma could be related to the severity of hypothalamic/pituitary lesions caused by these tumors and/or aggressiveness of therapeutic procedures.

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Ano-genital distance in children born of mothers with polycystic ovary syndrome – Odense Child Cohort

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Background
Higher testosterone levels during pregnancy in women with polycystic ovary syndrome (PCOS) could be associated with longer offspring ano-genital distance (AGD).
Aims
To compare AGD between offspring of mothers with PCOS and controls and to determine possible associations between maternal 3rd trimester testosterone levels and offspring AGD at three months of age.
Methods
The study was part of the prospective study, Odense Child Cohort. Maternal testosterone levels were measured by mass spectrometry at gestational week 28 in 1.127 women. Offspring measures included AGD from anus to posterior fourchette (AGDaf) and clitoris (AGDac) in girls and to scrotum (AGDas) and penis (AGDap) in boys, penile with, and body composition (weight and BMI standard deviation scores (SDS)), PCOS, $n=139$, Controls, $n=1.422$ controls) at age three months.
Results
AGD measures were comparable in offspring of women with PCOS compared to controls (all $P>0.2$) despite significantly higher total testosterone (mean: 2.4 vs. 2.0 nmol/l) and free testosterone (mean: 0.005 vs. 0.004 nmol/l) levels during pregnancy in women with PCOS (both $P<0.001$). AGD was positively associated with offspring BMI (all $P<0.001$). In boys born of mothers with PCOS, maternal total testosterone levels were positively associated with AGDas ($r=0.33$, $P=0.009$) and AGDap ($r=0.37$, $P=0.003$). In multiple regression analyses, the strongest predictor of AGD in boys and girls was offspring BMI at three months (models corrected for maternal age, maternal parity, maternal BMI, and offspring birth weight). Maternal PCOS status was an independent and positive predictor of AGDas and AGDap in boys. Maternal PCOS status and maternal testosterone levels did not predict AGD in girls.
Conclusions
AGD was similar in children born of mothers with PCOS compared to controls, but PCOS status could be associated with longer AGD in boys. Our data suggest that boys were more susceptible to maternal PCOS than girls.

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Diagnosis and management of severe hyperandrogenism in the context of tumoral suspicion: case-series report from a tertiary hospital

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Background
The finding of severe hyperandrogenemia, rapidly progressive clinical hyperandrogenism, defeminization and/or virilization in women of any age should raise the suspicion of an ovarian or adrenal malignancy. Similarly, moderate to severe hyperandrogenemia after menopause, and its clinic consequences, force clinicians to rule out a tumoral source.
Matherial and methods
Observational cross-sectional study conducted in patients derived to our clinic for the assessment of hyperandrogenism, from 1998 to 2018. We retrieved biochemical and radiologic data of those women fulfilling the following criteria: i) women of any age, in whom hyperandrogenic symptoms were severe and/or rapidly progressive, and/or total testosterone concentrations were >200 ng/dl, and ii) post-menopausal women with clinical or biochemical hyperandrogenism. Ovarian ultrasound and abdominal CT were performed in all these women.
Results
The data of 14 women were recorded. All but one were postmenopausal. Mean age was 61 ± 17 years-old. Total and free testosterone concentrations were 159 (107–466) ng/dl and 79 (56–246) pmol/l, respectively. Median time from the onset of clinical hyperandrogenism to the first visit to our clinic was 2 (0.75–5) years. Progressive hirsutism was the first sign of clinical hyperandrogenism in a majority of women [8 (58%)], followed by moderate-to-severe alopecia [6 (43%9]. Clitoromegaly as a sign of virilization was observed in five patients (36%). Ovarian ultrasound showed a solid tumor in four patients, mucinous cyst in one patient and a false positive in another one. One women had both an adrenal and ovarian tumor, while three of them had an adrenal incidentaloma, none of the latter were malign. Simultaneous venous adrenal and gonadal catheterism and sampling was necessary in 3 of these patients for establishing diagnosis. Twelve women underwent surgery, whereas the remaining received medical treatment. Histopathological assessment showed ovarian hyperthecosis in five out of twelve women (42%), whereas a tumoral androgen source was identified in seven patients (58%). From the latter, six women had a sex-cord stromal tumor. None of the patients had an adrenal source of androgen excess in our series.
Conclusion
Tumoral etiology should be ruled out in women with severely high of sex-androgens concentrations, and/or when symptoms are rapidly progressive. Ovarian hyperthecosis is a common cause of hyperandrogenism at menopause, although tumoral diagnosis must be always considered in the differential diagnosis.

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Ovarian reserve and exposure to environmental pollutants (ORExPo study)

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Background
Many chemicals present within the environment, as well as natural and artificial components of our diet, have the potential to interfere with the physiological role of hormones, interfering with hormone biosynthesis, signalling or metabolism. In the last years AMH, a protein secreted by granulosa cells, has emerged as a reliable marker of ovarian reserve. It is largely accepted the influence of age and smoking on AMH serum levels, although a clear effect of environment has not been demonstrated.
Purpose
To assess the association existing between environmental pollutants and anti-Mullerian hormone (AMH), a well know marker of ovarian reserve. The hypothesis is that high exposure to pollutants may be associated to an age-independent decrease in AMH, suggesting decreased ovarian reserve.
Methods
A longitudinal, observational, retrospective, real-world big data trial was performed. All laboratory AMH measurements of women living in the area surrounding the city of Modena performed from January 2007 to October 2017 at the Central Laboratory of Modena Hospital were extracted and collected in a large database. AMH serum levels were measured with commercial assay (Beckman Coulter). A computing data warehouse was created, in which AMH data were connected to patients' age and residential address. The database was completed, including environmental data and considering the city where each patient lived for geo-localization. The environmental exposure considered daily particulate matter (PM) and NO2 values.
Results
1,463 AMH measurements were collected for 1,318 women (mean 1.94 ng/ml, and median of 0.90 ng/ml). AMH was inversely related to patients' age ($Rho = -0.437$, $P < 0.001$), although not related to age in patients younger than 25 years (Adjusted R-squared 0.068 $P = 0.055$). On the contrary, AMH was inversely related to age after 25 years of age (Adjusted R-squared 0.120, $P < 0.001$). AMH was inversely related to environmental pollutants, such as PM10 ($Rho = -0.088$, $P = 0.001$), PM2.5 ($Rho = -0.062$, $P = 0.021$) and NO2 ($Rho = -0.111$, $P < 0.001$). This association was age–independent. No relationships were found between AMH and environmental temperatures.
Conclusion
This is the first big-data approach designed to evaluate the influence of environment on AMH serum levels. Increasing air pollution affects AMH serum levels. It is very well known that there is a large genetic component in the ovarian reserve at birth, but other factors may influence the extent of the follicular pool such as environmental factors. Results of this study strongly suggest that environmental factors may also modify the downward dynamics of AMH and ovarian reserve during adulthood.

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P312

Normosmic hypogonadotropic hypogonadism associated with a novel TACR3 mutation

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Introduction
Neurokinin B (NKB) is a neurotransmitter, regulating GnRH. NKB activates its receptor TACR3. Recessive mutations of TACR3 are associated with a phenotype of normosmic hypogonadism.
Case report
A 17 years old man born in Turkey, present with pubertal delay. He is treated 3 years with testosterone and he is reevaluated without treatment. He is 1.79 m and 1.85 arm span, testicular volume: 3 and 4 ml. He has no olfactory troubles. Testosterone 1.87 nmol/L, Estradiol <17 ng/L, LH 2,3 UI/L, FSH 1,6 UI/L. Pituitary MRI is normal.
Genetic analysis
A set of 16 causatives genes for IHH and KS were investigated by Next Generation Sequencing. We were able to identify a novel heterozygous TACR3 variant (c.530C > A, p.(Thr177Lys)) that is predicted to be deleterious by *in silico* analysis (Polyphen, Mutation Taster, Mutation Assessor). This variant is located in the 'GPCR, rhodopsin-like' protein domain and lead to the replacement of Thr177 by a Lysine residue. Functional studies are needed to evaluate the deleterious impact on the NKR3 receptor.
Conclusions
We describe a novel TAC3R mutation associated with normosmic hypogonadotropic hypogonadism. The phenotype is intriguing, because a second pathogen mutation is expected but it was not found with our panel. Further gene investigations will be undertaken.

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A novel rare case of normosmic congenital hypogonadotropic hypogonadism associating a GnRHR and a KISS1R variants

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Case report
We describe a 28 years old male patient born in IRAK, beeing referred to us because of suspicion of congenital hypogonadism. The patient was 1.86 m tall and 1.97 spam arm and he was no anosmic. He had a 2.5 cm micropenis, and a bilateral reduced testicular volume (3.6 and 3.9 ml). LH 1.7 U/l (2–10), FSH 3.1 U/l (1–8), testosterone 0.7 mmol/l, estradiol <12 ng/l, inhibine B 54 ng/l (105–439) Pituitary MRI was normal.
Genetic studies
A set of 16 causatives genes for IHH and KS were investigated by Next Generation Sequencing (KAL1, FGFR1, PROKR2, PROK2, CHD7, FGF8, KISS1, KISS1R, TAC3, TACR3, GNRHR, GNRH1, NELF, WDR11, HS6ST1, SEMA3A). We were able to identify two variants at the heterozygous state: one is a novel **KISS1R variant: c.389G>T, p.Cys130Phe**, that is predicted to be deleterious by *in silico* analysis (SIFT, Polyphen, Mutation Taster). This variant is localized in GPCR and rhodopsin-like protein domains, but it is difficult to predict the importance of the pathogenic impact without functional studies. The second one is a pathogenic variant described in several patients presenting GnRH deficiency and affect the gonadotrophin-releasing hormone receptor (**GNRHR: c.317A>G, p.Gln106Arg**).
Discussion
The kisspeptin receptor (KISS1R) is a G-protein–coupled receptor expressed in GnRH neurons and encoded by *KISS1R*. Relatively few inactivating *KISS1R* variants have been reported to date in patients with nCHH. Patients with KISSR and GnRHR mutations carry them in the biallelic state, in keeping with autosomal recessive transmission. Our findings expand the GnRHR and KISSR mutation spectrum and phenotype-genotype correlation in CHH.

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P314

Azoospermia revealing the uncommon Jacob's syndrome

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Introduction
Dysgonosomies are abnormalities of the number of gonosomes X and Y. They have fewer Phenotypic repercussions than the aneuploidies involving autosomes, and are mostly viable. The 47 XYY are generally boys with normal phenotype. The prevalence is around 1 per 1000 birth boy but undoubtedly under diagnosed given the often normal phenotype associated with this chromosomal formula, in addition to the lack of large-scale studies. There is no gonadal dysgenesis and often no infertility or criminality in the past.
Case report
Our case is a 48 years old patient consulting for primary hypofertility. The anamnesis finds a type 2 diabetes, High blood pressure, orchi-epididymitis at the age of 34 and bilateral unaccompared varicosele and hydrocele. The patient is an active smoker. Clinically, he is an over weighted patient (BMI: 27kg/m square) with 180 cm height.No other dysmorphia is noted. In the Spermogram, we find an azoospermia (00 SPZ), with 1 CC of ejaculation volume. Scrotal ultrasound shows a normal-sized testicles with micro calcifications in the epididymis tail with varicocele and bilateral hydrocele. An Epididymis Cytoponction recovering SPZ (without cryopreservation)
The hormonal status is:
FSH: 1.65 mIU/ml (0.95–11.95)
LH: 2.40 mIU/ml (0.57–12.07)
Testosterone: 5.65 ng/ml (1.42–9.23) or a correct gonadal assessment
Inhibin B 215.4 ng/ml (11.5–368.9) predicting the presence of SPZ in the biopsy
Caryotype 46 XY/47 XYY
The clinical examination and the exploration of the 31 years old partner is without anomalia.
The patient is programmed for testicular biopsy in the optic of a possible ICSI.
Conclusion
It appears that many men with 47,XYY syndrome will likely have decreased fertility potential. These patients may ultimately require assisted reproductive techniques in order to achieve pregnancy

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P315

Pituitary tumor as a cause of male infertility

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Context
Pituitary tumor can cause infertility. It can be hormonally active adenoma (mostly prolactinoma) or hormonally inactive. Hyperprolactinemia is the most common disorder. Prolactin interferes with pulsatile secretion of the hypothalamus gonadoliberin (GnRH) and consequent pituitary gonadotropins (FSH and LH), and then leads to abnormal gonadal function. As a result, a man gets impaired spermatogenesis and endocrine function of the testicles. Infertility and reduced testosterone secretion occurs.
Objective
We present a case report of a 33-year-old man. For 5 years, a couple have been diagnosed due to unexplained infertility. The reason for infertility was seen in a woman who underwent many different therapies. Because of the intensifying visual disturbances and headaches, the man came to the ophthalmologist. Based on the fundus examination, the brain tumor was suspected. Head tumor was confirmed through the head MRI. The reason for the infertility of the couple turned out to be a male pituitary tumor growing for many years.
Methods
The MRI describes a 3 cm pituitary tumor with pressure on the intersection of optic nerves. Hormonal studies showed hyperprolactinemia and hypogonadotropic hypogonadism. Due to the lack of erection it was impossible to perform a semen analysis. Diagnosis was established: inactive pituitary macroadenoma. A successful craniotomy operation was performed, removing the major part of the tumor, thus saving the patient's sight and life. After removal of the tumor (and damaged pituitary gland) eyesight improved, but multi-hormonal hypopituitarism occurred. However, it was not the biggest problem for our patient. The most difficult was to accept infertility.
Intervention
Due to the efforts to conceive a child, testosterone was discontinued and the treatment of gonadotropin started. FSH and LH were administered. FSH at a dose of 75 units 2 times a week and LH at a dose of 2500 units two times a week. Substitution with hydrocortisone, levothyroxine and vasopressin analogue continued.
Result
The therapy turned out to be extremely effective, after less than five months of treatment with gonadotropins, the woman became pregnant.
Conclusions
Pituitary tumors can cause infertility. Macroadenomas (tumors >10 mm) additionally give neurological symptoms: visual disturbances and headaches. Hyperprolactinemia in men most often leads to erectile dysfunction and decreased libido. With the time gynecomastia may develop. Testosterone substitution protects against the effects of hypogonadism. The erection and libido returns, but spermatogenesis is not improved. An effective therapy in such patients is the administration of exogenous gonadotropins.

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P316

The differences in steroid hormones levels in the peripartum period caused by fetal sex and delivery type

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The production and activities of steroid hormones during pregnancy have many interesting aspects. Their synthesis and metabolism are the result of complex metabolic pathways encompassing activities in the fetus, placenta, and mother. Progesterone, estrogens, androgens and glucocorticoids all play important roles during pregnancy, from implantation to delivery. Focusing on selected steroid hormones in the peripartum period, we defined reference ranges measured using LS-MS/MS, and assessed relationships with maternal age, pregnancy weight gain, delivery type, and fetal sex. Samples were taken from 142 healthy women with physiological gravidity at the 37th week, during the first period of labor, and from newborn mixed cord blood. The local ethical committee approved the study. We found higher cortisol and 17-OH-pregnenolone plasma levels in mothers at the 37th week that carried male fetuses ($P=0.03$), but no significant differences in any studied hormones in newborns of different sex. Neither maternal age, weight gain nor newborn birth weight had any relationships to any of the studied

hormones. However, there were differences depending on vaginal versus planned cesarean section deliveries. In women carrying a male fetus we found significantly higher levels of 17-OH-pregnenolone, progesterone, cortisol, corticosterone and significantly lower levels of estradiol in those undergoing spontaneous vaginal delivery. However, we found no significant differences in the cord blood of newborn males from either delivery type. We established reference ranges for our analysis methods, which should be useful for further studies as well as in standard clinical practice.

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P317

Characterization of the expression and physiological roles of thyroid-stimulating hormone receptor in the male testis

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Thyroid-stimulating hormone receptor (TSHR) is typically known to be expressed in the thyroid gland of mammals for the control of body metabolism. However, because the TSHR ancestor is the only glycoprotein hormone receptor found in invertebrates, we hypothesized that TSHR evolves much earlier than FSHR and LHR and thus can be expressed in mammalian gonads for certain uncharacterized impacts. To prove this, real-time PCR quantification against *Tshr* in all male mouse reproductive organs was performed. The results indicated, that *Tshr* is mainly expressed in the testis where it is increased in an age-dependent manner. TSHR is located mainly in Sertoli cells and moderately in germ cells; such a profile was further confirmed using isolated primary mouse Sertoli cells. Gene regulatory test using the TM4 Sertoli cell line showed that *Tshr* expression can be increased via the cAMP cascade. In terms of the cognate ligands for TSHR, we demonstrated that the testicular TSHR is likely to be activated via an endocrine loop by the pituitary-secreted TSH since the negligible level of the genes encoding TSH or thyrostimulin can be detected in male reproductive organs. Furthermore, using cultured testis tubules or explants, TSH treatment can not only promote the proliferation of germ cells *ex vivo* but also increase the transcripts of *Tgn*, *Tpo* and *Slc5a5*. Taken together, activation of the TSHR signaling *in situ* can influence spermatogenesis and may potentially regulate the amounts of thyroid hormones locally. Therefore, our findings overthrow the traditional concept regarding the physiological roles of TSHR and may open a new era of TSHR functions in the reproductive system.

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P318

Semen quality in uncontrolled acromegalic patients with hypogonadism

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Objective
Growth hormone (GH) activity might be implicated in male reproductive function. *One* previous study has suggested significantly reduced semen quality in untreated acromegalic patients due to both reduced sperm counts and motility.
Design and methods
A retrospective study comprising 10 uncontrolled hypogonadal acromegalic patients (median age 29y) who delivered semen for cryopreservation before initiation of testosterone therapy. Semen variables and hormone concentrations were compared to those of 10 non-acromegalic hypogonadal men with pituitary disease (age 31 years) and those of young healthy men ($n=340$).
Results
80 % of acromegalic patients vs 50% of non-acromegalic patients had total sperm counts above 39 million and progressive motile spermatozoa above 32% ($P=0.18$) (WHO criteria for normal semen quality based on sperm counts and motility). The corresponding number in healthy controls was 82%. The prevalence of normal semen quality in acromegalic patients vs healthy controls was 80% vs 82% ($P=0.55$) and in non-acromegalic patients vs healthy controls 50% vs 82% ($P=0.022$). Serum IGF-1 was higher in acromegalic patients vs non-acromegalic patients 1017 (421–1434) vs 211 (91–271) mg/l ($P<0.001$). For reproductive hormone levels there were no differences between acromegalic patients vs non-acromegalic patients (P-values between 0.10 and 0.61). Patients ($n=20$) vs healthy controls had lower serum testosterone 5.4 (2.2–7.6) vs 19.7 (15.5–24.5) nmol/l ($P=0.001$), calculated free testosterone 145 (56–183) vs 464 (359–574) pmol/l ($P<0.001$), LH ($P=0.002$), and inhibin b ($P<0.001$). Levels of FSH were similar ($P=0.63$).
Conclusions
Despite severe Leydig cell insufficiency acromegalic patients had semen quality similar to healthy controls based on determination of the number of progressively motile spermatozoa. By contrast non-acromegalic patients had reduced semen quality. Our data do not support reduced semen quality in acromegaly.

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P319

Characteristics, geographical distribution and age at diagnosis of patients with Klinefelter syndrome in Italy: a cohort study from the Klinefelter Italian Group (KING)

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Introduction
Klinefelter syndrome (KS) is the most frequent chromosomal disorders, occurring in 1:500 to 1:1000 live male births, associated to male infertility. Although significant research has been conducted, KS remains frustratingly underdiagnosed with a remarkable portion of cases being unidentified. Under diagnosis may be due to man's hesitancy about seeking medical counseling, low awareness of KS among health professionals, and failure by health professionals to perform routine genital examinations in adult men.
Aim
Our purpose was to describe the phenotypic characteristics and the hormonal patterns of a cohort of patients currently attending a national network of academic or general hospitals of the Klinefelter Italian Group (KING). Moreover, we focused our interest on the geographical distribution, and age at diagnosis of KS in Italy.
Methods
A multicenter, observational study of 594 KS was performed among the patients regularly attending the KING centers, after written informed consent has been obtained.
Results
The mean age was 37.4 ± 13.4 years (median IQR 28–46). The mean testicular volume was 3 ml in both testis, BMI was $26.6\pm5.5.8$ and 25.5% of KS meet the diagnostic criteria for metabolic syndrome (Mets). Mean total testosterone was 350 ± 9.1 ng/dl, LH and FSH mean levels were 16.6 (median IQR 8.8–22.5) and 28.5 (median IQR (17.5–39), respectively. A descriptive analysis performed in 594 KS, showed that 329 KS were referred to KING centers of Northern Italy, 65 and 200 KS patients to KING facilities in Central and Southern Italy, respectively. Analysis of variance showed significant statistical differences ($P<00000$) between the age at diagnosis of the KS of the three geographical groups. In particular, the age of KS patients was significantly lower in Southern Italy (33.3 ± 13 S.D.) compared to Central and Northern Italy (40.2 ± 12.5 S.D. and 39.2 ± 13.3 S.D.).
Conclusions
Our preliminary data showed that KS is highly underdiagnosed in Italy, raising the question of the true prevalence of KS. Our patients presented with a wide spectrum of the classical Klinefelter symptoms. KS were overweight and, surprisingly, only 25.5% of them were diagnosed with Mets. This figure is very close to the Mets prevalence in the Italian general population quoted around 26%. In adulthood, two features were consistently present in every subject: small testes and high FSH and LH/testosterone ratio, despite normal testosterone levels. The

differences of KS age between Italian geographical regions highlight the need for increased awareness leading to timely detection.

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P320

Gonadal Function in Human Immunodeficiency Virus (HIV)-Infected Men: comparison between Isotopic Dilution-Liquid Chromatography-Tandem Mass Spectrometry (ID-LC-MS/MS) and Chemiluminescent Immunoassay (CI)

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Background

HIV-infection is associated to premature decline of serum T. However, prevalence and biochemical characterization of hypogonadism in HIV-infected men are still to be well defined.

Aim

To evaluate the gonadal status in HIV-infected men by assessing circulating total T (TT) with either ID-LC-MS/MS or CI.

Methods

Prospective, cross-sectional, observational study on HIV-infected men with ongoing Highly Active Antiretroviral Therapy (HAART). Serum TT, gonadotropins and sex hormone-binding globulin (SHBG) were measured by CI (Architect, Abbott, USA). TT was also assessed by a validated in house ID-LC-MS/MS. Free T (FT) was calculated by Vermeulen equation. Hypogonadism was defined as serum TT levels below 320 ng/dl and/or free T levels below 64 pg/ml. ***Statistical analysis:*** Parameters were not normally distributed and Mann-Whitney U test, was used to compare continuous variables. Categorical variables were compared using Chi-Square test, while correlations were performed using linear regression models.

Results

315 consecutive HIV-infected men were enrolled (mean age 45.56 ± 5.61 years; average duration of HIV-infection 16.57 ± 10.45 years). Serum TT levels assessed by LC-MS/MS (mean $652.1 + 229.1$ ng/dl) were significantly lower compared to CI (mean $740.2 + 274.7$ ng/dl) ($P < 0.0001$). As a consequence, prevalence of T deficiency was significantly higher comparing LC-MS-MS to CI (5.4% vs 3.2%, $P < 0.0001$). 56 patients (17.8%) showed SHBG above the normal range (>71.4 nmol/l). Considering calculated FT, the prevalence of hypogonadism was 9.8% using LC-MS/MS and 7.0% using CI, with a significant difference between methodologies ($P < 0.0001$). TT assessed with LC-MS-MS was directly related to TT assessed with CI (Beta = 0.956, $R^2 = 0.913$, $P < 0.0001$), as well as FT (Beta = 0.934, $R^2 = 0.873$, $P < 0.0001$). TT combined with luteinizing hormone (LH) levels was used to classify hypogonadism. By including compensated form of hypogonadism, the prevalence raised to 15.6% for TT and to 17% for FT.

Conclusions

To the best of our knowledge, this is the first properly-designed prospective study aiming to investigate the gonadal status of HIV-infected men with both LC-MS/MS and CI, together with gonadotropins. Notwithstanding the strong correlation found between the two methodologies, the prevalence of hypogonadism results underestimated when CI is used compared to ID-LC-MS/MS in HIV-infected patients. In clinical practice, SHBG for calculated FT is essential for the detection of T deficiency, revealing the real prevalence of hypogonadism in this clinical setting.

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P321

Automated free testosterone assay: validation and usual values

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Introduction

Testosterone circulates under different forms in blood, mainly bound to proteins i.e. Sex Hormone Binding Globulin (SHBG) and albumin. Free testosterone (FT), the biologically active form, represents 2% of total testosterone (TT). FT measurement is mainly indicated when TT level is discordant with clinical picture but remains technically challenging. Indeed, as for all free hormones, gold standard method relies on equilibrium dialysis, unusable in routine. Direct immunoassays by competition have thus been designed, traditionally based on sensible radioactive detection signal (RIA). FT can also be calculated from TT, SHBG and albumin levels. Our work aimed to compare a new automated immunoassay to preexisting dosages and to propose adapted usual values.

Materials and methods

Analytical performances of this new FT assay were evaluated. FT was therefore determined in 164 patients (68 women, 96 men) using the new immunoassay (IS-5300, IDS-iSYS Free Testosterone), a RIA immunoassay (KIPI19000, DIAsource), and a calculation based on TT (RIA TESTO-CT2, Cisbio), SHBG, and albumin (Cobas ROCHE) concentrations. Usual values for the new dosage were established.

Results

Analytical performances of the new assay claimed by the manufacturer were confirmed and comparable with those of the RIA assay except for a higher detection limit. Correlation between immunoassays was satisfactory in men ($R^2 = 0.77$) but weaker in women ($R^2 = 0.45$), results with the new automated dosage being globally 30% lower. Correlation between both immunoassays and calculated FT was also satisfactory in men (respectively $R^2 = 0.68$ for automated and 0.76 for RIA immunoassays) and poor in women (respectively $R^2 = 0.15$ and 0.13). Calculated FT was much higher than measured FT, as the corresponding reference values proposed by the manufacturers. This discrepancy was confirmed by the analysis of external quality controls results whatever the direct immunoassay. We proposed preliminary usual values (minimal and maximum values observed in the subgroup of patients with normal testosterone and SHBG levels): 18.9–51.7 pmol/l in men $<$50 years old ($n = 23$); 7.4–39.5 pmol/l in men $>$ 50 years old ($n = 33$); $<$ 6.2 pmol/l in women $<$ 50 years old ($n = 34$) and $<$ 4.3 pmol/l in women $>$ 50 years old ($n = 23$).

Conclusion

IDS-iSYS FT assay is one of the first automated assays allowing FT dosage. Its analytical performances are suitable and provide valuable results in comparison to both RIA immunoassay and calculated FT, at least in men. Clinicians should pay attention to FT usual values indicated by the laboratories, given the large differences observed, particularly between direct immunoassays and calculated FT.

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P322

Assessment of biochemical hyperandrogenism in PCOs by liquid chromatography tandem mass spectrometry using a multisteroid kit: focus on testosterone and androstenedione

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Objective

The identification of hyperandrogenism represents the cornerstone for the assessment of polycystic ovary syndrome (PCOs). However, its definition has always been troubling, mostly because of the poor accuracy shown by routine

androgens assays. As suggested by literature, the application of more precise steroid measurement methods (such as liquid chromatography tandem mass spectrometry, LC-MS/MS) could improve the diagnostic workup. The aim of our study is to evaluate the impact of the assessment of testosterone (T) and androstenedione (A) by LC/MS-MS using a multisteroid kit in the diagnosis of PCOs and in the assignment to the different clinical phenotypes.
Design
We enrolled 98 consecutive patients (24.2 ± 6.2 years) referred for suspected PCOs (menstrual irregularities, hirsutism, alopecia). 10 patients were excluded because other diagnosis were made. T and A were measured both by routine assay (ECLIA and CLIA, respectively) and LC-MS/MS multisteroid kit in the 88 subjects included. Clinical and biochemical parameters associated with metabolic risk (blood pressure, BMI, waist, glucidic and lipidic metabolism) were recorded. 34 pre-menopausal Caucasian eumenorrhoeic, without clinical hyperandrogenism volunteers served as a control group to derive LC-MS/MS T and A reference ranges.
Results
According to the Rotterdam consensus, based on T measurement by ECLIA PCOS was confirmed in 65/88 subjects: 87.7% were oligoamenorrhoeic, 84.6% had clinical hyperandrogenism, 63% had polycystic ovaries and 54% high AMH levels. Measuring T by LC-MS/MS, PCOs was diagnosed in 67/88 subjects. High T (HT) was found in 43% and 56.7%, while high A (HA) was found in 47.6% and 59.7% PCOs patients respectively by routine assays and LC-MS/MS. Based on LC-MS/MS 19 (28.4%) patients were normoandrogenic, 8 (11.9%) had HT, 10 (14%) HA and 30 (44.8%) HT + HA. Routine assays misclassified 15 patients as normoandrogenic. Hyperandrogenic PCOs patients by LC-MS/MS showed a higher total cholesterol levels than normoandrogenic ones (161.8 ± 32.9 vs 144.8 ± 28.7 respectively, $P = 0.05$), glucidic metabolism and clinical parameters were comparable. No difference was observed between the two groups when hyperandrogenism was identified by routine assays.
Conclusions
LC-MS/MS is more sensitive than routine assays in identifying biochemical hyperandrogenism in PCOs patients. These patients seems to have a slightly worse metabolic profile. Regardless of the measurement method used, A is the most frequently elevated androgen in our PCOs patients cohort.

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P323

Effects of fludioxonil on cardiac differentiation of mouse embryonic stem cells

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Fludioxonil, a phenylpyrrole fungicide, is extensively used to protect particularly fruits and vegetables from fungi. On the contrary, it has been reported that fludioxonil caused low weight birth in rats at parentally toxic doses. However, its developmental toxicity on cardiac differentiation has not yet been understood. In the present study, the early developmental toxicity of fludioxonil on the cardiac differentiation of mouse embryonic stem cells (mESCs) was evaluated. Firstly, the effect of fludioxonil (10^{-5}–10^{-9} M) on mESCs viability was determined by the water soluble tetrazolium (WST) assay conducted for 5 days. The cell viability significantly decreased under 50% at 10^{-5} M fludioxonil, but there was no change in cell morphology by fludioxonil (10^{-5}–10^{-9} M). Then, the colony formation assay was performed to confirm the effect of fludioxonil on cell proliferation. Cell proliferation was suppressed by 10^{-5} M fludioxonil, compared to the control (0.1% DMSO) at 5 days, but it was re-increased at 10 and 15 days. In hanging drop assay to test embryoid body (EB) formation capacity of mESCs, fludioxonil reduced the EB size at 10^{-5} M. In the process of differentiation to cardiomyocytes derived from mESCs, 10^{-5} M fludioxonil completely inhibited the beating ratio (the ratio of the number of contracting cells to the number of attached EBs) of cardiomyocytes at early stage of differentiation (day 5), but the beating ratio gradually increased after 5 days at 10^{-5} M fludioxonil. It seemed that fludioxonil delayed the differentiation of mESCs to cardiomyocytes at 10^{-5} M compared to control. These results imply that fludioxonil may have a potential toxicity on the developmental process of mESCs, especially into cardiac lineage. For more information for developmental toxicity of fludioxonil, further studies on the mechanisms of fludioxonil to induce altered cell proliferation and cardiac differentiation of mESCs are needed.

Keywords: Pesticides, fludioxonil, mouse embryonic stem cells, cardiomyocytes
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P324

Monitoring testosterone gel administration: timing and dosage

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Background
Many testosterone (T) formulations are now available for treating male hypogonadism. Intramuscular injectable T esters and transdermal T gel are the most commonly used in clinical practice. Transdermal T gel is often preferred by patients due to ease of use and reduced fluctuations in serum T compared to injectable esters. A daily dosage of 20 mg – 80 mg mimicking circadian profile is recommended to adequately treat hypogonadal men.
Aim
There is conflicting evidence concerning intraindividual variability in serum T level after T gel administration. We aim to evaluate serum T level two hours and twenty-three hours after gel admnistration
Materials and Methods
Thirty-one male long-term hypogonadal patients were asked to apply 2 g of T gel (40 mg) in the morning to the upper arms/shoulders. Two blood samples were collected 2 hours after gel administration at peak serum T (T + 2) seven days apart. Subsequently, two blood samples were collected twenty-three hours after gel administration at nadir serum T seven days apart (T + 23).
Results
No significant difference in serum T was observed between the two samples taken at T + 2 (8.15 ± 8.24 vs 8.06 ± 7.09 ng/ml, $P = 0.818$) and T + 23 (3.41 ± 2.45 vs 2.91 ± 1.87 ng/ml, $P = 0.226$). Furthermore, as expected, a significant positive correlation between the two samples was found for serum T at T + 2 ($r = 0.973$, $P = 0.001$) as well as at T + 23 ($r = 0.482$, $P = 0.006$). Otherwise, average T values at T + 2 and T + 23 are significantly different (8.11 ± 7.61 vs 3.19 ± 1.90 ng/ml) and do not correlate significantly ($r = 0.062$, $P = 0.747$). At T + 23, 13 men (41.94%) showed serum T greater than 3.46 ng/ml, 14 (45.16%) showed serum T values below 2.31 ng/ml and 4 (12.9%) had serum T values in the 'grey zone'.
Discussion
T gel administration is not affected by day-to-day intraindividual variability when T is measured both at peak and at nadir. This data permits to avoid frequent blood samples to evaluate serum T response to gel administration. The lack of correlation between T + 2 and T + 23 shows that it is not advisable to estimate T peak level considering T nadir level. A measurement of T level both at its peak and at its nadir is suggested to evaluate T gel therapy. Finally, 40 mg T gel may not be enough to reach T reference range in all subjects undergoing treatment.

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P325

Menstrual cycle characteristics in women with premature ovarian insufficiency

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Premature ovarian insufficiency (POI) is characterized by cessation of ovarian function before the age of 40. Variable clinical presentation often postpones the diagnosis. The aim of our study was to assess whether there is a typical menstrual cycles pattern in patients with POI. We have evaluated 101 women, age 36.7 ± 5.78 y. FSH = 78.81 ± 37.43 IU/l, E2 < 50 pg/dl, with confirmed POI referred to our Clinic between 2014 and 2018. Menstrual cycles characteristics were defined according to the pattern of cessation: abrupt (amenorrhoea) or gradual. Gradual pattern was defined according to the length as: shortened (< 26 days), prolonged (> 33 days) or variable (first shortened than prolonged) and according to the quality of menstrual bleeding: normal, scarlet or heavy. Also, we have grouped our patients according to the age: < 35 (age 27.9 ± 4.7 FSH = 27.95 ± 4.76 IU/l) and 35–40 (age 37.53 ± 1.90, FSH = 37.52 ± 1.89 IU/l) years. Besides aforementioned and the basic anthropometric measurements (height, weight, waist to hip ratio, body mass index (BMI)) we have collected the information about the age of menarche and the age of mother's menopause. Overall, the most frequent pattern of menstrual cessation was gradual ($P < 0.001$). However, in the group of patients < 35 y. there was a substantial number of patients with the abrupt cessation of

menstrual cycle. Overall, patients had significantly higher number of prolonged ($P<0.01$) and heavy menstrual cycles ($P<0.001$) when compared to other types of menstrual cycle length and quality. When analyzed according to age, there was no significant difference in aforementioned parameters. According to the anthropometric measurements the older group had significantly higher waist ($P=0.025$) and hip circumference ($P=0.030$) and significantly higher BMI (23.29 vs 20.84 kg/m^2). There was no significant difference between the groups according to the age of menarche or age of mother's menopause. The results of our study show that patients with POI are expected to have gradual onset of menstrual cessation with prolonged menstrual cycles and heavy bleedings. However, when it comes to patients under 35 years of age it is important to bare in mind that even one missed cycle in women with previously regular menstrual cycles maybe a sign of POI.

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P326

Endocrine and menstrual disorders in adolescent girls: clinical parallels

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Menstrual disorders are common during adolescence. In many cases menstrual disorders associated with endocrine violations.

Objective

To study the frequency menstrual disorders and endocrine violations in adolescent girls.

Patients and methods

The study included 2527 adolescents- schoolgirls (aged 12–17 years, mean age was 15.5 ± 1.9 years). The main outcome measures were menstrual disorders. Adolescent girls without menstrual disorders formed the control group ($n=50$). A full clinical examination, hormonal analysis and thyroid and pelvic ultrasound examination were conducted. This study was carried out in accordance with the Helsinki Declaration. Data was analyzed using SPSS Statistics v 24.0.0.0. Data was compared using chi-square test and $P \leq 0.05$ was regarded as statistically significant.

Results

The median age of menarche in this investigation is 12.3 years. Dysmenorrhea and oligomenorrhea were the most common menstrual disorders in girls. The prevalence of dysmenorrhea was 62%. In girls with dysmenorrhea in 1% cases was diagnosed hyperprolactinemia, in 20% – inflammation of genitals and in 30%- ovarian cysts. Among the girls with dysmenorrhea thyroid diseases (endemic goiter) were revealed in 73% cases. Oligomenorrhea was diagnosed in 22% adolescent girls and was associated in 80% cases with hirsutism. The investigation showed that in 5 girls with oligomenorrhea and hirsutism was diagnosed nonclassic congenital adrenal hyperplasia due to P450c21 (21-hydroxylase deficiency), 18 girls had polycystic ovary syndrome. Pelvic ultrasound examination established that 65% patients with oligomenorrhea and hirsutism had multifollicular ovaries. In the control group thyroid diseases (endemic goiter) was diagnosed in 20% adolescent girls, hirsutism – in 1% and multifollicular ovaries – in 8% girls ($P<0.01$)

Conclusions

This study demonstrates a high frequency of menstrual disorders in adolescent girls. Dysmenorrhea associated with hyperprolactinemia, ovarian cysts and thyroid diseases, oligomenorrhea associated with nonclassic congenital adrenal hyperplasia, polycystic ovary syndrome and multifollicular ovaries.

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P327

Effects of percutaneous treatment of left varicocele on spermatogenetic and endocrine function of the testis: results from a 12-month follow-up

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Background

Varicocele repair is often suggested to improve reproductive outcomes, but there is no clear indications on which subjects are more likely to benefit from treatment. We assessed spermatogenetic and endocrine function of the testis in a population of young subjects with a 12-month follow-up following percutaneous treatment.

Methods

We retrospectively reviewed data from 77 young patients (mean age 23.3 years, range 18–35) followed in our center for treatment of isolated left varicocele and with no other condition possibly affecting testicular development, such as cryptorchidism, orchitis, testicular tumors and chromosomal aberrations. Varicocele recurrence was also considered as an exclusion criterion. Statistical analysis was performed with robust linear mixed effects regression models, with each subject acting as his own control. Spermatogenetic function was assessed by semen analysis following the WHO guidelines. Endocrine assessment included serum FSH, LH, inhibin B, total testosterone and estradiol.

Results

19/77 subjects (24.7%) had left testicular hypotrophy (LTH, >20% difference between left and right testicular volume). Treatment significantly improved sperm progressive motility during follow-up in subjects with pre-treatment LTH ($\beta = 7.46 \pm 2.27$, $P=0.007$), independently of testicular volume increase. A significant negative effect of pre-treatment varicocele grade was observed for sperm morphology at the end of follow-up for both grade 3 ($\beta = -3.72 \pm 1.6$, $P=0.024$) and 4 (-3.64 ± 1.82, $P=0.035$). No significant effects were observed for sperm concentration (both total and per ml), even after adjusting for LTH and varicocele grade. A significant increase in serum Inhibin B was observed during follow-up, and we observed a statistically significant effect of the change of FSH on serum inhibin B levels ($\beta = 34.2 \pm 11.75$, $P=0.008$).

Conclusions

Treatment of isolated left varicocele is associated with minor improvements in sperm parameters, but the clinical relevance of these findings is still debated. In regards to endocrine function of the affected testis, we observed a significant increase in inhibin B levels according to changes in FSH levels, suggesting that Inhibin B production by Sertoli cells is stimulated by FSH during follow-up.

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P328

Predictive factors of polycystic ovary syndrome in women with morbid obesity

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Introduction

Polycystic ovary syndrome (PCOS) is a common disorder in women. Hyperandrogenism and chronic oligo-anovulation are the prominent clinical features. The aim of our study was to determine the prevalence and the predictive factors of PCOS in a group of women with morbid obesity.

Methods

We performed a cross sectional study in 50 women with a body mass index (BMI) $\geq$ 40 kg /m^2 collected over a period of 6 months (October 2017–March 2018). Anthropometric assessment and review of medical records were performed. The ovarian morphology was evaluated by sus-pubic ultrasound. All patients had their metabolic and hormonal profiles evaluated. PCOS was diagnosed according to Rotterdam criteria.

Results

The average age of our patients was 34.2 ± 7.51 years.The mean BMI was 44.53 ± 3.97 kg /m^2 and the mean waist circumference was of 123.38 ± 10.89 cm. PCOS was identified in 40% of cases.There was no statically significant difference in anthropometric parameters in patients with or without PCOS. Menstrual irregularity and hirsutism were higher in patients with PCOS comparing with patients without PCOS (80% vs 20%; $P<0.001$ and 80% vs 23%; $P<0.001$; respectively). Ovarian ultrasound revealed that 36% had polycystic ovaries (65% in PCOS vs 17.9% in non PCOS; $P=0.04$). As for hormonal tests, a significant difference between the PCOS and non PCOS women was found regarding LH levels and LH/FSH (4.8 ± 2.1 vs 3.3 ± 2.02; $P=0.01$ and 0.9 ± 0.3 vs 0.5 ± 0.2; $P=0.001$, respectively). Predictive factors of PCOS in morbid obesity were the presence of menstrual disturbance (OR = 22.6; $P<0.001$), hirsutism (OR = 13.1; $P<0.001$), LH/FSH >1 (OR = 6.8; $P=0.007$) and an ovary volume > 10 ml (OR = 11; $P=0.001$).

Conclusion

Our study showed a high prevalence of PCOS in women with morbid obesity. In fact, due to the hyperinsulinemia, obesity causes a reduction in SHBG levels

responsible of the signs of hyperandrogenemia. Furthermore, PCOS is characterized by abnormalities in the gonadotropin hormone releasing hormone, or GnRH, pulse generator leading to preferential increase in LH release over follicle stimulating hormone (FSH). Thus, a routine screening by obtaining at least a menstrual history and a careful evaluation for hyperandrogenism may be indicated in severely obese women.

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P329

Randomised Controlled Trials in women with polycystic ovary syndrome do not represent the majority of patients who are in a primary care setting: systematic review and meta-analysis

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Introduction
Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, with important long term health consequences such as higher chance of developing Type 2 diabetes, reduced overall wellbeing with poor quality of life. Such a common condition is mainly treated and investigated in the primary care setting.We therefore set out to see if the randomized controlled trials (RCT) represent the most common setting of care.
Materials and Methods
We searched one major search engine (Pubmed) for 'Polycystic Ovary Syndrome' and extracted all the RCTs between 01/01/2010 and 31/12/2018. Only English language publications were included. Data on the source of recruitment and dropout rate from studies were extracted where available.
Results
Search yielded a total of 7380 abstracts on PCOS of which 287 RCTs met the criteria including 29460 women with PCOS. The most common source for recruitment was specialized departments and outpatient clinics ($n=25317$; 85.9%). Only 4.4% ($n=1297$) had been recruited from primary care and community advertisements or sites. Sources of recruitment were not clear in 9.7% ($n=2846$). The average dropout was 13.35% (27.69% for primary care and community advertisements or sites, and 12.61% for specialized departments and outpatient clinics).
Conclusion
The main pool of women with PCOS are in primary care and only a selected group are referred to specialist clinics. However, RCTs which inform the treatment guidelines have mainly recruited their patients from this selected group of patients in the secondary care setting. We suggest that clinical trials are needed in the primary care setting in order to better understanding the care for these patients in this more common clinical setting.

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P330

The awareness of the side effects of the use of AAS as a factor of the conscious rejection of their use: The price of a beautiful body

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Background
The motivation for the use of AAS by men engaged in recreational activities is the improvement of body composition and strength indicators. A deterrent to the use of AAS can be awareness of the side effects of their use, in particular the development of secondary hypogonadism.
Aim
To study the awareness of AAS users about the negative impact of this class of drugs on the body.
Methods
An individual anonymous correspondence questionnaire was conducted for men in gym. We studied information about the use of AAS, the attitude to use of AAS, awareness of the side effects of their use, patterns and duration of their use, the desire of respondents to obtain reliable information about steroids and their effects on health.
Results
762 questionnaires were provided for the assessment. 550 questionnaires were met the criteria. AAS was used by 30.4% of respondents ($n=167$). The main consumers of AAS were men aged 22 to 35 years old - 74.3%. The most common drugs were Testosterone propionate (51.5%). The most common dosage of injectable testosterone was 1000 mg per week (23.9%). The use of AAS over 9 months was indicated by 11% ($n=19$) of men. The main source of information on AAS was indicated by the Internet (48.7%). A negative attitude towards AAS was formed by 17.3% of respondents. 69.3% ($n=381$) of respondents gave a positive answer to the question about awareness about AAS, 30.7% - negative ($n=169$). Almost all respondents using AAS indicated that they have information on AAS - 96.4% ($n=161$). In the group of non-AAS users, the majority of respondents are informed about AAS - 57.4% ($n=220$), 42.6% ($n=163$) are not informed. Among all respondents to a clarifying question about awareness of side effects and complications of using AAS, an affirmative answer was 73.8% ($n=406$), negative - 26.2% ($n=144$). AAS users are more aware of AAS ($\chi^2=82.954$, $P<0.001$) and their side effects ($\chi^2=70,207$, $P<0.001$) compared to non-users. 22% ($n=121$) of the respondents were not informed with the side effects of steroids. 54.8% respondents expressed desire to receive qualified information about the AAS.
Conclusion
The survey data indicates a high awareness of the side effects of using AAS, which, surprisingly, does not lead to the conscious abandonment of their use by people engaged in recreational activity. However, a significant percentage of those wishing to receive qualified information about the dangers of steroids gives hope that the information can still become the main tool in limiting the use of doping drugs.

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P331

Fenhexamid increased the cell viability and metastasis of breast cancer cells via an estrogen receptor-dependent and PI3K/AKT pathway

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Fenhexamid (Fen) is a fungicide used to treat the gray mold of fruits and vegetables. In this study, the ER positive-MCF-7 breast cancer cells were used to examine the effects of Fen on breast cancer progression. MCF-7 cells were cultured with 0.1% DMSO (control), 17β-estradiol (E2; 1×10^{-9} M) and Fen (10^{-5}–10^{-7} M) in the absence or presence of ICI 182,780 (ICI, ER antagonist, 10^{-8} M) or Pictilisib (Pic, PI3K inhibitor, 10^{-7} M). In MTT assay, Fen increased MCF-7 viability about 2.5 times compared to a control like E2 (about 3 times). When co-treated with Pic or ICI, the cell viability increased by E2 or Fen was inhibited partially or completely. The cell viability increased by E2 or Fen was more inhibited by co-treatment with Pic and ICI than a single co-treatment of Pic or ICI. Likewise, E2 and Fen increased the ratio of MCF-7 cells that entered the S-phase of cell cycle, but co-treatment of Pic and ICI increased the cell ratio in the G0/G1-phase. And, the colony formation of MCF-7 cells was increased by E2 and Fen, while it was, in part, reversed in the presence of Pic or ICI and completely reversed by co-treatment with Pic and ICI. In wound-healing scratch assay, the scratched distance was reduced by MCF-7 cells treated with E2 or Fen compared with a control. However, the scratched distance was maintained to the control level by the co-treated with ICI or co-treatment with Pic and ICI. In migration assay, E2 or Fen increased migration of MCF-7 cells more than 5 times compared with a control, while co-treatment with ICI or co-treatment with Pic and ICI reversed E2 or Fen-induced migration. Collectively, Fen may induce cancer progression by increasing cell viability and migration via an ER dependent pathway and PI3K pathway. Hereafter, the mechanisms underlying the breast cancer progression induced by Fen will be identified by the examination on the protein expression of related genes.
Keywords: Fenhexamid, Estrogen receptor, PI3K/AKT pathway

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P332

Natural estradiol in combined oral contraceptive has a favorable inflammation and lipid profile compared with preparation containing ethinyl estradiol– a randomized controlled trial

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Study question
Does the combination of estradiol valerate (EV) and dienogest (DNG) have favorable effects on inflammation and lipids compared with ethinyl estradiol (EE) + DNG?
What is known already
Use of combined oral contraceptives (COCs) increases HDL-cholesterol and triglycerides and promotes low-grade inflammation. The metabolic effects of COCs depend on both estrogen and progestin components. To our knowledge this is the first study comparing COCs containing EE and EV combined with the same progestin.
Study design
Randomized, controlled, open-label clinical trial. Power calculation was based on primary outcomes of glucose metabolism. Sixty volunteers were recruited and randomized to use either EE + DNG, EV + DNG or DNG-only continuously for 9 weeks.
Materials & methods
Participants were healthy, young, non-smoking women with regular menstrual cycles. Wash-out period for hormonal medication was a minimum of two months. Mean age, BMI and WHR were comparable in all study groups at the beginning of the study. 56 women completed the study (EV + DNG $n=20$, EE + DNG $n=19$ and DNG-only $n=17$).
Main results and the role of chance
Serum hs-CRP increased during the use of EE + DNG (mean change ± s.d. 1.10 ± 2.11 mg/l) compared with EV + DNG (−0.06 ± 0.97 mg/l) or DNG-only (0.13 ± 0.68 mg/l) ($P=0.001$ and $P=0.021$ respectively). Pentraxin, another marker of low-grade inflammation, was also increased in the EE + DNG group compared with EV + DNG and DNG-only groups ($P=0.017$ and $P=0.003$). EE + DNG group displayed higher HDL cholesterol and triglyceride levels (HDL: EE + DNG 0.20 ± 0.24 mmol/l vs EV + DNG −0.02 ± 0.20 mmol/l, $P=0.002$, vs. DGN −0.02 ± 0.18 mmol/l, $P=0.002$; Triglycerides: EE + DNG 0.45 ± 0.21 mmol/l, vs EV + DNG 0.18 ± 0.36 mmol/l, $P=0.003$, DNG 0.06 ± 0.18 mmol/l, $P<0.001$). To conclude, the EV + DNG and DNG-only preparations seem to have better metabolic profile compared with EE preparation.
Limitations
The study period of 9 weeks is too short for conclusions about the possible long-term effects of the studied preparations. As the power calculation was based on glucose metabolism, there is a chance of type II error for statistically non-significant findings.
Implications of the findings
According to the present data, COCs containing EV and DNG-only have neutral effects on the markers of inflammation and lipids compared with EE containing preparations. As contraceptives often are used for decades, these results may have clinical significance when choosing preparation for patients with increased metabolic risk.
Trial registration number: NCT02352090

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P333

Modes and actions of inter-individual transfer of estradiol and progesterone among conspecifics in both mice and bats

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We have investigated inter-individual transfer of 17β-estradiol (E_2) and progesterone (P_4), and related it to mammalian 'pheromonal' effects. Assays of unconjugated E_2 and P_4 revealed their presence in male and female urine of laboratory mice and big brown bats (*Eptesicus fuscus*), which are phylogenetically very distant from each other. These small and lipophilic steroids readily pass through biological membranes. After cutaneous or nasal exposure, radiolabeled E_2 (^{3}H-E_2) or P_4 (^{3}H-P_4) arrived in blood and tissues, but only arrived in the brain after nasal exposure[1–4]. After 48 h of cohabitation with male stimulus animals treated with doses of ^{3}H-E_2 that represent a small fraction of their endogenous E_2, untreated females showed significant radioactivity in blood serum, uterus, and other tissues in both mice and bats. Seminal emissions of diverse mammals contain E_2, and we found that ^{3}H-E_2 transfers from males directly to the female's reproductive tract during mating[5]. Ovariectomized female mice were made sexually receptive by E_2 and P_4 injections. When these females were paired with males given ^{3}H-E_2, the amount of radioactivity in females' serum increased with the number of sexual intromissions, and females that received an ejaculation showed especially high radioactivity in the uterus. In other experiments, females were all mated to the point of insemination with young adult males given ^{3}H-E_2. Substantial radioactivity was observed in the males' epididymides, preputials, and vesicular-coagulating glands, and their copulatory plugs and semen taken from the females' reproductive tracts showed high levels of radioactivity that lingered there at least 18 h after mating. The uterus is densely populated with estrogen receptors. Male-to-female transfer of E_2 has been related to suppression of pregnancies sired by other males (Bruce effect) and male-induced acceleration of puberty (Vandenbergh effect), and may also relate to male-induced estrous cycling (Whitten effect) and ovulation[6]. Female-to-female transfer of ^{3}H-P_4 has been observed in mice[2], and it could possibly explain suppression of estrous cycling in group-housed female mice (Lee-Boot effect)[6]. Female-to-female transfer of ^{3}H-P_4 has also been found in big brown bats, which notably roost in very close contact in predominantly female groups[4].
References
1. Guzzo *et al*. 2012 *Reproduction* 143:539–48.
2. Guzzo *et al*. 2013 *J Endocrinol* 217:1–10.
3. deCatanzaro *et al*. 2014 *Gen Comp Endocrinol* 208:126–33.
4. Greville *et al*. 2017 *Gen Comp Endocrinol* 247:199–204.
5. deCatanzaro & Pollock 2016 *J Endocrinol* 231:245–57.
6. deCatanzaro 2015 *Horm Behav* 68:103–16.

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Definition of hormonal cut-off values for discriminating polycystic ovary syndrome from non classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Objective
The aim of this study was to define which hormonal cut-off values can discriminate polycystic ovary syndrome (PCOS) from non classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21-NCAH).
Patients and methods
We included 70 women in reproductive age who attended our Unit from 2003 to 2018 for a diagnosis of PCOS with a basal 17hydroxyprogesterone (17OHP) level in the follicular phase of the menstrual cycle ≥200 ng/dl measured by 17OHP Bridge RIA immunoassay (Adaltis, Guidonia, Italy). All patients performed CYP21A2 gene analysis by direct DNA sequencing and multiplex ligation-dependent probe amplification (MLPA), that we used to discriminate PCOS from 21-NCAH. They also performed a $_{1\text{-}24}$ACTH test in the follicular phase of the menstrual cycle.
Results
Twenty-three patients resulted affected by 21-NCAH, 15 were found to be heterozygotes for the 21-hydroxylase deficiency (21-HTZ) and 32 had no mutations for CYP21A2 gene (21-NM). As expected, the three groups significantly differed for basal 17OHP levels (21-NCAH: 2072 ± 2671 ng/dl; 21-HTZ: 298 ± 88 ng/dl; 21-NM: 322 ± 110 ng/dl; P value <0.001). Accordingly, 17OHP levels at 60 minutes of the $_{1\text{-}24}$ACTH test (17OHP60) resulted significantly higher in affected than in unaffected patients; (21-NCAH: 5022 ± 5203 ng/dl; 21-HTZ: 638 ± 393 ng/dl; 21-NM: 515 ± 290 ng/dl; P value <0.001). Cut-offs were generated for basal 17OHP and 17OHP60 by linear interpolation methods of determining quartiles. The cut-off values yielding the best sensitivity were ≥350 ng/dl for basal 17OHP and ≥677 ng/dl for 17OHP60. Using these cut-off values 1/23 patient with 21-NCAH (4%) could be diagnosed as PCOS, whereas 4/47 PCOS (8%), 3 of 21-NM group and 1 of 21-HTZ group, could be diagnosed as 21-NCAH.
Conclusion
We found that the contemporary use of basal and stimulated 17OHP is a valid diagnostic method to distinguish 21-NCAH from PCOS. The best thresholds seem to be 350 ng/dl for basal 17OHP and 677 ng/dl for 17OHP60, as measured by RIA immunoassay, still being nowadays the most used way to measure 17OHP in italian labs.

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Lipid parameters during pregnancy

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Introduction
The basic characteristics of metabolism in pregnancy are changes from anabolic to catabolic conditions with an increase in insulin resistance, moderate, reversible increase in lipid concentration in the blood, and accumulation of fat stores in the mother's tissues. Lipid metabolism is essential for the development of healthy pregnancy, and fatty acids are a significant source of energy and a key element for membrane synthesis, while cholesterol, in addition to the construction of membranes, is necessary for the synthesis of steroid hormones. The lipid profile changes atherogenically during normal pregnancy. These changes do not reflect the pathological condition, but they represent the necessary adjustment of the mother's physiology in order to satisfy the energy needs of the fetus and prepare the organism of the mother for delivery and lactation. The lipid profile that mimics the pathological finding of Metabolic Syndrome is a common finding during the second half of pregnancy. The mechanisms of lipid metabolism change are not entirely clear.
Aim
The aim of this study is to analyse concentration of lipid parameters during pregnancy.
Matherial and methods
This study included 77 healthy pregnant women in the first trimester of pregnancy registered in Center for endocrinology CC Kragujevac. Blood samples were collected for tHol, HDL, LDL and TAG during 1., 2. 3rd trimester, as well 2 months after delivery.
Results
The mean age of patients was 30.8±4.7 years. The prevalence of thyroid disorder was in 9%, hypertension 5.2%, gestational diabetes 23.4% and smoking in 23.4% patients. It has been shown that as pregnancy progresses, the value of lipid parameters increases, especially total cholesterol and triglycerides. The highest increase was seen in the 3rd trimester of pregnancy. The difference in parameters of liporegulation during pregnancy occurs in the 2nd and 3rd trimesters, while it does not appear in the 1st trimester.
Conclusion
This study demonstrates that as pregnancy progresses, the value of lipid parameters increases, especially total cholesterol and triglycerides.
Keywords: Lipid parameters, pregnancy

Table 1 Mean values of lipid parameters during pregnancy.

$\bar{X}$±SD *(95%CI)*	1.trimester	2. trimester	3. trimester	After delivery
***tHol* (*mmol/L*)**	4.69±0.96 (4.42–4.86)	6.52±1.35 (6.22–6.83)	7.37±1.54 (7.02–7.72)	5.76±1.28 (5.46–6.05)
***HDL*- cholesterol (*mmol/L*)**	1.49±0.39 (1.4–1.58)	1.92±0.41 (1.83–2.01)	1.83±0.45 (1.73–1.93)	1.51±0.39 (1.42–1.59)
***LDL*- cholesterol (*mmol/L*)**	2.67±0.85 (2.48–2.86)	3.87±1.17 (3.61–4.14)	4.44±1.34 (4.13–4.74)	3.84±1.26 (3.55–4.13)
triglycerides (*mmol/L*)	1.12±0.63 (0.97–1.26)	1.88±0.78 (1.71–2.06)	2.68±1.13 (2.42–2.93)	1.37±0.84 (1.18–1.65)

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P336

Dysmenorrhea prevalence and its impact on daily functioning of university nursing students in greece

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Background
Dysmenorrhea is defined as pain during menstruation and might be caused by increased endometrial prostaglandin production. It is a highly prevalent medical condition (45–95% of women internationally) which can be part of a woman's reproductive life. Throughout the literature, dysmenorrhea has been shown to affect daily functioning such as socialization, work and academic performance during menstruation and quality of life. However, dysmenorrhea and its impact in Greek women had not been investigated yet.
Aim
To evaluate the prevalence of dysmenorrhea and the impact of its severity on daily functioning in a sample of nursing students at a Greek University.
Methods
A cross-sectional descriptive study was conducted recruiting 637 nursing students via convenience sampling at a university in Athens. Appearance, severity (mild, moderate or severe pain) and the impact of dysmenorrhea were assessed by administering a questionnaire which included a 10-point Visual Analogue Scale (VAS) of pain magnitude.
Results
The majority of students (89.2%) reported experiencing pain during menstruation. Only severe dysmenorrhea was reported to affect daily functioning in situations that can be avoided (all $ps < .05$). However, functioning in situations that cannot be avoided (clinical placement and exam attendance) were less affected by dysmenorrhea no matter its severity ($ps > .1$).
Conclusions
Dysmenorrhea is highly prevalent among nursing students in Greece and its severe form seems to affect important aspects of daily and academic functioning. However, the situations that cannot be easily avoided (exam and clinical placement attendance) were not affected and future research could further investigate this finding. These findings suggest that there is a need for doctors, nurses and midwives to educate women with dysmenorrhea on recognizing and properly treating and copying with their menstrual pain to alleviate its impact on daily functioning.

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Thyroid 1

P337

The serum thyroglobulin level after discontinuation of two weeks of thyroid hormone in patients with differentiated thyroid cancer can be used to determine the therapeutic dose of radioiodine

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Purpose
This retrospective study is intended to determine the dose of radioactive iodine using thyroglobulin levels measured after two weeks of thyroid hormone withdrawal in patients with differentiated thyroid cancer.
Methods
Patients who were diagnosed as differentiated thyroid cancer and treated with radioiodine after total thyroidectomy were enrolled. Serum thyroglobulin test (preTG; ng/dl) was performed 1 week before radioiodine treatment and 2 weeks after thyroid hormone stoppage. They received 30 mCi, 100 mCi, and 150 mCi of radioactive iodine in consideration of preTG, post-operative pathologic stage, surgeon's recommendation, and patient selection. After 6 months of radioiodine treatment, complete ablation was investigated. Complete ablation was defined as showing no uptake in diagnostic I-131 scan, stimulated thyroglobulin of less than 1.0 ng/dl and thyroglobulin antibody of less than 100 ng/dl. Patients with preTG less than 3.09 were divided into 30 mCi, 100 mCi, and 150 mCi groups, and the complete ablation of each group was investigated and statistically analyzed.
Results
Seventy patients (female = 55, mean age = 48 yrs; 21–78 yrs) with a preTG level of 3.09 or less were investigated. Patients were divided into 30 mCi ($n = 7$, mean preTG = 1.11; 0.04–3.09), 100 mCi ($n = 51$, mean preTG = 0.80; 0.04–3.09), 150 mCi ($n = 12$, preTG = 1.23; 0.1–2.8) groups. Complete ablation rates were 71.4% (5/7), 86.3% (44/51) and 75.0% (9/12), respectively. When each group was compared through the Kruskal-Wallis test, there was no statistically significant difference in complete ablation between treatment groups ($P = 0.458$). There was no statistically significant difference between the two groups in the Mann-Whitney test (30 mCi vs 100 mCi, $P = 0.313$; 30 mCi vs 150 mCi, $P = 0.868$; 100 mCi vs 150 mCi, $P = 0.340$).

Conclusion
30 mCi is recommended if thyroglobulin levels measured after two weeks of thyroid hormone withdrawal in patients with differentiated thyroid cancer is 3.09 or less than.

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P338

Thyroid-associated orbitopathy and quality of life: correlation of GO-QoL with clinical activity score and severity in 101 patients

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Thyroid-associated orbitopathy (TAO) is a classic and sometimes severe complication of autoimmune process associated with thyroid diseases, more common in Graves' disease. Due to its functional impairment and disfiguring clinical presentation, TAO affects the quality of life of patients. Few studies have examined the importance of this impact in these patients. The main objective of this retrospective study is to determine if there is a correlation between the deterioration of quality of life in patients seen in a multidisciplinary orbitopathy consultation and the severity or inflammatory of the TAO. 101 patients (75 women, mean age 51 ± 12 years, 93 Graves' diseases) consulting for a TAO between March and November 2017, completed the GO-specific quality of life questionnaire, GO-QOL, validated by EUGOGO. This questionnaire is sub-devised in two subscales, one measuring the consequences of diplopia and decreased visual acuity on visual functioning, and one measuring the psychosocial consequences of a changed appearance. Clinical activity was evaluated using the Clinical Activity Score (CAS) and clinical severity based on three criteria (decrease of visual acuity, oculomotor disorders, proptosis). 9.9% of patients had active TAO (CAS ≥ 3) and 47.5% had severe impairment. No significant correlation was found between quality of life, both for visual functioning and for appearance, and TAO severity (respectively $P = 0.89$ and 0.88). However, inflammatory activity was significantly associated with impairment of the quality of life for visual functioning ($P = 0.01$) and there was a non-significant trend for appearance ($P = 0.08$). The deterioration of the quality of life in terms of appearance was significantly more important for women ($P < 0.001$). This study confirms an alteration in the quality of life among patients with TAO, correlated with inflammatory activity, which is more important in women because of appearance consequences. During TAO treatment, the GO-QoL questionnaire could be useful for early detection of patients needing psychological support.

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P339

The influence of thyroid gland subclinical form on hypercholesterolemia patients in Latvia

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Introduction
It is a well-known fact that in Baltic Sea region there is low level of ecological selenium and iodine in soil and water, which can lead to subclinical hypo-activity of thyroid gland. By epidemiological data of that region, chronic stress and low insolation favour the decrease of metabolic rate, hypercholesterolemia and obesity in 30% of population.
Method
In Dietological Centre of Jurmala, Latvia, 87 obese patients, in the age group of 25–37, were observed in this study. During 7–10 days patients were given low calorie (180–300 kcal per day) cascade diet. In that period of time and 5 weeks after they were given 150 mkg of selenium and 150 mkg of iodine from kelp extract per day as nutritional supplements. Patients were tested by standard biochemical methods – levels of TSH; free T_3 and T_4; total cholesterol; LDL cholesterol as well as they got weighed – before and after the course.
Results
After the course 75% of patients detected the normalization of these parameters:

- TSH: 0.28 ± 0.02 to 0.34 ± 0.03 mIU/l
- T_3: 0.68 ± 0.04 to 0.90 ± 0.03 mIU/l
- T_4: 4.4 ± 0.02 to 4.8 ± 0.04 mIU/l

Lipid metabolism was normalized as well: In average total cholesterol reduced for 38%; LDL cholesterol reduced for 21%; weight reduced for 11–13%.
Conclusion
Using selenium (Se) and iodine (I) as nutritional supplements can correct lipid metabolism and improve psychological condition in people with subclinical hypothyroidism.

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P340

Endocrinopathies post Immune check point inhibitors

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Introduction
Immune adverse related events are commonly recognized complications of immune check point inhibitors. Here we identify multiple endocrinopathies occurring concurrently in the same patient. In addition to highlighting the common immune adverse effects seen in other cases.
Case 1
33F Refractory Hodgkins Lymphoma tried on several therapies. She was started on Nivolumab (PD-1) with remarkable response. She developed symptoms of Amenorrhea, galactorrhea, vaginal dryness and hot flushes, and was found to have hyperprolactinaemia and partial hypopituitarism. MRI pituitary: lesion in clivus with possible infiltration of pituitary gland. This was discussed in Skull MDT and was felt to be a chordoma/sarcoma, unrelated to underlying lymphoma. Prolactin 4806 mU/L FSH <0.3 LH <0.3 Oestradiol <18.4 pmol/l IGF1 and Short synacthen test normal. She was started on continuous estradiol patches with medroxyprogesterone for her bone health and general well-being. Soon after, she was admitted with a sudden presentation of DKA (BM >33.1 Ketones: 6.4) and hyponatremia (Na: 117). Upon investigation was found to have a newly diagnosed diabetes (HbA1c: 107 mmol/mol, islet cell antibodies negative) and hypothyroidism (Anti-TPO Abs Positive, TSH: 153 T42.8 T3:0.7), commenced on insulin and levothyroxine. Final diagnoses: Type 1 Diabetes, Hypothyroidism, Hyperprolactinaemia and partial hypopituitarism (possibly related to tumour). She is currently under endocrinology follow up. It was discussed with her that these endocrinopathies are likely side effects of Nivolumab, however she opted to continue on it with continued medical management these side effects.
Case 2
88M Stage 4 squamous cell lung CA T4 N3 M1a. Started on palliative treatment with Pembrolizumab (PD-1). After 8 cycles he developed hypothyroidism (TSH: 90, T4: 90) and started on levothyroxine. Previous records show a background of subclinical hyperthyroidism. He is currently well maintained on the levothyroxine.
Case 3
75M Metastatic adenocarcinoma of the lung T3 N3 M1b.Started on palliative therapy with Pembrolizumab (PD-1). Background of subclinical hyperthyroidism (TSH 0.08 T4 14.8) 2010, developed hyperthyroidism (TSH 0.08 T4 26) 2018. Endocrinopathies are well recognised Immune related adverse effects with immunotherapy due to enhancement of immune system with these agents. However the presentation of multiple endocrinopathies as demonstrated above in case 1 is a rare occurrence. With further widespread use of immunotherapy we are yet to see further effects of these drugs. These cases highlight the importance of early monitoring for endocrine adverse events as well as the importance of involving endocrinologist early in their care to provide better outcomes.

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P341

Hashimotos encephalopathy in Graves' disease

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Introduction
Hashimoto's encephalopathy is a neurological disorder of unknown cause associated with thyroid autoimmunity. It is easy to misdiagnose or overlook and the symptoms frequently lead to mistaken neurological diagnoses. The disease may present in two types – a sudden vasculitic type or a progressive subacute type associated to cognitive dysfunction, confusion and memory loss.

Case report
A 34 year old male presented to our emergency department with impaired conscious level, tonic clonic convulsions with a 3-day history of loss of appetite,vomiting and altered mentation before admission. He is known to be thyrotoxic on carbimazole 30 mg/day, propranolol 40 mg however he was not compliant to treatment A week before admission he was diagnosed as bipolar disorder for which lithium carbonate 600 mg/day was prescribed. On physical examination: temperature 36.6°C, heart rate of 111/minute, blood pressure of 140/88 mm Hg, respiratory rate of 24/minute, and an oxygen saturation of 98% on room air. Glasgow coma scale 10 With no signs of lateralization. The laboratory findings: Hematologic and biochemical laboratory findings were normal, TSH:0.01, FT3:5.81, FT4:2.79, cerebrospinal fluid (CSF) normal, EEG demonstrated nonspecific slow waves without spikes, normal CT brain. The MRI revealed bilateral symmetrical cerebellar patchy areas. Lithium was stopped toxicity was suspected (level 1.3 mmol/l (0.4–2 mmol/l), anti microsomal antibodies >1300 IU/ml (n; <10.0 IU/ml), anti-TgAb titrers 382 IU/ml (n; <10.0 IU/mL),negative toxicology screen. Metabolic cause of coma was suspected. He was prescribed prednisolone (30 mg/d).subsequently increased to 50 mg/d with little improvement. Intravenous pulse methylprednisolone regimen (1 g/day) was introduced for three days together with 5 sessions of plasmapheresis. All cognitive dysfunction and neurologic symptoms resolved by 13 days. He was discharged on carbimazole 45 mg/day, prednisolone 60 mg/day tapered over 1 month.
Conclusion
Hashimoto encephalopathy is an extremely important, though rare, diagnosis. Hashimoto encephalopathy should be suspected and screened for in patients with encephalopathy due to unknown causes due to excellent response to treatment.

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P342

Role of lipid peroxidation in the progression of autoimmune thyroiditis

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Introduction
The issue of autoimmune thyroiditis (AIT) today is topical for modern endocrinology both due to the relatively high incidence among the population and the large number of organs and systems involved in the pathological process as a result of loss of the thyroid gland hormone-producing function and a decrease in thyroid hormone levels in the blood.
Aim
The aim of the research is to study the state of the processes of lipid peroxidation and enzymes of the antioxidant protection system in autoimmune thyroiditis with nodular forms.
Materials and methods
We examined 36 patients (men and women, 25–40 years old) with nodular forms of chronic autoimmune thyroiditis with a past history of more than 5 years. Patients were divided into 2 groups. The first group included patients with uncompensated hypothyroidism ($n=17$), the second group included patients who were in euthyroid state ($n=19$). The control group consisted of patients with euthyroid goiter without an autoimmune component ($n=10$). The study of peroxidation processes (LPO) was carried out by determining the induced chemiluminescence of blood plasma.
Results
Showed that in patients with AIT with protracted course and complicated hypothyroidism, an increase MDA and AHP in blood levels is observed in both the first and second group of patients. In the first group of patients, there was a significant increase in the level of MDA by 3.1 times, AHG – 2.8 times. In patients with hypothyroidism who are in the euthyroid state, an increase in the level of MDA by 1.5 times and AHP by 1.2 times was found respectively compared with the results of the control group. The study of indicators of the antioxidant protection system shows that in patients of the first group there is a decrease in SOD by 43%, CT –57%. In patients of the second group, these indicators decreased by 27% and 19% respectively.
Conclusion
Thus, in patients with nodular forms of chronic AIT, with and without hypothyroidism, an increase in free radical activity and a decrease in the local antioxidant protection system are observed, in the development and progression of which the key role is played by activation of the cellular immunity with a predominant production of cytokines, including interleukin-2, which mediate the cytotoxic effect of immunocompetent cells on follicular cells and, subsequently, the development of thyroid hypofunction.

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P343

Clinical evaluation of TSH-receptor antibody measured by a third generation fully automated electrochemiluminescence immunoassay method in Turkish patients with Graves' disease

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Objective
Despite the high sensitivity of TRAb measured by modern assay methods, some patients with Graves' disease (GD) may still have normal TRAb levels. Therefore, the purpose of this study was to determine the clinical utility of TRAb measured by a third generation assay method, and to determine it's relationship with clinical and laboratory parameters in Turkish patients with GD.
Methods
In this study, 328 consecutive treatment-naive patients with GD (248 female (%75.6), mean age 42 ± 12.75 years old), who were admitted between January 2014-December 2018, were retrospectively analyzed. TRAB levels were assessed by electrochemiluminescence immunoassay (Elecsys 2010, Roche Cobase, Mannheim, Germany, manufacturer's cut-off: 1.75 IU/L). TSH, fT3, and fT4 levels were assessed using a chemiluminescence immunoassay method. The goiter size of the participants were obtained from computer records. The diagnosis of GD with normal TRAb values was made according to clinical features and/or Tc-99m thyroid uptake values.
Results
Mean TRAb, TSH, fT3 and fT4 levels were $10.43\pm10,58$ IU/l, 0.027 ± 0.35 mIU/l, 10.88 ± 6.36 pg/ml and 4.07 ± 12.03 ng/dl, respectively. Fifty-eight (17.8%) patients with GD had normal TRAb levels. Mean TRAb levels were higher in male patients compared to female patients (13.98 ± 11.61 vs 9.28 ± 9.97 IU/l, $P=0.001$). GD with normal TRAb levels was more frequent in female patients compared to male patients (48 (19.5%) vs 10 (12.5%), $P<0.001$). A positive correlation was found between TRAb and fT3 levels ($r=0.29$, $P<0.001$). A strong positive correlation was also found between goiter size and TRAb levels (grade-1: 6.40 ± 8.18 IU/l, grade-2: 12.04 ± 10.84 IU/l and grade-3: 16.78 ± 10.59 IU/l, $P<0.001$ for all comparisons). Nevertheless, no correlation was found between TRAb titers with fT4 levels and age ($r=-0.015$, $P=0.44$ and $r=-0.02$, $P=0.67$).
Conclusions
Despite of the reported high sensitivity and specificity of TRAb, measured by third generation assay methods, TRAb levels, measured by a third generation fully automated ECLIA, were normal in 17% of the cases with GD in this study. TRAb negative GD was more frequent among females and TRAb titers were also lower in females compared to male patients. Therefore, the presence of TRAb negative disease should always be taken into consideration in patients with hyperthyroidism, irrespective of the TRAb assay method used, and further studies should be performed to assess the clinical utility of TRAb, mesured by ECLIA in different populations with GD.

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P344

Association between hypothyroidism and venous thromboembolism and the effect of levothyroxine in the adult: a nationwide Cohort study

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Background
Thyroid hormone plays a potent role in many physiological processes, including the impact on blood coagulation. But, there are some contradictory results on the effect of hypothyroidism on the changes in homeostasis. Venous thromboembolism (VTE), commonly defined as deep vein thrombosis (DVT) or pulmonary embolism (PE), is a major health problem worldwide. Little was known about the association between hypothyroidism and VTE. Our study aimed to evaluate the association between hypothyroidism and VTE, and the possible effect of levothyroxine treatment on risks of VTE in hypothyroidism group.
Design
Nationwide population-based retrospective cohort study.
Setting
Taiwan's National Health Insurance Research Database.
Participants
Individuals with ($n=5,488$) and without ($n=21,952$) hypothyroidism.

Measurement
Individuals with and without hypothyroidism were matched 1:4 for age, sex, and index year. Those with hypothyroidism were further divided into levothyroxine treatment and without levothyroxine treatment. Incidences and hazard ratios (HR) for risks of developing VTE were calculated using Cox proportional hazard regression models. Deep vein thrombosis and pulmonary embolism were analyzed individually.
Results
During mean follow-up of 6.9 years, 89 participants in the hypothyroidism cohort and 214 participants in the non-hypothyroidism cohort developed VTE events. Having hypothyroidism was significantly associated with risk of developing VTE events and DVT (adjusted HR (aHR) = 1.34, 95% confidence interval (CI) = 1.04–1.74, $P = 0.026$, DVT: aHR = 1.33, 95% CI = 1.01–1.75, $P = 0.044$). But, there was no associated with risk of developing PE. We also analyses the effect of levothyroxine. Hypothyroidism without levothyroxine had the greater risk of of developing VTE events and DVT (VTE: aHR = 1.82, 95% CI = 1.24–2.67, $P = 0.002$, DVT: aHR = 1.76, 95% CI = 1.17–2.65, $P = 0.0007$). Besides, hypothyroidism with age younger than 40 were associated with greater risk of developing VTE (multivariate mode, adjusted HR = 2.4, 95% CI = 1.14–5.05, $P = 0.02$). However, there was no statically associated with risk of developing VTE events and DVT in hypothyroidism treated with levothyroxine (VTE: adjusted HR = 1.17, 95% CI = 0.86–1.58, $P = 0.311$, DVT: aHR = 1.14, 95% CI = 0.83–1.58, $P = 0.417$), even in any age and gender.
Conclusion
Hypothyroidism was independently associated with increased risks of VTE and DVT. However, hypothyroidism treated with levothyroxine did not have association with increased risks of VTE and DVT.

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P345

Should narrower TSH and free thyroid hormone levels be targeted to reduce the cardiovascular risk of euthyroid subjects?

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Aim
Thyroid hormones have many effects on the cardiovascular system. May studies have showed that apparent or subclinical hypothyroidism increase the risk of hypertension hyperlipidemia and so lead to atherosclerosis susceptibility. This risk can be reduced by treatment. But, studies on the relationship between thyroid function tests and cardiovascular risk in euthyroid subjects are contradictory. This study was designed to investigate the effect of TSH, free T_3, free T_4 and Hashimoto thyroiditis on cardiovascular risk factors in euthyroid subjects.
Method
A cross-sectional study of 144 euthyroid drg-free subjects was made. Serum TSH, freeT_3, free T_4, anti-thyroid antibodies, fasting blood glucose (APG), fasting lipid profile, fasting insulin, C-reactive protein (CRP), asymmetric dimethylarginine (ADMA), ischemia modified albumin (IMA), IMA-edited according to albumine were analysed. HOMA-İR score and LDL/HDL ratio were calculated. Thyroid ultrasonography was performed to all participants. HT was detected in 61 subjects. Analyzes were performed according to 1, 1.5, 2, 2.5, 3, 3.5 and 4 μIU/ml values for TSH.
Results
In all participants, no difference detected according to 1, 2, 3 and 3.5 μIU/ml values for TSH. In subjects with TSH < 1.5 μIU/ml, APG, insuline and HOMA-IR were higher (respectively $P = 0.039$, 0.017 and 0.016). In TSH < 2.5 μIU/ml group, CRP was lower ($P = 0.042$), trigliseride was lower at border ($P = 0.051$) and ADMA was higher at border ($P = 0.055$). In TSH < 4 μIU/ml group, trigliseride was lower ($P = 0.009$). Negative correlation was detected between free T4 and age ($P = 0.025$, $r = -0.188$). Free T_3, HT and gender were not related with other parameters. Weak positive correlations between İMA, IMA-edited according to albumine with free T_4 were determined ($P = 0.014$, r:0.206 ve 0.207).
Conclusion
In participants withTSH < 1.5 μIU/ml APG, insuline and HOMA-İR were higher and trigliseride was lower in subjects with TSH < 4 μIU/ml. These results were thought that target range for TSH could be 1.5–4 μIU/ml. Free T_4 was negative correlated with age and positive correlated with IMA-edited according to albumine. Thus, free T_4 could be an useful marker to determine the cardiovascular risk of euthyroid subjects. The number of participants must be increased for supporting these findings.
Keywords: TSH, free T_4, free T_3, Hashimoto thyroiditis, ADMA, IMA, IMA-edited according to albumine

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P346

Thyroid dysfunction in Egyptian HCV patients: prevalence and possible triggering factors

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Introduction
The contribution of chronic hepatitis C virus (HCV) infection per se in thyroid autoimmunity and dysfunction remains controversial.
Aim
To investigate the prevalence of thyroid disorders and the possible association between thyroid dysfunction and different factors in a cohort of HCV untreated patients.
Material and methods
A total 1050 patients with untreated HCV infection were enrolled in this study. Thyroid function tests (TSH, FT_3, FT_4), antiperoxidase (TPO-Ab), antithyroglobulin (Tg-Ab), thyroid ultrasound, real-time polymerase chain reaction (RT-PCR) to assess HCV RNA viral load, and fibroscan to determine degree of hepatic fibrosis were done.
Results
Thyroid dysfunction was found in 17.1% of patients: 11.5% hypothyroidism and 5.6% hyperthyroidism. Subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism and overt hyperthyroidism were detected in 8.6%, 2.8%, 3.3%, and 2.3% of patients, respectively. Thyroid ultrasound showed abnormality in 10.2% of subjects. TPO-Ab and Tg-Ab were positive in 5.1% and 6.4% of patients, respectively. There was no statistically significant difference between euthyroid patients and patients with hypothyroidism or hyperthyroidism regarding age ($P = 0.12$), gender ($P = 0.05$), viral load ($P = 0.83$) or fibrosis stage ($P = 0.77$). However, TPO-Ab was more frequently positive in hyperthyroid patients compared to euthyroid ($P < 0.001$) and hypothyroid ($P < 0.001$) subjects. Furthermore, positive TPO-Ab was only significantly associated with thyroid state ($P < 0.001$) and duration of HCV infection ($P = 0.02$)
Conclusion
In the current study, the prevalence of thyroid dysfunction is 17.1% of patients with HCV infection. Furthermore, thyroid disorder is related mainly to thyroid autoimmunity independent of age, gender or level of viraemia.
Keywords: thyroid, hepatitis C virus, thyroid antibodies

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P347

Management of refractory hypothyroidism with intramuscular levothyroxine: a clinical case

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Introduction
There are a few hypothyroid patients who are refractory to standard thyroid hormone replacement treatment and require unexpectedly high doses of levothyroxine. In addition to clinical situations where hypothyroid patients are non-compliant (pseudomalbsortion), or where there is the possibility of excipient-induced disease exacerbation, therapeutic failure may be due to impaired absorption of the administered drug. The common approach to managing patients is to escalate the dose of levothyroxine until targeted TSH levels are achieved. We present a case of refractory hypothyroidism treated with intramuscular levothyroxine.
Case report
A 66 year old woman with hypothyroidism after a total thyroidectomy performed 8 years before, and in treatment with 250 μg per day of levothyroxine

(3.67 μg/kg/day), presented at our outpatient clinic of endocrinology with a TSH level > 150 μU/ml and FT4 0.40 ng/dl. We review pathological and non pathological causes of refractory hypothyroidism. We excluded concomitant gastrointestinal disease (H.Pylori infection, inflammatory bowel disease, celiac disease, lactose intolerance, atrophic body gastritis or gastrointestinal surgery), a poor conversion of T4 to T3, Addison's disease, cystic fibrosis, nephrotic síndrome or amyloidosis. Also we revised pseudomalabsortion and drugs and dietary considerations that may affect levothyrxine absortion. After that, we switched to a generic levothyroxine with different bioavailability (without lactose and later, a liquid formulation). With both of them, first, FT4 reached normal values, but after 4 weeks TSH returned > 150 μU/ml, FT4 0.24 ng/dl and FT3 0.5 pg/ml. We also tried with a combination T3/T4 therapy with the same result (an initial correction and again a severe hypothyroidism) Finally we performed a thyroxine absorption test: we administrated a single large dose of 1000 μg and blood samples were taken for baseline and at 60 min intervals up to 240min after the ingestión. Also we took blood samples at 24 and 48 h later. During the test TSH values remains stable and FT4 only rose up to 0.43 ng/dl. At this point we started treatment with intramuscular levothyroxine, 500 mcg per week. Her TSH and FT4 levels became normal. Currently the latest values are a TSH 2.33 μU/ml, FT4 1.29 ng/dl and FT3 2.4 pg/ml.

Conclusion

This is a case of refractary hypothyrodism due an isolated levotiroxine malabsortion. Intramuscular levothyroxine can be an effective alternative.

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P348

Thyroid angiosarcoma: in the light of a case

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Introduction

Angiosarcoma is a highly malignant tumor, very rare and even more so when it comes to a thyroid localization. It is characterized morphologically by its vascular differentiation and cytological polymorphism. The objective of this study is to report a case of this entity with its evolution in the postoperative period.

Observation

patient of 54-year-oldm, with no pathological history. Operated (total thyroidectomy) for compressive multihetero-nodular goitre, revealing left toto-lobar angiosarcoma. The post-operative evolution was marked by the installation of a cervical hematoma, with a greater recurrence (10 days later): 9.8 * 8.3 * 7.7 cm extending in endothoracic and infiltrating the para-vertebral space. An additional thoraco-abdominopelvic scanner was performed in search of the primary tumor, returning without abnormality. The patient was subsequently referred in oncology for additional care.

Discussion

Angiosarcoma is a malignant tumor, very rare and fatal. His thyroid localization is exceptional. His diagnosis is the site of many controversies concerning his diagnosis and treatment: angiosarcomatous origin or angiomatoid variant of anaplastic carcinoma? Some complications such as haemorrhage, thrombocyto-penia and heart failure can be observed. Local recurrences are very frequent and metastases are early and frequent. His treatment is based on the administration of propranolol, corticosteroids and metronomic chemotherapy.

Conclusion

Metastasis or localization of angiosarcoma in the thyroid is possible with poor survival. Acute onset and rapid extension pose enormous difficulties to treatment.

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Collision tumor: A case report of tall cell variant of papillary thyroid carcinoma and laryngeal squamous cell carcinoma

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Collision tumors (CT) refers to the coexistence of two histologically distinct malignant tumors within the same mass. CT involving the thyroid gland (TG) and/or the neck are specially uncommon and present a diagnostic and treatment challenge.

Case report

A 69-year-old male presented with a one year history of bilateral cervical lymph node growth, a four-month history of progressive dysphagia and a dyspnea associated with a rapidly expanding, painless mass in the right side of the neck. He denied smoking, exposure to radiation or history of cancer. A physical examination revealed a firm, immovable 5 cm mass in the right side of the neck and a firm, fixed 8 cm mass in the right TG. A computed tomography scan inform a mass in the right lobe of the TG, infiltrating parapharyngeal spaces, airway compression, with supraclavicular extension and enlarged lateral bilateral lymph nodes in the neck. The laryngeal biopsy reported, connective tissue infiltrated by papillary carcinoma of probable thyroid origin, and US-FNA reported papillary carcinoma thyroid. The patient underwent total thyroidectomy combined with incisional laryngeal biopsy as well as paratracheal lymph node and bilateral selective neck dissection, tracheostomy was performed. The laryngeal biopsy specimen revealed a laryngeal squamous cell carcinoma. The right lobe of the thyroid gland contained a tall cell variant of papillary thyroid carcinoma with invasion and penetration of regional soft tissues and laryngeal mucosa. Sectioning of multiple bilateral cervical lymph nodes revealed metastases from the thyroid papillary carcinoma and squamous cell carcinoma.The diagnosis was a collision tumor from a tall cell papillary thyroid carcinoma and a laryngeal squamous cell carcinoma. After one month, laryngectomy was performed, a mass of 4 cm was reported with focus on the oropharynx with extension towards the tongue and the larynx and with carcinomatous lymphangitis.The histopathological diagnosis was collision tumor originating from a tall cell papillary thyroid carcinoma and a laryngeal squamous cell carcinoma. The patient presented with a expanding painless, firm and fixed 7 cm mass, in the in the middle neck, at one month post-surgery and he start palliative treatment with radiotherapy and cisplatin. After one more month, the patient has acute dyspnea with blood secretions from the tracheostomy and he died.

Conclusion

Management of collision tumor is complex because the duality of the pathology, treatment should be patient specific. Generally, the most aggressive neoplasm should guide treatment.

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Outcomes of surgery and radioiodine treatment for neck recurrence in papillary thyroid cancer

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Background

Persistent/recurrent disease in the neck is frequent in patients with papillary thyroid cancer. The main goal of this study was to evaluate the efficacy of the reoperation and radioiodine (RAI) treatment for persistent/recurrent disease after the initial treatment. Patients and Methods: A total of 30 patients (13 M/17 F) with papillary thyroid cancer were enrolled in this study. Seven cases (23.3%) had an aggressive subtype of papillary carcinoma. All had been submitted to reoparation for local persistent/recurrent disease. Mean age at initial thyroidectomy was 41.4 ± 15.2 years and the follow up interval was 5.6 ± 3.6 years, median 4.0 years. Fourteen patients had unifocal and 16 multifocal disease. Initial T status was T1 in 22 cases, T2 in 4 cases and T3 in 4 cases. Initial N status was N0 in 2 cases, N1 in 15 cases and Nx in 13 cases. All patients had M0 status. All patients had normal levels of anti-TG antibodies. Wilcoxon test was used for statistical analysis.

Results

Reoperation: In 17 patients (56.7%) the recurrence was diagnosed after a fine needle aspiration biopsy of the suspicious lymph nodes and in the rest of the patients by neck ultrasound. Persistent/recurrent disease was detected after 1.8 ± 2.6 years with a median time of 1 year (range 3 months to 12 years). The median number of lymph nodes dissected at reoperation was 26 (range 1 to 60). *Biochemical Findings:* Reoperation reduced significantly the TG serum concentration from 76.13 ± 165.5 to 20.18 ± 28.8 ng/mL, $P = 0.054$. The RAI treatment provided to 19 patients after the lymph nodes resection reduced further the TG values from 30.09 ± 32.74 to 11.93 ± 20.87 ng/mL, $P = 0.014$. After the lymph nodes resection TG levels were reduced in 24 patients (80%), by 13–99%, 2 patients (6.6%) had stable TG levels and 4 patients (13.3%) had increased TG levels up to 30%, 51%, 233% and 253% respectively. Classifying the patients after reoperation according to the dynamic risk stratification, 7 patients (23.3%) had complete response, 4 (13.3%) had biochemically incomplete response, 9 (30.0%) had indeterminate response and 10 (33.3%) had still structural incomplete response.

Conclusions
1. Surgery for local persistent/recurrent disease in papillary thyroid carcinoma reduces tumour burden, improves the biochemical and structural disease.
2. Administration of therapeutic RAI after lymph node resections appears to further improve biochemical disease.

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Anaplastic thyroid carcinoma or radiation-induced sarcoma: About a case

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Introduction
Anaplastic thyroid cancer has long been considered as a mesenchymal tumor (sarcoma). To date, it is difficult to differentiate between the two types. Radio-induced sarcomas of the head and neck are a very rare entity. Their annual incidence is 0.06 to 0.17%.
Observation
We report the case of a 83-year-old patient, with a history of breast neoplasia treated with radiotherapy 7 years ago. Followed for a year for papillary carcinoma of the thyroid in its papillo-vesicular form classified PT3NxMx. During the follow-up, the cervical ultrasound was normal and the Tg was at zero. After 3 months, she had a 5 cm cervical mass, with lymph nodes; and a very fast evolution with significant compressive signs, and lung metastasis. Fine needle aspiration evokes anaplastic carcinoma. This mass fistulised spontaneously, and the anatomopathological study concluded a radio-induced sarcoma. The patient died quickly after the diagnosis.
Discussion
The long-term carcinogenic potential of ionizing radiation is well established. Although pleomorphic undifferentiated thyroid sarcoma (WHO 2013 classification) is extremely rare, this diagnosis should be considered in patients with rapidly progressive mass with compressive signs (similar signs to anaplastic carcinoma). In order to propose a treatment by complete and wide surgical exeresis. Although traditionally, they are considered very aggressive tumors with poor prognosis.

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The relationship between thyroid receptor antibody and anti mullerian hormone in Graves' disease

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Introduction and Aim
Thyroid dysfunction is the most common autoimmune endocrine disorder in women of reproductive age. Autoimmune thyroid disease is related to menstrual irregularities, anovulation and infertility. Thyroid dysfunction is thought to disrupt follicular growth and maturation. Autoimmunity may have a negative effect on fertility, independent of age. The relation between TSH (Thyroid Stimulant Hormone), thyroid antibodies and AMH (anti-mullerian hormone) is a topic that interesting and resulting different outcomes on last days. Graves is an autoimmune disease. The aim of this study is to investigate whether there is a relationship between TRAB (TSH Receptor Stimulating Antibody) and the primary ovarian reserve indicator AMH in Graves' disease.
Materials and Methods
Our population includes only women patients which are appeal to endocrinology and internal medicine polyclinics at T.C. Health Ministry Bakirkoy Dr Sadi Konuk Hospital between September 2017 and September 2018. We compare 64 TRAB positive Graves patient with any fertility problem as working group and 51 patient with no known outoimmunity disorder as control group. Sociodemographic data form was applied to all patients included in the study, TSH, sT3, sT4, Anti-TPO, Anti-Tg, TRAB values were noted. 3–4 cc venous blood samples were taken and stored at $-80°C$ to calculate AMH after approach enough patient.
Results
The mean age of the study group was 31.78 ± 7.75 (year) and the mean age of the control group was 31.64 ± 7.71 (year). Age, AMH, fT3, fT4, TSH, Anti-TPO, Anti-Tg results were compared between control and working group. No significiant difference is detected between age and AMH on two groups. On working group there is no significant difference betweeen TRAB, TSH, Anti TPO, Anti TG, fT3, fT4 values and AMH value. On control group there is no significant difference betweeen TRAB, TSH, Anti TPO, Anti TG, fT3, fT4 values and AMH value. *Result*: In our study, there was no significant relationship between the level of TRAB and AMH, a raised antibody in Graves' Disease. We also showed that the levels of Anti-TPO and Anti-Tg were not correlated with AMH levels. Among the reasons for this, the number of patients, working method, disease activation periods can be among the effective factors. More Large patient group and prospective comparison studies are needed.

Keywords: Graves Disease, Anti Mullerian Hormone, TSH Receptor Stimulating Antibody, ovarian failure

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Infrared thermography in association with indirect calorimetry: a new methodology for diagnosis and follow-up of subclinical hypothyroidism

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Infrared Thermography (IT) is a non-invasive method and complementary to other diagnostic techniques to identify inhomogeneity of the thermal emission of the skin. We used IT (InfRec R500, Nippon Avionics Co.; 640×480 pixel, spatial resolution 0,87 mrad, sensitivity $0.03°C$ at $30°C$, accuracy $\pm 1°C$) to assess the variations of skin temperature of the neck region: higher mean temperature, greater thyroid function. Primary outcome of this study was to compare the temperature of the neck skin superficially to the thyroid gland and Resting Energy Expenditure (REE) measured by indirect calorimetry. Secondary aims were to analyze the correlation between thermographic values and: 1) BMI 2) TSH 3) total cholesterol. Eighty patients ($BMI = 33.02 \pm 5.94$ kg/m^2; age 49.45 ± 15.12 years; 53 females and 27 males) recruited in the outpatient setting were studied. Neck skin temperature correlated directly with REE ($r = 0.34$; P-value < 0.01) and reversely with BMI ($r = -0.27$; P-value < 0.01). TSH and total cholesterol were evaluated only in 25 subjects. A weak, not significant, direct correlation ($r = 0.21$; P-value $= 0.14$) and a significant inverse correlation ($r = -0.23$; P-value < 0.01), respectively, was found. Our preliminary results suggest that infrared thermography could represent a useful tool in clinical thyroidology as it is quick, safe for the patient and the operator, easy to perform and that can provide important information not only on the structure and on the presence of nodules but also on the functionality of the thyroid gland. Furthermore, the association of this technique with the measurement of the REE with indirect calorimetry can provide a valuable tool in the diagnosis of thyroid dysfunction, especially in subclinical and overt hypothyroidism.

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How much the implementation of an expert surgical team can improve the incidence of postoperative hypoparathyroidism

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The experience and expertise of a thyroid surgery team is a relevant factor in the development of postsurgical hipoparathyroidism (hypoPP). In 2005, we published a 9.6% prevalence of permanent hipoparathyroidism among patients operated on for thyroid cancer (TC) at our centre between 1985 and 2001. Since 2002, an expert surgery team was implemented as part of a multidisciplinary committee. The aim of the present study is to assess the prevalence and risk factors associated with permanent hypoPP after total thyroidectomy (TT) because of TC after the expert surgery team was introduced.
Methods
Retrospective analysis of a cohort of 56 patients attended consecutively in an endocrinology clinic between January and March 2018, having been operated on for TC from 2002 onwards and who had at least one-year follow-up since surgery (TT). Prevalence of transient (up to 6 months), prolonged (up to 12 months) and permanent (>12 months) after surgery hypoPP was calculated. Uni and multivariant logistic regression analysis were used adjusting for confounding variables and the Odds Ratio (OR) (95% CI) of presenting hypoPP was estimated. It was considered significant when $P<0.05$.
Results
56 individuals were included (41 F, 15 M), average age (SD): 49 (13.9) years old. TT was undergone by an expert surgery team in 34 cases (60.7%). In 35 cases (62.5%) TT + lymphadectomy (LF) was performed: 18 central and 17 central + lateral. In 7 cases (12.5%), a two-stages TT was conducted. Overall, 1 (1.8%) patient presented permanent hypoPP, 4 (7.1%) prolonged hypoPP and 22 (39.3%) transient hypoPP. The univariate analysis showed the risk of developing hypoPP immediately after surgery was greater if LF (OR: 5.4 (1.6–18.2)), extrathyroid extension (OR 5.8 (1.5–21.2)) or lymph node metastases (OR 8 (1.9–33)) were present. The multivariant analysis (adjusted for local extension, performing LF and presence of lymph node metastases) revealed that surgery by the expert team reduced the risk of hypoPP with an OR of 0.18 (0.04–0.82). This model explained 44% of the variability of the risk estimation.
Conclusions
The presence of locoregional extension and the performance of lymphadectomy are predictive factors of postsurgical hypoPP in patients undergoing total thyroidectomy due to thyroid cancer. The implementation of an expert surgical team was independently associated with an 80% risk reduction of postsurgical hypoPP. Based on these results, centres where thyroid cancer surgery is performed, should implement an expert surgical team, coordinated within a multidisciplinary committee, for surgical management of this pathology.

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An ununsual thyroid cause for Pyrexia of unknown origin (PUO)

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Introduction
Granulomatous thyroiditis (GT) is one of the various types of autoimmune thyroiditis. It usually occurs in women of reproductive age in perigestational period. Clinical picture in is predominantly painful goiter with radiating pain to ears with low grade fever lasting for few days, sometimes associated with mild hyper or hypothyroidism. The treatment is symptomatic and supportive with no curative option. There are meagre anecdotal reports of thyroidectomy role for cure. In this context, we report an unusual clinical presentation and impact of total thyroidectomy on GT.
Case details
A 60 year old gentleman had history of continuous low fever since 4 months with quotidian spikes up to 100–101^{0}F. These spikes were sometimes associated with chills. Gets symptomatic relief with paracetomol and steroids. He was worked with a battery of investigations for chronic liver disease, renal disease, viral causes, tuberculosis and any autoimmune connective tissue disorders such as SLE, scleroderma etc., All the investigations were within normal limits with no definite etiology. Fine needle aspiration of goiter showed picture of thyroiditis with few macrophages and colloid. He was empirically started on anti-tuberculous medications (ATT) since 3 months with no significant alleviation from fever. At this stage he was referred to our hospital. On clinical evaluation, there was a large grade 2 diffuse firm, slightly tender goiter and no cervical regional lymphadenopathy. No evidence any neurocutaneous markers of any autoimmune syndromes. Biochemical profile was suggestive of subclinical hyperthyroidism. Anti-thyroid peroxidase antibody titer was 45 IU/L (0–34). ESR was 86 mm/hr. After careful intradepartmental discussion and patient (family) counseling, we withdrew ATT and planned total thyroidectomy suspecting thyroiditis as cause for this pyrexia of unknown origin (PUO).
Results
Total thyroidectomy was performed with uneventful morbidity. No postoperative complications or hypocalcemia occurred. Surprisingly, from 5th postoperative day his fever has resolved completely with no further spikes. ESR was 15 mm/hr at 2 weeks after surgery. Histopathology was reported as Granulomatous thyroiditis with non- caseating granulomas, macrophages, destroyed follicles and lymphocytic infiltrates. Body temperature has normalized and he never experienced any episodes of fever till last followup at 6 months.
Conclusions
Granulomatous thyroiditis can have protean clinical manifestations. Here, GT unusually presented with pyrexia of unknown origin. Exact pathophysiology is enigmatic, but pyrogenic cytokines released by GT process may cause PUO. Total thyroidectomy appears to be a viable curative option for GT causing PUO, probably by reversing this pathophysiology.

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Relationship among T- and B-lymphocytes of the peripheral blood and thyroid tissue in patients with Graves' disease

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The exact pathogenesis and causative interaction between T- and B-lymphocytes in peripheral blood and thyroid gland immune-mediated mechanisms of Graves disease (GD) are still unknown. Detailed knowledge about lymphocyte subpopulation composition in peripheral blood and thyroid tissue will therefore enhance our understanding of the pathogenesis of GD and might support the development of new immunomodulatory treatment approaches. Aim: to study the relationship between helper- (Th-cells), regulatory T-cells (Treg) and B lymphocyte composition of peripheral blood and thyroid tissue in patients with GD undergoing epifascial thyroidectomy.
Materials and methods
The study included 43 women with GD, mean age 39.95 ± 14.38, who were performed the epifascial thyroidectomy and 67 healthy women were examined as a control. The median of thyroid stimulating hormone (TSH), autoantibodies to TSH receptor, free thyroxine and triiodothyronine level was respectively 0.08 (0.01; 0.58 mIU/L, 10.25 (6.85; 24.68) IU/ml, 16.89 (11.39; 31.5) and 5.93 (4.6; 7.7) nmol/ml. All women treated with Antithyroid drugs (ATDs) for at least 1 month before surgery. Phenotypic composition of Th-cells, Treg and B-lymphocytes were measured by flow cytometry, using direct immunofluorescence, respectively, of whole peripheral blood and lymphocytes isolated from thyroid tissue. Analysis of stained cells was performed on a flow cytometer FC-500 (Beckman Coulter, USA). Each sample was analyzed at least 50,000 lymphocytes.
Results
In peripheral blood of GD patients we revealed the positively interaction between the relative amount of B-lymphocytes with Treg and activated T-helper cells ($r=+0.39$, $P=0.009$), B2-cells and naïve B-lymphocytes with $CD3^+CD4^+CD25^+$- ($r=+0.49$, $P<0.001$ and $r=+0.42$, $P=0.003$, respectively) and $CD3^+CD4^+CD127^{Low}CD25^{High}$-cells ($r=+0.49$, $P<0.001$ and $r=0.37$, $P=0.012$, respectively). In thyroid tissue the Treg is completely excluded from the system of interactions with activated B-lymphocytes. In thyroid tissue of GD patients the relative number of $CD3^+CD4^+$-cells interact with the level of $CD19^+CD5^+CD23^+$-lymphocytes ($r=+0.79$, $P=0.036$) and the percentage number of $CD3^+CD4^+CD25^+$-cells with $CD19^+CD23^+$- ($r=+0.85$, $P=0.014$), $CD19^+CD5^-CD23^+$- ($r=0.80$, $P=0.034$), $CD19^+CD5^+CD23^+$- ($r=+0.93$, $P=0.025$) and $CD19^+CD27^+CD23^+$-lymphocytes ($r=+0.82$, $P=0.023$).

Conclusion
Emerging evidence suggests that ATDs may functionally hinder the proper development of autoimmune process and alter T- and B-cell interactions with antigen presenting cells in immunological synapse of thyroid gland in GD. Thus, this interaction contribute directly to the key mechanism underlying the development of organ-specific autoimmunity functioning in peripheral blood and that may associated with ATDs and their potential functional effects on thyroidal immune dysregulation.

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Association between vitamin D receptor gene polymorphisms and Graves' disease: a systematic review and meta-analysis

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Introduction
The pathogenesis of Graves' disease (GD) and Graves' orbitopathy (GO) is not completely understood. On the other hand, vitamin D receptor (VDR) gene polymorphisms have been associated with susceptibility to a variety of chronic autoimmune diseases. The primary aim of this study was to synthesize the best available evidence regarding the association between VDR gene polymorphisms and risk of GD. Secondary aim was to search for their association with GO.
Methods/design
A comprehensive search was conducted in PubMed, CENTRAL and Scopus, up to December 8th, 2018. Data were expressed as odds ratio (OR) with 95% confidence intervals (CI). Heterogeneity was quantified with I^2 index.
Results
Ten studies were included in the qualitative and quantitative analysis. TT subtype of TaqI polymorphism was associated with an increased risk of GD compared with Tt and tt polymorphisms (OR: 1.42; 95% CI, 1.05–1.94, $P=0.025$), whereas tt was associated with a lower risk of GD, compared with TT and Tt polymorphisms (OR: 0.79; 95% CI, 0.62–0.99, $P=0.043$). No association was found for ApaI, BsmI and FokI polymorphisms. When subgroup analysis was conducted according to ethnicity, a significant association was found for BsmI polymorphism and GD in both Asian (OR for the comparison of bb with the combination of BB plus Bb: 0.67; 95% CI, 0.49–0.92, $P=0.013$) and Caucasian populations (OR for bb compared with BB plus Bb:1.31, 95% CI, 1.04–1.65, $P=0.022$). Association was also found for TaqI polymorphism only in Caucasian population (OR for the comparison of tt with TT plus Tt: 0.74, 95% CI, 0.61-0.90, $P=0.002$). No eligible study was found regarding the association between VDR gene polymorphisms and the risk of GO.
Conclusions
The TT subtype of the TaqI polymorphism was associated with a higher susceptibility for GD compared with Tt and tt. Regarding BsmI, the bb subtype was associated with increased GD risk in Caucasians, whereas it is protective in Asians.

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Thyroid dysfunction after Alemtuzumab treatment for multiple sclerosis: diagnostic and therapeutic modalities

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Introduction
Alemtuzumab is a humanized monoclonal antibody against CD52, located on the surface of the lymphocytes, used in the treatment of relapsing-remitting multiple sclerosis (RRMS), that can induce novel secondary autoimmune diseases. Autoimmunity may be related to the pattern of T- and B-cell depletion and repopulation following Alemtuzumab treatment. The most frequently reported autoimmune disorders observed with alemtuzumab involve the thyroid gland in up to a third of patients, followed by thrombocytopenia and nephropathies. We report our experience in treating these complications in five patients among 20 RRMS patients that received Alemtuzumab.
Case reports
A patient received Alemtuzumab in 2015 and 2016. Hashimoto thyroiditis (HT) occurred in 2017 with hypothyroidism and peroxidase antibodies (TPOAb). A second patient received Alemtuzumab in 2016 and 2017. In 2018, she suffered transient hyperthyroidism, followed by euthyroidism, and then a recurrence of subclinical hyperthyroidism, without the need for treatment. TPOAb, thyroglobulin antibodies (TGAb) and TSH receptor antibodies (TRAb) were positive. A third patient received Alemtuzumab in 2015 and 2016. Hypothyroidism occurred in 2017, and supplementation by Levothyroxine was introduced. In 2018, transient hyperthyroidism led to discontinuation of supplementation. Then, a resurgence of hypothyroidism was observed and Levothyroxine was resumed. TPOAb, TRAb and TGAb were positive. A fourth patient received Alemtuzumab in 2011 and 2012. In 2014, Graves' disease (GD) occurred with overt hyperthyroidism, TPOAb and TRAb. He received radioiodine (RAI). A month later, hypothyroidism occurred. A fifth patient with RRMS received Alemtuzumab in 2016 and 2017. In 2019, HT appeared with hypothyroidism, TPOAb, TRAb and TGAb.
Discussion
As suggested by cases 2-to-5, Alemtuzumab-associated thyroiditis is more likely to be mediated by TRAb. Indeed, reconstitution autoimmunity is more frequently autoantibody-mediated rather than Th1-mediated, like HT. *Alemtuzumab-associated GD is an intriguing autoimmune paradigm*. First, conversion from hyper to hypothyroidism, and inversely, can be observed, like in case 3. The change from stimulating to blocking TRAb may be the mechanism for this switch. Second, these patients have a better remission rate, spontaneously or under treatment, as illustrated in case 2. Therefore, first-line treatment in Alemtuzumab-related GD should consist of antithyroid drugs, while RAI or surgery are less conservative, and should be second-line therapies.
Conclusion
Alemtuzumab-related thyroiditis is a model potentially leading to further inside into thyroid physiopathology. A TSH monitoring is recommended before starting Alemtuzumab, until 48 months after the last delivery. We suggest a longer follow-up, and to measure both TPO and TRAb.

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A rare cause of goiter

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Introduction
Amyloidosis is a rare systemic disease of unknown etiology characterized by the extracellular deposition of proteinaceous (amyloid) material in different organs of the body. About 40-50% are of secondary cause (Amyloidosis AA) Amyloid goiter is a rare condition, usually associated with the secondary form.
Case
We reported a 41-year-old male with a history of non-steroidal anti-inflammatories, high blood pressure and smoking habit. Maintains follow-up in nephrology for stage V chronic kidney failure secondary to AA amyloidosis and receives hemodialysis periodically. In one of his reviews, a goiter was found by chest CT scan, which is why is referred to endocrinology unit, where an increase in the thyroid gland was confirmed by cervical ultrasound at the expense of both lobes (Third grade) and showed besides, a heterogeneous echoestructure with hyperechoic predominance, with patchy hypoechoic areas, diffusely, without associated adenopathies. The thyroid profile was within normal range, with negative antithyroid antibodies. The scintigraphy showed a generalized hypocaptation compatible with thyroiditis in resolution or hypothyroid goiter, but could not rule out a thyroid block by drugs or iodinated contrasts. Two needle aspiration with fine needle were performed with non-diagnostic results. Cervical nuclear magnetic resonance showed a marked decrease in thyroid tissue attenuation, similar to fat, and a large goiter that compresses the trachea and enters the retrosternal region. The patient reported an associated cervical compressive clinic, so finally it is decided to surgically intervene through thyroidectomy. The anatomopathological results confirm amyloid goiter.
Conclusions
Only a small percentage of amyloidosis produces a symptomatic goiter. The thyroid function of these patients may be normal, although they are frequently hypothyroid and rarely hyperthyroid. Clinically, it is usually presented as a non-painful mass in cervical region, and in isolated cases can produce local symptoms by compression of neighboring structures. The treatment, in the absence of compressive symptoms, should be limited to the control of thyroid function and

associated diseases, and carry out total removal of the gland when symptoms appear. The definitive diagnosis will be given by the anatomopathological study of the surgical piece

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Changing practice in the management of differentiated thyroid carcinoma – experience at Brugmann Hospital in Brussels

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Aim of the work
In patients with differentiated thyroid cancer, the basic goal of the therapy is to improve overall and disease-specific survival, reduce the risk of persistent/recurrent disease while minimizing treatment-related morbidity and unnecessary therapy. In 2015, the American Thyroid Association (ATA) published evidence-based guidelines for the staging and management of differentiated thyroid cancer, including the possibility of avoiding systematic complementary 131-iodine therapy in low-risk patients. Based on these new recommendations, we have modified our management, treatment and monitoring of thyroid carcinoma. The current study aimed at evaluating the influence of these modifications on the therapeutic efficacy in patients with thyroid cancer before and after 2015.
Methods
We conducted a retrospective study in a cohort of patients diagnosed and treated at the Brugmann Hospital between 2007 and 2017. A few patients with metastatic disease were treated several times. Patients were divided into two groups: before (Group 1) and after 2015 (Group 2). We compared the two groups in terms of general characteristics, risk of recurrence (based on the 2015 ATA recommendations), cumulative administered 131-iodine activity and biological and morphological response to therapy. Due to the repeated treatment in some patients, the distribution of cumulative activity was not Gaussian.
Results
A total of 98 patients were included: 53 in Group 1 and 48 in Group 2, with a mean age of 50 vs 43 years. Both groups were different in terms of risk stratification: in Group 1, 37.7% were classified as low risk, 45.3% as intermediate risk and 17% as high risk. These figures were respectively 16.7%, 54.2% and 29.2% in Group 2 ($P=0.048$). The median cumulative activity of 131-iodine was significantly higher in group 1 (3700MBq, range 1110–14800 MBq) than in group 2 (1110 MBq, range 1110–20350 MBq), $P=0.000012$. Excellent response, meaning no clinical, biological or morphological evidence of residual/recurrent disease, was found in 90.5% in Group 1 vs. 89.5% in Group 2 ($P=0.347$).
Conclusions
The publication of the ATA evidence-based guidelines for the staging and management of differentiated thyroid cancer in 2015 modified our therapeutic management. After 2015, although the number of patients with a high risk of recurrence was greater and the median administered 131-iodine activity significantly lower, including no systematic iodine administration in low-risk patients, the rate of excellent therapeutic response remained unchanged.

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Intraoperative Neuromonitoring of the laryngeal nerves in thyroid surgery

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Topicality
Thyroid nodules are detected by palpation in 4–8% of the adult population and in ultrasound in 10–41%. However, most of them (90%) are benign tumors and require monitoring. Indications for surgery are compression symptoms and/or hyperthyroidism, as well as cosmetic issues. One of the severe complications of the operation is intraoperative damage of the recurrent laryngeal nerve.
Research objective
Minimize the risk of damage to the laryngeal nerves during surgery on the thyroid gland.
Inclusion criteria – patients with benign symptomatic nodular formations of the thyroid gland; TIRADS/Bethesda: TIRADS2, TIRADS3, TIRADS4a/THY2.
Exclusion criteria – Patients with suspected malignant formation of the thyroid gland; TIRADS/Bethesda: TIRADS4c, TIRADS5/THY1, THY3 (a, b, c), THY4, THY5.
Materials and methods
The object of the study was 453 patients treated in the Samara Regional Clinical Oncology Center from June 2015 to December 2017. The average age of patients in the main group (operation using IONM) was 58.0 ± 25.6 years (18–82), totaling 232 patients, in the control group (operation) – 53.9 ± 23.5 years (27–68) only 221 patients. The average size of the nodes in the main group was 4.3 (1.5–11.5) cm. The average size of the nodes in the control group was 3.5 (1.5–9.5) cm. Before performing the operation, the patients of both groups had the necessary diagnostic manipulations and performed voice control. In both groups, operations were performed according to the standard procedure (hemithyroidectomy, thyroidectomy). In the main group, hemithyroidectomy/thyroidectomy: 198/34, in the control group hemithyroidectomy/thyroidectomy: 194/27. Introoperative neuromonitoring (IONM) of the laryngeal nerves, ISIS C2 neuromonitor, non-stimulation electrodes, electrodes for recording EMG were used in the main group during the operation. After the operation on the second day, the fifteenth day and after three months, the patient's voice was monitored: laryngoscopy and laryngo-stroboscopy with video recording, sonographic study of the function of the vocal folds.
Results
In the main group, unilateral transient paresis of the larynx was observed in 19 patients (8.2%), in the control group in 33 patients (14.9%). Three months after the operation, a permanent unilateral laryngeal paralysis was noted in the main group for 4 patients (1.7%), in the control group for 9 patients (4.0%).
Findings
Thus, intraoperative neuromonitoring of the laryngeal nerves is a reliable and safe technology in the patients treatment with thyroid nodules with high clinical efficacy, which allows to significantly reduce the number of postoperative complications associated with damage to the laryngeal nerves.

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Weekly dose of L-thyroxine as a first line treatment for hypothyroidism in young and middle aged working females

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Objective
To demonstrate the effectiveness and compliance to L-thyroxine in the treatment of hypothyroidism in a weekly dose of seven times of normal dose as an alternative to daily dosing in young and middle aged females.
Methods
Randomized trial on 40 female patients aged between 25 to 55 years with long standing hypothyroidism of 5 years or more, currently on daily dose of L-thyroxine, were assigned weekly dose of seven times of normal dose. The patients were randomized in 2 groups G1 and G2.
G1: 20 Female patients with an established diagnosis of hypothyroidism of 5 years or more with TSH value of 4.2 μIU/l or less, currently on daily dose. The patients were assigned a weekly dose of L-thyroxine which was changed to seven times of normal dose.
G2: 20 Female patients with an established diagnosis of hypothyroidism of 5 years or more with elevated TSH value of more than 4.2 μIU/l. The dose in this group was individualized as per the body weight and TSH value.
All patients in both the groups were screened for malabsorption and were not receiving any drugs which interfere with the absorption of L-thyroxine. The minimum to maximum dose of L-thyroxine used in this study was 175–1050 μg.
Results
We achieved complete restoration of euthyroidism in all 20 patients in the G1 at D 84 and it continued to D 168. In G2 we achieved complete euthyroidism in 16 patients at D 84 and it increased to 18 patients with some dose adjustment at D 168. We could not achieve euthyroidism in 2 patients at D 168. The unlike cause can be attributed to other metabolic disorders like diabetes and obesity.
Conclusion
Once weekly dose of L-thyroxine as an alternative to daily dosing regimen was shown to be efficacious and safe for the treatment of hypothyroidism in young and middle aged females. Once a week L-thyroxine can be considered as a first line therapy in young and middle aged working females facing impaired absorption due to early breakfast (no need to wait 30–45 min for breakfast).

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Analysis of clinical and biological predictors of malignancy in thyroid nodules

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Background
Thyroid nodules are the most common thyroid disease. In the majority of cases, they are benign. However, 5 to 15% of nodules are cancer. The aim of our study was to determine the clinical and biological predictive factors of malignancy in thyroid nodules.
Methods
We performed a retrospective descriptive study including 100 patients collected in the endocrinology department of La Rabta hospital over 18 year old period (2000–2018). All these patients underwent thyroidectomy for one or more suspicious thyroid nodules on clinical, ultrasound or cytological criteria. For each patient, the epidemiological, clinical and biological data and the histological result of the surgical specimen were collected. Predictive factors of malignancy were determined by the calculation of Odds Ratios.
Results
The average age of our patients was 49.9 ± 17.4 years and the sex ratio (F/M) was 6.69. The prevalence of malignant nodules was 20%. It was of 22% in women and 8% in men ($P = 0.4$). Multiple nodule were more likely to be associated with benign nodules (OR = 0.2; $P = 0.004$). The clinical predictors of malignancy were a right sided nodule (OR = 3; $P = 0.03$), an upper sided nodule (OR = 20; $P < 0.001$), the hard consistency (OR = 15.5; $P < 0.001$) and the fixed nodule (OR = 21; $P < 0.001$). As for biochemical characteristics, there were no significant difference concerning thyroid stimulating hormone (TSH), FT4, calcium level and parathyroid hormone between benign and malignant thyroid nodules. However, hyperthyroidism was significantly associated with benignancy (OR = 0.1; $P = 0.01$). Primary hyperparathyroidism was more frequent with malignant nodules (20%). However, the association was not statistically significant.
Conclusion
Our study shows that the evaluation of thyroid nodules needs a careful study of all its clinical and biochemical characteristics.

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Sensitivity and specificity of ultrasound features in predicting malignant thyroid nodules

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Background
Ultrasound is valuable for identifying many malignant or potentially malignant thyroid nodules. The aim of this study was to evaluate the efficacy of ultrasonographic (US) features in predicting the malignancy of thyroid nodules in a group of Tunisian patients.
Methods
We conducted a retrospective descriptive study including 100 patients collected in the endocrinology department of La Rabta hospital. All these patients underwent thyroidectomy for one or more suspicious thyroid nodules on clinical, ultrasound or cytological criteria. For each patient histological result of the surgical specimen was collected. Univariate analyse was performed to calculate the sensitivity, specificity, negative and positive predictive values of each US feature.
Results
Of the 100 patients, 87% were female. The overall mean age was 49.9 ± 17.4 years (range: 12–79 years). On histocytopathology, 20% of the nodules were malignant. Ultrasound predictors of malignancy were a nodule size < 20 mm (OR = 3.6; $P = 0.009$), the solid composition (OR = 52.6; $P < 0.001$), the ill-defined margins (OR = 3.4; $P = 0.014$) and the central vascularity (OR = 8.5; $P = 0.008$). The sensitivity and specificity of ultrasound features in predicting malignancy were microcalcification 45% and 69%; hypoechogenecity 85% and 29%; ill-defined margin 50% and 23%; solid echostructure 40% and 99%; heterogenicity 90% and 3%, central vascularisation 25% and 96%. Each ultrasound feature had negative predictive value ranging from 50% to 88% in malignant nodules.
Conclusions
Our study shows that no single US sign was reliable in differentiating all benign from malignant thyroid nodules, but many US features help in predicting the benign or malignant nature of a given nodule. Thus, a predictive model for malignancy using a combination of clinical, biochemical, and radiological characteristics may support clinicians in reducing unnecessary invasive procedures in patients with thyroid nodules.

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Comparison of G-CSF and non-G-CSF treatment of agranulocytosis in patients with hyperthyroidism: a meta-analysis

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There are potential benefits and risks to receive Granulocyte-Colony Stimulating Factor (G-CSF) as a general treatment in hospital. To assess the clinical effect of G-CSF or non-G-CSF on recovery duration for agranulocytosis patients with hyperthyroidism, we analyzed the overall clinical outcomes by meta-analysis. We included published seven retrospective studies and 1 prospective study. Individual data were obtained from eight trials (376 patients: 215 with G-CSF, 161 with non-G-CSF treatment). The heterogeneity was acceptable ($I2 = 47.4\%$, $P = 0.055$) and the fixed-effect model was applicable. Compared with the non-G-CSF group, G-CSF group presented with shorter recovery duration with weighted mean difference (WMD) = −2.94d, 95% confidence interval (95% CI): −3.90, −1.97 ($Z = 5.98$ $P = 0.000$). However, we found that different regions and recovery criteria influence the results. European and South American patients have significant clinical outcome with WMD = −4.34d (95% CI: −7.37, −1.31), compared to Asian patients with WMD = −2.77d (95% CI: −3.82, −1.72). At the same time, varied recovery criteria, the duration of granulocyte count over 1.0 or 1.5×10^9/l with −4.34d (95% CI−7.37, −1.31) present better treatment effect in our analysis. So, we concluded that G-CSF was able to significantly shorten the recovery duration of hyperthyroidism patients accompanied with agranulocytosis, especially in Europe and South America region and for granulocyte count over 1.0 or 1.5×10^9/l.

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Ocular cavity metastasis from poorly differentiated thyroid carcinoma

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Introduction
Poorly differentiated thyroid carcinoma is a tumor of follicular origin with morphological and biological characteristics between anaplastic and well differentiated carcinoma. It accounts for less than 5% of all thyroid tumors and is characterized by adverse prognosis, aggressive behavior and frequently distant metastases, mainly to lungs and bones and to a lesser extent to brain, liver, kidney, breast and skin. Incident presentation: We report a case of a patient with poorly differentiated thyroid carcinoma, that during the progression of the disease presented a left orbital mass, a rare site of metastasis. The patient at 48 years of age was subjected to total thyroidectomy and histology revealed a poorly differentiated follicular thyroid carcinoma of the left lobe, 5.6 cm in diameter with capsular and vascular infiltration. The patient received 100 mCi I131 and TSH suppressive therapy was prescribed. Three years later the first relapse of the disease was presented with cervical lymph nodes metastasis, and during the upcoming 6 years metastases were appeared in cervical lymph nodes, lung and lateral abdominal wall. The treatment included, as far as possible, surgical removal of accessible lesions and administration of I131 (total 825 mCi). During the progression of the disease, due to the increased thyroglobulin and negative WBS, PET/CT was performed which revealed pathological uptake in two lung nodules, as well as in a cervical lymph node. Tyrosine kinase inhibitor was prescribed. Two years later, MRI revealed a lesion in the left orbit, 1.5 cm in diameter. Complete surgical removal of the lesion was performed, and histology revealed a metastatic thyroid carcinoma of low differentiation (negative thyroglobulin expression). The patient showed progress of the disease under TKI treatment.

Conclusion
Secondary localization of thyroid carcinoma in the orbit is extremely rare and almost always occurs in patients with long history of malignancy and widely spread disease. Therapeutic options are tumor removal, external radiation, brachytherapy, radioactive iodine, targeted therapies, and if eye loss is occurred, surgical excretion of the eye is recommended.

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Giant cystic pheochromocytoma: A clinically silent entity

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Introduction
Pheochromocytomas (PCCs) are rare neuroendocrine catecholamine secreting-tumors derived from chromaffin cells of the adrenal medulla. PCCs are usually solid tumors but rarely occur as a cystic lesion. Cystic pheocromocytomas (CPCCs) are usually asymptomatic, unilateral and of a large size without typical radiological and biochemical features of pheochromocytomas. Non-specific abdominal pain has been reported in several cases.
Case Presentation
We present a case of a 48-year-old female patient who is referred to our department due to an incidentally discovered large left adrenal mass, detected during preoperative imaging test for bariatric surgery. The patient was obese but with no Cushingoid features or other signs of hormonal excess. She did not report headache, palpitations, excessive sweating or hypertension. On clinical examination her pulse rate was 80 beats/min and her blood pressure was 120/70 mmHg. Blood count, liver and renal function tests were within normal range. A complete laboratory test of adrenal function was performed, which was negative for excess secretion of catecholamines or their metabolites. CT scan of the abdomen revealed a mass of 9.3 cm in diameter in the left adrenal gland. MRI revealed central cystic compartment and hemorrhagic areas in the above mentioned mass. The patient underwent open left transabdominal adrenalectomy without any intra- or perioperative complications. Histological section revealed morphological features of pheochromocytoma with cystic degeneration. Immunohistopathological staining was positive for chromogranin A and synaptophysin.
Conclusion
In contrast to patients with solid pheochromocytomas patients with cystic pheochromocytomas are usually asymptomatic and they have a negative biochemical evaluation which may lead to misdiagnosis. Consequently, the time of diagnosis is delayed, and tumor size tends to be larger once is detected. In this report, we present a case of a 48-year-old female patient with a giant cystic pheochromoytoma, who was asymptomatic and with normal biochemical profile. The presence of a pheochromocytoma should be considered in the differential diagnosis of cystic adrenal lesions even in the absence of symptoms or abnormal biochemical profile, because of the potential hemodynamic instability during surgery as it was published in other case reports.

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Glucocorticoid Functional Reserve in Hashimoto Hypothyroidism before and after LT4 replacement

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Introduction
It has been generally accepted that adrenal function might be impaired in patients with primary hypothyroidism. A transitory low glucocorticoid production has been identified in cases with severe hypothyroidism. We tried to evaluate adrenocortical glucocorticoid function using the low-dose Synacthen test, in patients with primary hypothyroidism. The primary endpoint was to contrast the cortisol response to low-dose Synacthen before L-T4 replacement and after normalization of thyroid function tests.
Patients and methods
Seven patients (2 men and 5 women), aged 18 to 70 years, with a diagnosis of primary hypothyroidism and naïve to L-T4 treatment, were included. Primary hypothyroidism was documented by the results of a High TSH levels >4.5 mUI/L and positive antibodies to thyroid peroxidase confirmed Hashimoto disease. We excluded individuals with other endocrinopathies, glucocorticoid use in the last 24 months, and current use of oral/nonoral contraceptives or drugs that may interfere with cortisol metabolism, transport, or the hypothalamo-pituitary-adrenal axis. A low dose Synacthene 1 ug was performed before and 6 months after LT4 replacement. Blood samples for serum cortisol were taken at T0, T30 and 60 min. A serum cortisol value equal to or greater than 180 ng/L at 30 or 60 min after stimulation was defined as a normal glucocorticoid response.
Results
When cases were compared before and after L-T4 therapy, mean serum cortisol values were lower before thyroid hormone normalization. Statistical significance was found only at 30-minute time (112.6 ± 33.1 versus 253.2 ± 38.3 ng/L). Taking 180 ng/L or more as the normal cortisol response at 30 or 60 minutes after Synacthene stimulation, 4 out of 7 cases had insufficient glucocorticoid reserve before L-T4 treatment. After L-T4 therapy, 3 out of 4 cases reached a normal cortisol response and the other case stayed with glucocorticoid insufficiency.
Conclusion
Patients with primary hypothyroidism showed, using the low-dose Synacthene test, an improved cortisol response after normalization of thyroid hormone levels. The mechanism of impaired cortisol secretion in cases with hypothyroidism still has to be elucidated but our data support an adrenal rather than a pituitary affection. The incidence of adrenal insufficiency was 6.7–18.3% and more than 50% of the cases had a normal cortisol response after L-T4 therapy. This finding could have important clinical implications especially in the setting of acute stress situations occurring during the period while a euthyroid state is still not achieved.

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Impact of thyroid autoimmunity on obstetric and perinatal outcomes in pregnant women with subclinical hypothyroidism

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Introduction
Maternal clinical thyroid disorders can cause reproductive complications. However, the effects of mild thyroid dysfunction are controversial. The impact of SH and thyroid autoimmunity on miscarriages, obstetric and perinatal outcomes are not yet well established and the effect of levothyroxine replacement in pregnant women with SH is unclear. The aim of this study was to evaluate the impact of thyroid autoimmunity in early pregnancy on obstetric and perinatal outcomes in pregnant women with SH.
Subjects and Methods
A retrospective cohort study in 108 women diagnosed of HS in the first trimester of pregnancy (TSH 4, 20–10 μU/mL, normal FT4). Based on the presence of thyroid autoimmunity defined as thyroid peroxidase antibodies (AbTPO) >34 IU/ml, we analysed clinical features and obstetric and perinatal outcomes. All women received levothyroxine replacement since week 11 of pregnancy until delivery.
Results
Mean age was 32 ± 6.6 years. 13.9% of women had positive AbTPO. Women with thyroid autoimmunity had TSH values greater than women with negative AbTPO (9.8 *vs* 5.45 μU/mL; $P=0.028$). We did not find any differences in miscarriages, gestational diabetes, preterm delivery, Apgar test, children weight or development of postpartum thyroiditis between both groups.
Conclusions
In our population of pregnant women with SH, we did not find any impact of thyroid autoimmunity on obstetric and perinatal outcomes. It is unknown the effect of levothyroxine replacement on these parameters.

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Abstract Unavailable.

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Navigating thyroid storm: The role of plasmapheresis in a patient also needing urgent aortic valve replacement surgery

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Thyroid storm requires a multiple-step pharmacological approach. While there is limited evidence for it, plasmapheresis has been shown to be an effective treatment when patients fail conventional therapy and other comorbidities complicate the clinical course. A 65-year-old woman presented with 6 months of symptoms of thyrotoxicosis and dyspnea, treated initially as an outpatient for pneumonia with no improvement. Eventually requiring admission for her dyspnea, laboratory testing revealed a suppressed TSH of <0.01 mIU/L and FT4 of 36 (12–22 pmol/L) and a chest x-ray consistent with interstitial edema. The patient was started on propylthiouracil, lugol's solution, hydrocortisone, cholestyramine and propranolol, however continued to have cardiac and neuropsychiatric symptoms. Further work-up for her hyperthyroid disease revealed anti-thyroid receptor antibodies consistent with Graves' disease. Interesting to this case, a transthoracic and transesophageal echocardiograms performed to evaluate for her heart failure, that was initially felt to be secondary to her thyroid storm, revealed the presence of severe aortic stenosis with a bicuspid aortic valve and 3+ mitral regurgitation. Cardiac surgery evaluation recommended in-house dual valve replacement surgery as valvular disease was predicted to not entirely improve with current treatment of her thyrotoxicosis. Given the need for urgent in-house dual valve replacement, and her persisting symptoms despite being on adequate treatment for 6 days and, the patient was started on therapeutic plasma exchange (TPE). She underwent three rounds of TPE which improved both her clinical and biochemical markers. Her FT4 decreased from 36 to 19 pmol/L. Furthermore, in preparation for her cardiac surgery, the patient underwent definitive treatment of her hyperthyroid state with a complete thyroidectomy after completing the TPE treatments. She was started on levothyroxine post thyroidectomy. Repeat TEE post thyroidectomy showed significant improvement in the severity of mitral regurgitation and was likely secondary to her thyrotoxic state; however, there was persisting severe aortic stenosis. The decision was made to proceed with single valve replacement and, on day 29, the patient underwent open aortic valve replacement surgery without any complications. While the medical treatment of thyroid storm is well established, patients may not have the appropriate response in first 24–48 hours. In cases where medical management fails and/or patients require urgent surgical intervention, as discussed above, therapeutic plasma exchange can be used to achieve both clinical and biochemical improvement from their thyrotoxic state.

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Prognostic factors for lymph node metastases in patients with papillary thyroid microcarcinoma

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Background and objective
Papillary thyroid microcarcinoma (PTMC) is recognized as a separate entity by the World Health Organization. Biological behaviour and clinical outcomes of PTMC are heterogenous. Presence of lymph node metastases (LNM) in this group of patients increases the risk of recurrence and makes optimal management in PTMC controversial (observation, lobectomy with or without preventive central ipsilateral dissection). The aim of this study was to describe risk factors for lymph nodal involvement in patients with PTMC.
Patients and methods
The Cadit-CAM study was designed to retrospectively analyze the clinical characteristics, treatments and outcomes of patients diagnosed of differentiated thyroid cancer (DTC) in Castilla La Mancha (CAM), a region in the central part of Spain. The cohort in Cadit-CAM study included 1434 patients from seven hospitals enrolled from 2001 to 2015. Patients with tumours ≤ 1 cm were selected. All underwent total thyroidectomy or lobectomy. Clinicopathological characteristics of patients with PTMC were reviewed. Univariate (χ^2 and Student's *t* test) and multivariate logistic regression analysis were used to identify predictors of LNM.
Results
426 PTMC were included, women 78.9% with mean age at diagnosis 50.6 ± 13.5 years. LNM were present in 12.7%. After surgery 54.2% received radioiodine. In univariate analysis male gender, age at diagnosis <45 years, multifocality, tumour size >5 mm and extrathyroidal extension were associated with LNM. The presence of thyroid autoimmunity was not associated with LNM. In multivariate analysis factors independently associated with LNM in PTMC were: male (OR 2.1 IC 95% 1.1–4.6 $P<0.05$), age at diagnosis <45 years (OR 2.6 IC 95% 1.4–4.9 $P<0.01$), multifocality (OR 2.8 IC 95% 1.5–5.4 $P<0.01$) and extrathyroidal extension (OR 6.0 IC 95% 2.6–15.5 $P<0.001$). 4 patients died from DTC. At final follow up 83.8% had excellent response, 13.8% indeterminate response, 0.9% biochemical incomplete response and 1.9% structural incomplete response.
Conclusions
PTMC in male younger patients (<45 years), with multifocal tumours and extrathyroidal extension are at risk of LNM. Treatment options in PTMC should be adapted to initial patient and tumour characteristics rather than tumour size.

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Histological characteristics in thyroid carcinoma: our experience in the last fifteen years

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Background and objective
The incidence of differentiated thyroid carcinoma (DTC) is increasing worldwide. Due to a increased use of improved radiological techniques, especially ultrasound. This study aims to analyze histological characteristics of DTC diagnosed in our hospital in the last fifteen years.
Patients and methods
It is a restrospective descriptive study. We have included all operated patients in our center between 2001 and 2015 with a final biopsy of DTC. We have analyzed three main variables. Ultrasound guided fine needle aspiration (FNA) cytology previous surgery: insufficient (Betestha I) benign (Betestha II), undetermined (Betestha III,IV,V) and malignant (Betestha VI). Histological type: Papillary Thyroid Carcinoma or Folliculary Thyroid Carcinoma and variants. Size of tumor.
Results
A total of 187 patients were diagnosed of DTC, 78.7% were women with a mean age at diagnosis of 49.47 ± 15.88 years. Ultrasound-FNA cytology was malignant (Betestha VI) in 33.1% of patients, undetermined (Betestha III, IV,V) in 43.4% of patients, benign (Betestha II) in 13.9% of patients, insufficient (Betestha I) in 9.6% of patients. In 22 cases ultrasound-FNA wasn't performed. Papillary Thyroid Carcinoma accounted for 91.5% of cases, whose main subgroup correspond to Classical variant (40.1%) followed by Microcarcinoma (28.5%) and Encapsulated (22.1%) Follicullary Thyroid Carcinoma was found in 8.5% of cases, mayor subgroup was the Minimally Invasive (50%) followed by Hurtle (37.5%). The comparison between preoperative cytology and final biopsy showed that 63.6% of malignant cytologies correspond to Classical Papillary. And 52.2% of benign cytologies are Microcarcinoma Papillary in final biopsy. Undetermined cytologies in the end were classified as 29.2% Classical Papillary, 27.8% Encapsulated Papillary, 23.6% Microcarcinoma Papillary. Statistic difference was found in all groups ($P=0.08$). Most tumors have a size between 1 and 4 cm (52.1%). Under 1 cm 36.7%. Tumor size has been decreasing with the pass of years. In 2001 it was 28 ± 6.1 mm and in 2015 it was 17.16 mm ± 13.1 mm. No statistic significance was found in any group.

Conclusion
According to the literature, the most common CDT type is Papillary. However, the amount of Microcarcinoma and Classical variant is very similar in literature data, around 33%. But in our center Classical variant is the most frequent. Tumor size is lower at the end of follow-up with no statistic differences. As further studies are needed to reach a bigger population.

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P374

Impact of total thyroidectomy on quality of life: the prospective ThyrQoL multicenter trial

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Introduction
Health-related Quality of Life (HR-QoL) is usually impaired in patients with thyroid diseases compared to the general population. Thyroidectomy is largely performed in case of benign thyroid disease, and can be associated with severe long-term complications: vocal cord palsy (VCP), hypoparathyroidism. Our goal was to report the long-term HR-QoL outcomes after thyroidectomy using the MOS 36-item short form health survey (SF-36) self-questionnaire.
Methods
The prospective ThyrQoL multicenter trial (NCT02167529) included 800 patients who underwent total thyroidectomy in seven French referral hospitals between 2014 and 2017. Exclusion criteria were extensive malignant disease, age <18 years, preoperative voice disorders with confirmed VCP. HR-QoL was assessed using the SF-36 self-questionnaire with a 6 months follow-up.
Results
We observed a significant improvement of HR-QoL 6 months after surgery ($P<0.0001$). Postoperative complications were associated with a non-significant impairment of HR-QoL. In multivariate analysis, Graves' disease was associated with a significant improvement of HR-QoL (OR $=2.39$ [1.49; 3.84]) and thyroid malignant disease with an impairment of HR-QoL (OR $=1.44$ [0.99; 2.08]) after total thyroidectomy. Compared to general population, HR-QoL was significantly impaired in patient with thyroid disease ($P<0.0001$); despite significant postoperative improvement, HR-QoL remained significantly impaired ($P<0.0001$) after thyroid surgery compared to general population.
Conclusions
We observed a significant improvement of HR-QoL 6 months after total thyroid surgery for benign and non-extensive malignant thyroid disease. Our results may help provide better information to both patients and physicians/surgeons, in order to choose the most appropriate treatment.

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P375

Can urinary iodine be used in the diagnosis and follow up of subacute thyroiditis?

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Introduction
Subacute thyroiditis is an iflammatory disease of the thyroid gland characterized by pain, tenderness and swelling in the neck. Less frequently, it may present with painless or silent thyroiditis that occurs spontaneously or in the postpartum period. In a few studies in the literature, urinary iodine was reported to be high in patients with postpartum thyroiditis, but it was not evaluated in patients with subacute thyroiditis. We aimed to evaluate urinary iodine in patients with subacute thyroiditis and determine whether it might have any role in the differential diagnosis.
Materials and methods
Patients diagnosed with subacute thyroiditis between April 2018 and January 2019 were included in the study. Patients younger than 18 years old, with a history of exposure to iodinated contrast media and pregnant or lactating women and patients with postpartum thyroiditis were excluded. Demographic features, thyroid functions, thyroid autoantibodies, serum thyroglobulin, erhytrocyte sedimentation rate (ESR), C-reactive protein (CRP), urinary iodine, thyroid ultrasonography and Tc^{99m} pertechnatate scintigraphy results were evaluated.
Results
There were 23 patients (16 female and 7 female) with a mean age of 38.65 ± 7.99. At the time of diagnosis, median serum thyrotrophin was 0.140 mIU/mL (min-max: 0.001–0.25) (normal levels: 0.27–4.2 mIU/mL), mean serum free triiodothyroxine and free thyroxine were 8.29 ± 3.53 pg/mL (normal levels: 1.8–4.6 pg/mL) and 3.56 ± 1.34 ng/dL (normal levels: 0.9–1.7 ng/dL), respectively. There was 1 (4.3%) patient with positive antithyroid peroxidase and 6 (26.1%) patients with positive antithyroglobulin. Median serum thyroglobulin was 116 ng/mL (min-max: 2.7–500) (normal levels: 0–78 ng/mL), mean ESR was 52.24 ± 25.47 mm and median CRP was 63 mg/L (min-max: 4.2–188) (normal levels: 0–5 mg/L). Ultrasonographically, thyroiditis was observed in 22 (96.7%) patients and 5 (21.7%) patients had thyroid nodules. Median urinary iodine was 441 mcg/L (min-max: 255–1843) and it was higher than 250 mcg/L in all patients. Thyroiditis was controlled with nonsteroidal antiinflammatory drugs and beta blockers in 13 (54.5%) patients, while additional corticosteroid treartment was required in 10 (45.5%) patients.
Conclusion
In patients with subacute thyroditis, urinary iodine was very well above normal limits. This might be helpful in the differential diagnosis and follow up of the disease. While, high iodine levels may be a consequence of thyroid follicle epithelial cell damage, the possibility of being an etiological factor should not be ignored. Large-scale prospective studies are required to determine the role of iodine in subacute thyroiditis

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P376

Comparative analysis of Hashimoto's and Riedel's thyroiditis morphology and immunohistochemistry

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The issues of Riedel's Thyroiditis etiology are controversial: There are two different topical pathogenic theories: Riedel's Thyroiditis as an autoimmune disease or as independent, primary fibroplastic process. Problem is to determine the possibility of malignisation in thyroid parenchym during the autoimmune thyroiditis - Hashimoto and Riedel's. Just due this questions, In parallel to the routine histological research, has been studied follow markers: 1. Highly sensitive CD56, which is expressed in the normal, non-neoplastic thyroid follicular cells, but its expression decreases in the thyroid neoplasm, especially during the thyroid gland papillary carcinoma (PTC) and 2. Tumor protein p63 (TP63), a member of p53 transcription factors, a stem/progenitor cell regulator, which is determine as precancerous precursor cells. Observation was carried out on operative materials (total number of cases 32) females, with average age ≈ 37. Riedel's – $n=10$, Hashimoto – $n=22$. Riedel's and Hashimoto's comparative study has shown the following results. During Hashimoto's thyroiditis CD56 negative or weak positive reaction was detected, indicating the existence of probable malignant potential in the tested case. As seen from the results, while the CD56 adhesive factor shows a high affinity in the colloid and in fact a negative receptor response to glandular cells. Especially remarquable is the CD56 negative answer to the disglatic districts. In case of PTC (as positive control) CD56 receptor-positive area only found in the colloid and p63 - was positive in the apoptotic nuclei. In the case of Riedel's thyroiditis in the active fibroplasia transformation of thyroid gland parenchyma, the weak reaction of p63 was shown. Certainly, in Riedel's thyroiditis p63 protein as the 'cancer stem cells' marker receptors do not appear in the thyroid parenchyma, therefore we purpose that Riedel's type of autoimmune thyroiditis displays minimal malignisation potential. Riedel's parenchyma, unlike Hashimoto's thyroiditis, revealed CD56 positive reaction in the colloid, as well as in the papillary carcinoma, and in the follicular cells the expression was not detected. We can conclude, that Riedel's thyroiditis is characterized by acellular fibrosis and residual follicles background, CD56 negative glandular cells, the negative p63's receptiveness. The data, obtained by two specific factors, indicates that in Riedel's thyroiditis, unlike Hashimoto's thyroiditis, malignant potential and cells transmutation not developes, which indicates at the real prognostic differences between this two major types of autoimmune Thyroid disease.

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P377

Is total thyroidectomy and bilateral central lymph node dissection essential for patients with unilateral cN1a papillary thyroid carcinoma?

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Background
The 2015 ATA guidelines recommend total thyroidectomy with therapeutic central lymph node dissection (CND) for papillary thyroid carcinoma (PTC) patients with clinical central lymph node metastasis(CLNM). The purpose of this study is to verify that total thyroidectomy with therapeutic bilateral CND is necessary for all patients with unilateral cN1a PTC.
Methods
This study retrospectively reviewed 899 PTC patients who had total thyroidectomy with bilateral CND from January 2012 to June 2017. The patients were divided into two groups according to the pre-operative central lymph node (CLN) status: cN0, no suspected CLNM; cN1a, suspicious CLNM. We compared the clinicopathologic features of both groups.
Results
The mean age was younger in cN1a group ($P=0.002$). Post-operative complications did not differ between the two groups. Chronic lymphocytic thyroiditis was more common in cN1a patients. In multivariate analysis, cN1a patients were associated with the number of CLNM >5 (OR$=2.24$, $P=0.006$) and the maximal size of CLNM ≥ 2 mm (OR$=3.67$, $P<0.001$) in final pathology. However, unilateral cN1a did not increase the risk of contralateral lobe or contralateral level VI involvement. Among cN1a patients, 33 out of 106 (31.1%) patients were both CLNM ≤ 5 and largest CLNM <2 mm, implying lobectomy with CND could have been sufficient.
Conclusions
Most of cN1a patients belonged to the intermediate risk group of recurrence and needed total thyroidectomy. However, if carefully selected, lobectomy and unilateral CND can be safely performed in about 30% of patients. Pre-operative careful clinical examination, rigorous radiologic evaluation, and intra-operative frozen section are prerequisite for this approach.

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P378

Should the dose of levothyroxine be changed in hypothyroidism patients fasting during Ramadan?

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Objective
Muslims worship by fasting from pre-dawn (suhoor) until sunset (iftar) for 30 days in the religious month of Ramadan. In addition to prolonged hunger, patients fasting with a diagnosis of hypothyroidism take their doses of levothyroxine outside of daytime fasting hours. This study compares thyroid functions of fasting hypothyroidism patients with the values before Ramadan.
Methods
One hundred patients aged 18–65 years were included in the study, who were followed with a diagnosis of hypothyroidism, who fasted during Ramadan, and who had no change of levothyroxine dose for at least for 6 months.
Results
The median serum thyroid-stimulating hormone (TSH) level of patients prior to fasting was 2.1 mIU/l (0.04–9.09), while median serum TSH after fasting was 2.8 mIU/l (0.01–21.21). Serum TSH values after Ramadan increased significantly compared to those prior to Ramadan ($P<0.01$). No significant difference was seen in serum sT4 levels. A statistical difference in TSH increase was not determined between patients taking their levothyroxine dose at iftar and patients taking it at suhoor. A positive correlation was found with sT4 levels and a negative correlation was found with serum TSH levels for daily drug dose and serum TSH levels after Ramadan.
Conclusion
Our study demonstrates a significant increase of serum TSH levels after Ramadan but no significant change of serum sT4 levels in hypothyroidism patients who are fasting. Therefore, we suggest the precaution of a small increase in levothyroxine dose before Ramadan for hypothyroidism patient who plan to fast.

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P379

Iodine status of schoolchildren of Belarus in 2017–2018

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Background
The problem of iodine deficiency in Belarus remains topical, due to the historical understanding of iodine deficiency in the environment and the negative impact of iodine deficiency on health. Strategy for elimination of iodine deficiency among the population was developed and implemented in the Republic of Belarus.
Aims
To determine iodine sufficiency in children living in Belarus.
Materials and methods
The study included 873 schoolchildren aged 9–12 years of both sexes, of which 650 children were in regular schools, and the remaining children in boarding schools. Questioning, determination of urinary iodine concentration and thyroid volume with ultrasound was carried out.
Results
Urine Iodine Median was 191 μg/l in the 873 children in 16 regions of Belarus. Thyroid volume corresponds to the normative values in children. According to the survey, 81% of households used iodized salt, constantly - 46%.
Conclusions
Currently adequate iodine supplementation in school age children has been achieved. The prevalence of thyroid gland diseases caused by iodine deficiency in children decreased significantly.

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P380

The Effect of Ramadan fasting on thyroid hormone levels in patients on levothyroxine treatment

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Aim
Contradictory results in limited number of studies were reported about the effects of Ramadan fasting on thyroid hormones. We aimed to evaluate the thyroid functions in Ramadan, and compare late evening or pre-sahour use of levothyroxine in patients being treated for hypothyroidism.
Methods
Patients taking levothyroxine for hypothyroidism who were seen in the last one week before Ramadan (8–15 May 2018) and had normal thyroid functions were recruited. Patients were offered to take levothyroxine at 22.30–23.00 pm before sleep (Group-1) or between 01:30 and 03:00 am at least 30 min before sahour (Group-2).
Results
Basal thyrotophin (TSH) was 2.01 ± 1.05 μIU/ml and significantly increased at the end of Ramadan (3.09 ± 3.38 μIU/ml, $P=0.008$). Free-triiodothyronine (FT3) decreased while free-thyroxine (fT4) increased ($P<0.001$, $P=0.028$). Eighteen patients were in Group-1 and 44 were in Group-2. There was unsignificant increase in TSH and FT4 in Group-1 ($P=0.160$, $P=0.425$), while both increased significantly in Group-2 ($P=0.022$, $P=0.008$). FT3 decreased in Group-1 and 2 ($P=0.016$, $P<0.001$). At the end of Ramadan, TSH increased in 39(%63.9), decreased in 22 (%36.1) and did not change in 1 patient. Anti-thyroid peroxidase antibody was positive in 65.5% of patients with increased TSH and in 35.3% of patients with decreased TSH ($P=0.047$).
Conclusion
Although mean TSH increased significantly,about one third of patients had lower TSH indicating for the need to evaluate every patient individually and follow closely during this month. Use of levothyroxine in late evening seems to maintain more stable thyroid hormones compared to pre-sahour. Clinical studies with larger sample sizes will be helpful to determine the optimal time for levothyroxine use during Ramadan.

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P381

Switch from tablet to oral liquid or softgel capsule L-thyroxine ensures lower serum TSH levels and favorable effects on blood pressure, total cholesterolemia and glycemia in thyroxine-replaced postmenopausal women under simultaneous calcium supplementation.

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Fifty postmenopausal hypothyroid women (age 71.7±5.1 year) had been under replacement L-T4 therapy for 4.4±2.0 years before adding calcium carbonate (CC) (taken 1–2 h after L-T4). CC and tablet L-T4 were taken for the subsequent 2.3±1.1 years. Because serum TSH increased compared to L-T4 taken alone (3.33±1.0 vs 2.0±0.5 mU/l (baseline), $P<0.001$), with 9/50 having TSH values >4.12 mU/l, we instructed all 50 women to postpone CC after 6–8 h after L-T4 ingestion. This delay was unsatisfactory in the 9 women (2.88±0.37 mU/l vs 4.91±0.96 (delay of 1–2 h, $P<0.001$) and vs 2.19±0.45 mU/l (baseline, $P<0.01$), but it was satisfactory in the remaining 41 women (2.0±0.41 mUl vs 2.98±0.51 (delay of 1–2 h, $P<0.001$) and vs 1.90±0.40 mU/l (baseline, not significant)). Because of the relationship between TSH with blood pressure (BP), total cholesterolemia (CHOL) and fasting glycemia (FG), changes in these indices were evaluated from baseline through postponement of CC at 6–8 h after tablet L-T4. All indices worsened when CC was taken 1–2 h after L-T4 but decreased significantly when CC was taken 6–8 h after L-T4. However, these last values were greater than baseline, with FG significantly greater both in the 9 and 41 women. To assess whether TSH, CHOL, FG, SBP and DBP would decrease further under novel L-T4 formulations, we proposed to switch from tablet to the preferred formulation (liquid solution or softgel capsule) while maintaining the same daily dose of L-T4, timing from breakfast and 6–8 h delay from CC. Sixteen women (group 1) accepted (1/9 and 15/41; 9/16, liquid solution, and 7/16, capsule) while 34 women remained on tablet L-T4 and CC 6–8 h later (group 2). After 3 months, in group 1, TSH fell (1.23±0.49 vs 1.80±0.37, $P<0.01$), CHOL decreased borderline significantly (163±13 vs 171±13 mg/dl) and FG significantly (80.7±7.9 vs 83.4±6.3 mg/dl, $P<0.05$); SBP and DBP remained unchanged. In contrast, in group 2, TSH (2.43±0.89 vs 2.33±0.52) insignificantly increased, and all other indices increased too, DBP borderline significantly (69.7±9.0 vs 66.3±6.5 mmHg) and FG significantly (93.2±14.8 vs 89.5±14.5 mg/dl, $P<0.01$). Postponing the ingestion of CC by 6-8h after tablet L-T4 is not sufficient to ensure optimal levels of TSH and TSH-sensitive indices. In contrast, this goal can be achieved by either novel formulation of L-T4.

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P382

Targeting the pentose phosphate pathway in thyroid cancer cells

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The pentose phosphate pathway (PPP) plays an important role in the biosynthesis of ribonucleotide precursor ribose-5-phosphate and NADPH. Glycolytic reprogramming of cancer cells frequently involves dysregulation of PPP flux. A previous study suggested that the expression of transketolase like 1 (TKTL1) was associated with invasiveness of papillary thyroid cancer. In the present study, we found that the combination of G6PD and transketolase inhibitors exerted a synergic effect on cell growth inhibition in thyroid cancer cells. Furthermore, targeting PPP significantly increased cellular reactive oxygen species (ROS) and induced endoplasmic reticulum stress and apoptosis. Suppressed cell viability could be partially rescued with treatment with a ROS scavenger or apoptosis inhibitor but not the inhibitor of protein kinase R-like endoplasmic reticulum kinase. Taken together, PPP blockade leads to an impairment of NADPH production and causes ROS-mediated apoptosis in thyroid cancer cells.

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P383

Clinical presentation of patients with Autoimmune Polygranular Syndrome III (APS III)

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Background
The autoimmune polyglandular syndromes are clusters of endocrine abnormalities that occur in discreet patterns in subjects with immune dysregulation and that permit treatment and anticipation of associated systemic or other hormonal deficiencies. Three major entities are recognized, APS I, APS II and APS III. They are considered rare syndromes, but they are possibly not always thoroughly investigated. APS III, in contrast to APS I and II, does not involve the adrenal cortex. In APS III, autoimmune thyreoiditis occurs with another organ-specific autoimmune disease.
Patients and methods
We present 12 cases of patients who present with autoimmune thyreoiditis and APS III.
1. Woman 76 years old:
Atrophic gastritis and gastric NET G1
Rheumatoid arthritis, at 45 years old
Vitiligo at 40 years old
Positive islet cell and anti-GAD autoantibodies
2. Woman 61 years old:
Alopecia areata at 58 years old
Premature ovarian failure (last menstruation at 38 years)
3. Woman 61 years old:
Alopecia areata at 5 years old
Vitiligo at 36 years old
Atrophic gastritis
4. Woman 55 years old:
Alopecia areata at 4 years old
LADA, positive islet cell and anti-GAD antibodies at 54 years old
5. Woman 72 years old:
Autoimmune gastritis at 63 years old.
6. Woman 46 years old:
Graves' disease at 43 years old
LADA, positive islet cell and anti-GAD antibodies at 45 years old
7. Woman 60 years old:
Sjögren syndrome at 50 years old
Systemic lupus erythematosus at 50 years old
Atrophic gastritis and hyperplasia of gastric neuroendocrine cells at 48 years old
8. Woman 69 years old:
Coeliac disease at 65 years old
9. Woman 74 years old:
Vitiligo at 30 years old
10. Woman 60 years old:
Autoimmune hepatitis at 59 years old
11. Male 66 years old:
Chronic atrophic gastritis with positive antibodies to parietal cells and intrinsic factor at 60 years old
12. Woman 35 years old:
Premature ovarian failure at 20 years old.
Conclusion
Endocrinologists often treat patients with autoimmune thyroid disease. It is important, when indicated, to investigate for other autoimmune diseases in order to detect an APS III, which may cause serious illnesses, such as diabetic ketoacidosis or neuroendocrine tumors of the stomach due to atrophic gastritis.

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P384

Prevalence of celiac disease in autoimmune thyroid diseases, and its associaton with other autoimmune disesases: a single center study in Argentina

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Patients with autoimmune thyroid diseases (AITDs) are likely to develop celiac disease (CD) among other autoimmune disorders. The prevalence of CD in

general population is about 1–1.5% and the frequency of AITDs-CD association is about 1.2–4.8%. CD can be asymptomatic in adults. Our objectives were to determine the prevalence of CD in adult patients with AITDs and the presence of other endocrine and non-endocrine autoimmune diseases in a single center in Buenos Aires. We evaluated the presence of CD antibodies in our patients with AITDs. In those with positive antibdies, CD was confirmed by endoscopy and duodenal biopsies. A total of 757 patients with AITDs were consecutively included in the study. The following antibodies were screened: Tiroperoxidase by MEIA, TSH receptor by Radioreceptor assay, IgA Endomisium by IFI, IgA and IgG transglutaminase by ELISA. We registered the presence of other autoimmune diseases. In 757 patients with AITDs: 86.7% had Hashimoto's thyroiditis (HT), 12.6% had Graves' disease (GD) and 0.7% Hashi-Graves; 84% were female, mean age: 52 ± 17 years; 35 patients (4.7%) had AITDs-CD. Five were previously affected with CD and 30 patients were newly diagnosed. Astenia, alopecia, osteoporosis, infertility, vitamine D deficiency, hypocalcemia and anemia were found as predominant findings in these 30 patients; 33/35 patients with AITDs-CD association had HT and 2/35 GD. Eighty four patients had another autoimmune disease: rheumatoid arthritis: 20, vitiligo:16, type I diabetes: 8, Sjögren syndrome: 7, 21-hydroxilase antibodies without adrenal insufficency: 7, Addison's disease: 5, premature ovarian failure: 4, pemphigus: 3, antiphospholipid syndrome: 3, systemic lupus erythematosus: 3, psoriasis: 3, alopecia: 3, pernicious anemia: 2, ulcerative colitis: 2, autoimmune hepatitis: 2, thrombocytopenic purpura: 1, discoid lupus: 1, myasthenia gravis: 1, scleroderma: 1, seronegative spondyloarthropathy: 1, vasculitis: 1. Six patients (18.1%) with HT-CD had a third autoimmune disease; 6 patients (0.9%) with HT had 2 other autoimmune diseases, but not CD. Conclusions: In our patients with AITDs, the prevalance of CD was 4.7%, 4 times over the prevalence in the general population as it was reported in other studies. We suggest assessing the presence of CD in subjects with AITDs who present unspecified symptoms as the ones found in our patients in order to prevent complications resulting from non-diagnosed CD and to consider the presence of other autoimmune diseases.

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Synchronous papillary carcinomas in thyroglossal duct cyst and micro carcinomas in thyroid gland: report of 3 new cases

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Introduction
Thyroglossal duct carcinoma (TDCCa) is a very rare finding and its presentation is similar to a benign cyst. Carcinoma arising in this tract is uncommon. It is still debated whetherTDCCa originates from the thyroid gland, from the thyroglossalduct it self (de novo theory) or from both. Although the differentiation may be difficult, this distinction can play a crucial role in treatment decisions regarding the inclusion of thyroidectomy as part of the treatment.
Case reports
We report three cases of concomitant papillary duct carcinoma in the thyroglossal duct cyst and thyroid gland.The mean age was 68 years with a male:female ratio of 2:1. There was no medical history was for thyroid gland or neoplastic diseases. A rapid enlargement of the mass and dysphagia was reported in two cases. Physical examination revealed a painless well-demarcated mass localized in the midline of the neck above the thyroid gland in all cases. The thyroid gland was apparently normal and no significant cervical lymphadenopathy was found. Thyroid function tests were normal. The neck ultrasound and CT scan revealed a pattern suggestive of a malignant thyroglossal duct cyst in two cases. A Sistrunk intervention associated with total thyroidectomy and central neck dissection was performed. Histopathological examination of the specimen revealed papillary carcinoma arising in the TGDC and papillary microcarcinoma of the thyroid gland without extrathyroidal extension and without metastasis in central neck lymph nodes. Surgical procedures were followed by iodine scan and radioactive iodine therapy with 131I ablation. Thyroid hormone replacement therapy was given regularly.
Conclusion
We present three rare cases of synchronous papillary carcinomas appeared in thyroglossal duct cysts and thyroid gland.These cases highlight that thyroglossal duct cyst can serve as malignancy of thyroid gland. Surgeons must be aware and include this entity while examining a patient with a neck mass located around hyoid bone with physical examination suspected malignancy. Considering the embryological development of the thyroid, the ideal treatment consists in the sistunk intervention associated with total thyroidectomy and central lymph nodes dissection.

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P386

Evaluation of the diagnostic algorithm when a suppressed tsh is found in the laboratory

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Introduction
Abnormal thyroid function is the most common disease in endocrinology and its screening of made by plasmatic (TSH), followed by (fT4) determination if abnormal. (fT3) determination is only used when pathological (TSH) and normal (fT4) are found, even if there is no evidence supporting this procedure, apart from the greater technical difficulty of measuring (fT3) due to its lower plasma concentration.
Material and Methods
Observational retrospective study of every sample containing TSH determination in a central laboratory of a tertiary referral center in a non-iodine deficient area from 02/01/2017 to 03/31/2017. In every sample with (TSH) < 0.1 mUI/l, (fT4) and (fT3) were measured. In patients without thyroxine treatment, their diagnosis was identified by their electronic medical records.
Results
We found 389 samples with (TSH) < 0.1, 5 of them belonged to duplicated patients and 34 of them were not properly registered on the clinical record. Out of the remaining 350 samples, 168 were being treated with thyroxine, 64 with antithyroid drugs and 118 were not being treated. Out of the 182 non hypothyroid patients, 103(61.3%) showed normal (fT4) and (fT3), 41(22.5%) showed both hormones elevated, 32(17.6%) only elevated (fT3) and 6(3.3%) only elevated (T4L). Out of those 6 patients, 3 were amiodarone related thyroiditis, 2 had an excessive iodine supplementation and 1 was toxic multinodular goiter. 68 patients had TSI mediated Graves' disease, 24(35.3%) of them had normal (fT4) and (fT3) , 26(38.2%) of them had both hormones elevated and 18(26.5%) of them only elevated (fT3). The mean relative level of (fT3) according to upper limit of normal (xULN) among the non-hypothyroid patients was 1.19xULN (s.d.:0.81) and the mean (fT4) level was 0.93 × ULN (s.d.:0.46). Among the non-hypothyroid patients with both hormones above the ULN the mean level of (fT3) was 2.25xULN (s.d.:1.11) and the mean level of (fT4) was 1.54xULN (s.d.:0.58). Comparing both results with the Wilcoxon test, there was statistically significant differences in both of them ($P < .001$).
Discussion
The (fT3) level is significantly higher than (fT4) level among hyperthyroid non levothyroxine dependent patients. (fT3) determination following a supressed (TSH) determination allowed detecting 73 out of 79 patients with elevated thyroid hormones, while the (fT4) determination allowed detecting 47 out of 79 patients. Measuring fT3 when a suppressed TSH may be more cost effective than the usual practice of determining fT4.

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A novel TPO mutation by next generation sequencing in congenital hypothyroidism and the functional analysis of thyroid peroxidase activity

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Thyroid peroxidase(TPO) deficiency due to biallelic TPO mutation is known as a representative genotype of congenital hypothyroidism (CH). CH is a congenital endocrine disorder that appears in 1/2,000 to 4,000 newborns. In most cases CH is caused by embryogenesis of the thyroid but the minority is caused by errors in thyroid metabolism. TPO mutation is known as a cause of rare genetic defects in thyroid metabolism. We hereby report a new homozygous TPO mutation (9491; ex 11; c. G 1964 T: p. C 655 F) as a result of the genetic screening based on the next generation sequencing. TPO is an enzyme that plays an important role in thyroid hormone production, and around 70 TPO mutations have been announced around the world, but this mutation is different from any known mutations. The male patient, the fourth child of healthy Japanese parents, born at term after an uneventful pregnancy and delivery. His parents are consanguineous married. He did not have thyroid stimulating hormone based new born screening. In Japan, mass screening for congenital hypothyroidism has been in effect since 1979, but his birth was before that. He continued to be somnolent, could not drink breast milk, was hospitalized immediately after birth. Hypothyroidism was revealed by examination at half a year after birth. Thyroid hormone replacement therapy was started from that time and thyroid function was kept normal up to adult. Although

he has a mild intelligence decline, with no difficulty in daily life and there was no problem in the growth process including the second growth. This patient has been treated with levothyroxine, and now thyroid hormone levels are within normal range. He has a very mild goiter, and the palpation touches the soft thyroid gland. Also, the size of the thyroid gland has no obvious left-right difference. In vitro functional analysis using CHO cells, whether the novel TPO mutation causes a partial loss of enzyme activity or not is under investigation. This TPO mutations (G1964T:p.C655F) was introduced by site-directed mutagenesis. Stable CHO cell lines expressing each TPO protein (WT, G1964T:p.C655F) were established using the piggyback system according to the manufacturer's protocol. On the day's announcement we would like to present the data of Western blotting using anti-TPO rabbit monoclonal antibody ab109383 and the results of the assay for quantifying thyroid peroxidase activity using Amplex Red reagent and H_2O_2.

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P388

Isotretinoin associated hypothyroidism

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Background
Many drugs are known to cause thyroid dysfunction. We describe a patient with hypothyroidism due to isotretinoin.
Case
A 28 year-old Chinese gentleman presented with 2-year history of fatigue and cold intolerance. He has acne vulgaris and has been taking isotretinoin for the last 3 years (20 mg daily for 1 year then 10 mg daily). He has a positive family history of thyroid disorders. He did not report any history of thyroiditis or known autoimmune disorders and is not on any other medications. Non-thyroidal illness was unlikely as he was otherwise well. Examination did not reveal any goiter or suggestion of autoimmune diseases. Laboratory investigations: free thyroxine (fT4) 11.4 pmol/l (RI: 8–20) and thyroid stimulating hormone (TSH) 6.17 mIU/l (RI: 0.45–4.5). Repeated thyroid function in a different laboratory: fT4 11.1 pmol/l (RI: 8–20) and TSH 8.08 mIU/l (RI: 0.45–4.5). Thyroid peroxidase antibody was negative. He reported increasing fatigue. As there were no other potential etiologies, the thyroid abnormality was attributed to isotretinoin. The patient was not willing to stop isotretinoin therapy and was started on replacement thyroxine 50mcg daily, which relieved his symptoms of hypothyroidism. At the last visit, thyroid function was normal: fT4 12 pmol/l (RI: 8–16) and TSH 2.72 mIU/l (RI: 0.45–4.5).
Discussion
Isotretinoin is known to be associated with lipid abnormalities and liver dysfunction but few are aware of its association with thyroid abnormalities. Proposed mechanisms include central gene-related inhibition and increased peripheral degradation of thyroid hormones via a non-deiodinase-mediated pathway. Even at a reduced dose of isotretinoin, our patient continued to exhibit symptoms of hypothyroidism, with abnormal thyroid function test results. Studies have shown significant decrease in levels of fT4 and TSH at both high and low doses. However, isotretinoin might not have an influence in them with intermittent treatment. It is likely that effects on thyroid metabolism may be dose-dependent but this requires further studies. Hypothyroidism is reported to show improvement with stopping isotretinoin. Given the anti-thyroid effects of isotretinoin, there has been a lower threshold for checking thyroid function tests.
Conclusions
We encourage routine thyroid function tests to be done at baseline and regular intervals thereafter, even in patients taking low doses of isotretinoin, given the effects it has on thyroid function. However, more studies are required to fully understand related dose-dependent changes. If the patient is not keen to stop medication, supplemental thyroxine will be beneficial in the treatment of isotretinoin-associated hypothyroidism.

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Role of subclinical hypothyroidism in modification of metabolic syndrome key components in the Chernobyl accident survivors within three decades

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More that three decades have passed since the Chernobyl nuclear power plant accident (ChNPPA). Several million survivors of the accident were exposed to radioactive iodine and mixture of other radioactive isotopes. Endocrine glands occurred among the target organs of radiation exposure in survivors. Insulin resistance and metabolic syndrome (MS) are among the ChNPPA health consequences.
Objective
Evaluation of the role of abnormal thyroid function in presentation of MS key components among the ChNPPA survivors three decades upon.
Results
Clinical examination was carried out in the 265 persons (143 males and 122 females) born in 1956–1968 (49–61 years old now) having thyroid disease with concomitant MS. Study group included the ChNPPA clean-up workers ($n=119$), residents of radiologically contaminated territories ($n=102$), and a control subgroup ($n=44$). Nodular goiter was the predominant disease in survivors with an incidence ($26.7\pm5.7\%$) three-fold exceeding a respective value in the control subgroup ($8.1\pm2.2\%$) ($P<0.05$). Subclinical hypothyroidism was also tree-fold more frequently revealed in survivors vs. in the control subgroup ($35.4\pm6.3\%$ and $12.5\pm39\%$ respectively, $P<0.05$). A direct correlation between the thyroid-stimulating hormone (TSH) level and MS main components, namely the systolic and diastolic blood pressure, levels of total cholesterol and triglycerides, body mass index was found in the ChNPPA survivors in a late post-accidental period ($r=0.851$, $P=0.001$; $r=0.764$, $P=0.001$; $r=0.819$, $P=0.001$; $r=0.854$, $P=0.001$; $r=0.823$, $P=0.001$ respectively). Inverse correlation was revealed between the free thyroxin level and above mentioned MS components ($r=-0.605$, $P=0.001$; $r=-0.572$, $P=0.001$; $r=-0.521$, $P=0.001$; $r=-0.497$, $P=0.001$; $r=-0.541$, $P=0.001$ respectively). When using the FINDRISK scale a correlation was found between the TSH increase and risk of diabetes mellitus ($F=3.75$, $P=0.015$), which coincides with the Rotterdam study data. The cardiovascular risk scores according to the SCORE scale are also worse in patients having a subclinical hypothyroidism ($F=3.43$, $P=0.038$).
Conclusions
Subclinical hypothyroidism both with low normal thyroxin level state lead to worsening of all the MS components, namely, affect the clinical course of arterial hypertension, dyslipidemia and abdominal obesity, worsen cardiovascular risks and risk of diabetes mellitus, requiring timely correction of thyroid dysfunction.

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Cofilin is a mediator of RET-promoted medullary thyroid carcinoma cell migration, invasion and proliferation

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Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor that originates from parafollicular thyroid C cells and accounts for 5% -10% of thyroid cancers. In all inherited cases of MTC, and in about 40% of sporadic cases, activating mutations of the receptor tyrosine kinase proto-oncogene RET are found. Constitutively active RET triggers signaling pathways involved in cell proliferation, survival and motility, but the mechanisms underlying malignant transformation of C-cells have been only partially elucidated. Cofilin is a key regulator of actin cytoskeleton dynamics. A crucial role of cofilin in tumor development, progression, invasion and metastasis has been demonstrated in different human cancers, but no data are available in MTC. Interestingly, RET activation upregulates cofilin gene expression. The aim of this study was to investigate cofilin contribution in invasiveness and growth of MTC cells, and its relevance in the context of mutant RET signaling. We found that cofilin transfection in human MTC cell line TT significantly increased migration ($178\pm44\%$, $P<0.001$), invasion ($165\pm28\%$, $P<0.01$) and proliferation ($146\pm18\%$, $P<0.001$), accompanied by an increase of ERK1/2 phosphorylation (2.2-fold) and cyclin D1 levels (1.4-fold). Accordingly, all these responses were significantly reduced after genetic silencing of cofilin ($-55\pm10\%$ migration, $P<0.001$, $-41\pm8\%$ invasion, $P<0.001$, $-17\pm3\%$ proliferation, $P<0.001$). The inhibition of constitutively active RET in TT cells by both the RET pharmacological inhibitor RPI-1 and the transfection of dominant negative RET mutant (RETΔTK) resulted in a reduction of cofilin expression ($-37\pm8\%$, $P<0.001$ and $-31\pm16\%$, $P<0.01$, respectively). Furthermore, RPI-1 inhibitory effects on TT cell migration ($-57\pm13\%$, $P<0.01$), but not on cell proliferation, were completely abolished in cells transfected with cofilin. In conclusion, these data indicate that an unbalanced cofilin expression, induced by oncogenic RET,

contributes to promote MTC invasiveness and growth, suggesting the possibility of targeting cofilin pathway for more effective treatment of MTC.

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P391

Frequency of comorbidity in primary care patients with hypothyroidism

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There are few valid data that describe the frequency of comorbidity in primary hypothyroidism patients seen in family practice. This study aimed to investigate the prevalence of comorbidities and their association with elevated ($\geq$4.0%) thyroid-stimulating hormone (TSH) using a large sample of hyhpothyroidism patients from primary care practices.

Materials and methods

A cross-sectional study in which multivariate logistic regression was applied to explore the association of comorbidities with elevated TSH. Altogether, 925 patients with hypothyroidism were under observation.

Results

In total 759 (82.1%) participants had comorbidity. The mean number of comorbidities was 1.7 (SD 1.02). Diseases of the circulatory system were the most common (689, 74.5%), followed by endocrine and metabolic diseases (322, 34.8%), and diseases of the musculoskeletal system and connective tissue (165, 17.8%). After adjustment for age and sex, the number of comorbidities was significantly associated with TSH. The higher the number of comorbidities, the higher TSH level. Patients with obesity, and those with dyslipidaemia and ischaemic heart disease were more likely to have increased TSH. The prevalence of physicians' inertia was statistically significantly and negatively associated with the number of comorbidities (Mann–Whitney U test, $Z=-12.36$; $P<0.005$; $r=-0.14$).

Conclusion

There is a high prevalence of comorbidity among hypothyroidism patients in primary care. A positive association of number of comorbidities and TSH is probably moderated by physicians' inertia in treatment of hypothyroidism strictly according to guidelines.

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P392

The presence of tall cells, even if

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Background

CV-PTC is often indolent with excellent long-term response, while TCV-PTC ($\geq$50% of tall cells) have aggressive features and worse clinical behavior. Less is known about the clinical behavior of CV-PTC with tall cells $<$50% (TC/CV-PTC) that, so far, is considered as low risk tumor.

Aim

To evaluate the histological presentation of CV-PTC, TC/CV-PTC, TCV-PTC and their clinical behavior after 6 years of follow up.

Methods

We evaluated the data of 610 consecutive patients affected by PTC, divided in: group A (CV-PTC; 417/610–68.4%), group B (TC/CV-PTC; 64/610–10.5%) and group C (TCV-PTC; 129/610–21.1%).

Results

No difference in gender, tumor dimension, multifocality, bilaterality, histological thyroiditis, central compartment lymph node dissection, pN1, number of metastatic lymph nodes and prevalence of ^{131}I avid metastases at RRA, was found among the groups. Patients of group C were significantly older ($P=0.02$). Neoplastic emboli were more frequent in group B (23.4%) vs C (13.2%) and A (9.8%), while mETE in group C (73.6%) vs B (57.8%) and A (39.6%) ($P<0.01$). Low risk were prevalent in group A (50.4%) vs B (20.3%%) and C (0%) and Stage I was more frequent in group A (94.7%) and B (96.9%) vs C (82.2%) ($P<0.01$). In group A (87.1%), most patients were treated with lower activities of ^{131}I (30 mCi) vs B (79.7%) and C (74.4%) ($P<0.01$). After 6 years, 18/610 (2.9%) were lost at follow up and the remaining were re-evaluated. No differences were found when considering excellent (ER) and indeterminate response (IR), while biochemical incomplete (BiR) was more frequent in group A (6.1%) vs C (4%) and B (1.6%), but above all, structural incomplete (StR) was more frequent in group B (13.1%) vs C (8.9%) and A (4.9%) ($P<0.01$). This difference is remarkable for CV/TC-PTC with tall cells 20–40% (14.5%) while CV/TC-PTC with tall cells $<$10% showed no StR. Moreover, no differences were shown in re-treatments performed during the follow up (i.e. surgeries or ^{131}I).

Summary

1) Older age, presence of neoplastic emboli and mETE were significantly more frequent in the TC-PTC and TC/CV-PTC with respect to CV-PTC; 2) After 6 yrs of follow up, BiR was more frequent in CV-PTC, while StR in TC-PTC but in particular in TC/CV-PTC.

Conclusion

The presence of tall cells, also if $<$50%, identifies a subgroup of PTC with an aggressive behavior and should be considered at intermediate-risk similarly to the conventional TC-PTC

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A rare case of suppurative lymphadenitis after treatment with granulocyte-stimulating factor for carbimazole-induced agranulocytosis

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Objective

Agranulocytosis is a rare but severe side effect of thionamide use in patients with hyperthyroidism. Treatment involves cessation of offending drug, treatment of sepsis, and the use of haematopoietic growth factors. Most patients recover uneventfully, and rarely present with further complications after treatment of the acute episode. We present a case report of suppurative lymphadenitis after treatment with granulocyte-stimulating factor (GCSF) and recovery from carbimazole-induced agranulocytosis.

Case Presentation

A 38-year-old lady with Graves' disease presented with a 2-day history of fever, sore throat, diarrhea and vomiting. Her Graves' disease had been in remission, until she relapsed and was started on carbimazole 30 mg daily 3 weeks prior to admission. Investigations revealed primary hyperthyroidism (Free Thyroxine 48.0 pmol/l and Thyroid-Stimulating Hormone $<$0.01 mIU/l) and agranulocytosis (absolute neutrophil count 0×10^9/L). She was diagnosed with impending thyroid storm and carbimazole-induced agranulocytosis. She was started on cholestyramine, lithium, glucocorticoids and beta-blockers. Carbimazole was withheld, and broad-spectrum intravenous antibiotics were administered. The patient was started on daily subcutaneous GCSF after Haematology consult, and required 8 days before recovery of ANC to $>1\times10^9$/l. Blood cultures were negative, and pharygodynia completely resolved after 8 days of IV antibiotics. She underwent I-131 therapy before being discharged well. However, she was readmitted 1 week later with fever and bilateral tender neck swelling. Imaging studies revealed bilateral cervical suppurative lymphadenitis with subsequent abscess formation. No other source was found despite extensive investigation; blood and fluid cultures were negative, with biopsy revealing only inflamed granulation tissue with abscess formation. The patient eventually responded to a prolonged course of antibiotics and drainage of lymph nodes.

Discussion

The development of suppurative lymphadenitis after GCSF and recovery from agranulocytosis has not previously been described. The patient's prior treatment history suggests that bacterial seeding from initial episode may have occurred, with flare of symptoms after neutrophil recovery. Clinical progress was reminiscent of immune reconstitution inflammatory syndrome, which has been previously described in patients following neutrophil recovery after chemotherapy, but not in patients with thionamide-induced agranulocytosis.

Conclusion

Patients and clinicians should be cognizant that further subclinical infections may be unmasked after recovery from agranulocytosis secondary to thionamides.

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Gastric acidity determines the more appropriate preparation of oral thyroxine

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Recent reports have proven gastric pH as key for both dissolution and bioavailability of oral thyroxine. This is clinically relevant in patients with gastric disorders to tailor an individualized treatment. *In vitro*, the softgel preparation of thyroxine possess a superior dissolution profile at increasing pH than the tablet T4. No data are available analyzing the correlation between the gastric pH and the softgel T4 performance *in vivo* and the present study is aimed at investigating this topic. Twenty height hypothyroid patients (24F/4M; median age = 48 years) in need for endoscopy were enrolled. These patients were treated since at least 2 years with a stable dose of tablet T4 (median dose = 1.65 μg/kg per day) and pledged to take thyroxine in fasting conditions, then abstaining from eating or drinking for at least one hour. The compliance with LT4 treatment has been checked by interviewing patients and confirmed by stable TSH values (< 0.8–2.5 mU/l). All these patients underwent endoscopy for either dyspepsia or follow up of gastric disorders. Gastric juice has been sampled during endoscopy to measure H+ concentrations in gastric juice. Then they have been shifted to softgel LT4 at a minimum effective dose, individually titrated to obtain a similar TSH concentration for at least six months. In the whole sample, the median concentration of H+ in the gastric juice was 52 mEq/l. Based on this value, patients were subdivided in two groups: Group A ($n = 16$) with a normal median H+ concentrations of 77 mEq/l (median pH = 1.5) and Group B ($n = 12$) showing a very low median H+ concentrations of 13 mEq/l (median pH = 4.3). The concentration of H+ correlated with the dose of LT4 in both groups although to a different extent(tablet: $r = 0.5810$ $P < 0.0001$ and softgel: $r = 0.2079$; $P = 0.0147$). In the group A (normal gastric acid), following the switch tablet/softgel, no patients showed a lower T4 requirement. In contrast, in the group B (very low acidity) 10/12 (83%, $P < 0.0001$; RR = 6; PPV 100%) required a reduced dose of softgel T4. The median dose in these latter patients was reduced from 1.92 to 1.67 μg/kg per day (−15%).The findings of this in vivo evaluation revealed that the dose of both tablet and softgel thyroxine correlates with gastric acidity but softgel T4 formulation should be the preferred one in hypothyroid patients with impaired gastric acid secretion.

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An unexpected finding of a bronchogenic cyst mimicking thyroid cyst

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Introduction
Bronchogenic cysts are rare benign congenital anomalies related to the abnormal budding of the tracheobronchial tree during embryological development. They are usually located in the mediastinum and intrapulmonary regions. Localization in the cervical area is unusual, and specially, bronchogenic cysts presenting as thyroid cyst are quite rare.
Case report
A 43-year-old woman presented with a seven months' thyroid mass. The patient had no history of radiation exposure, no symptoms of hyperthyroidism or hypothyroidism nor any difficulty breathing. On examination, the patient had a 3 cm mass of the right thyroid gland that approached the midline of the neck. There were no other palpable nodes. Ultrasonography confirmed the existence of a cystic well defined mass on the right thyroid lobe measuring 3 cm. A fine-needle biopsy of the mass was performed and yielded yellow fluid. The patient underwent surgical exploration of the neck, which revealed a right thyroid mass extending to the isthmus. it seemed to be cystic and fluctuant with fibrous adhesions to the surrounding tissue. A right thyroid lobectomy was performed. The histologic appearance was characteristic of a bronchogenic cyst. The post-operative recovery was uneventful.
Conclusion
Although rare, cervical bronchogenic cysts are difficult to differentiate clinically from other cystic thyroid masses because of their location, radiologic characteristics, and evolution. The curative treatment consists of complete surgical resection.

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Is detection of braf mutation enough to decide prophylactic central neck dissection (CND)?

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Introduction
Most recent ATA thyroid nodule/DTC guidelines recommend thyroidectomy without prophylactic CND for small (T1 or T2), non-invasive, clinically node-negative PTC (cN0). However, some studies have suggested an association between the BRAFV600E mutation and the risk of nodal disease. Moreover, BRAF V600E mutation have recently showed significant association with recurrence in solitary intrathyroidal PTC between 2 and 4 cm (pT2) making suitable a more aggressive treatment (doi:10.1093/jnci/djx227).
Objective
Assess the influence of BRAFV600E mutation status in nodal disease in central compartment in a series of patients with PTC smaller than 4 cm operated on in one tertiary center.
Methods
We select patients with pathological diagnosis of PTC without clinical lymph node metastasis, no surgical evidence of extrathyroidal invasion and no distant metastasis at the time of surgery, who underwent total thyroidectomy and CND between 2005 and 2017. Microscopic extension beyond thyroid capsule, multifocality and BRAF mutation status were included as variables to predict nodal disease. Results were evaluated in all patients and after excluding microcarcinomas, and considering the extent of nodal disease (relevant if 5 or more affected nodes or foci in affected nodes bigger than 2 mm). BRAF V600E mutation was detected by RT_PCR (Cobas 4800 BRAF V600 mutation test, Roche).
Results
210 patients were included, 158 of them with tumors larger than 10 mm. Multifocality was present in 80 cases. From 158 PTC over 10 mm, 104 had unifocal disease. Microscopic extrathyroid extension appeared in 42 cases, 34 of them larger than 10 mm. Prophylactic CND obtained 2479 nodes (mean: 11.8/patient), without differences between both groups of BRAF mutation. BRAFV600E was evaluated in 148 of 210 cases (109 of 158 PTC > 10 mm). BRAFV600E mutation was significantly associated with the rate of nodal disease in CND in all groups (global, monofocal tumors, intrathyroidal tumors and both, monofocal and intrathyroidal tumors) independently of size. Moreover, BRAFV600E mutated PTC also showed more number of affected nodes than non-mutated PTC in all the groups studied. Significant association of the BRAF V600E mutation with relevant nodal disease in CND was present when evaluated throughout the group and among PTC greater than 10 mm, but there were no significant differences in their incidence between mutated and non-mutated monofocal PTC, intrathyroidal PTC or tumors with both characteristics.
Conclusion
BRAFV600E mutation increase the risk of central nodal disease, including intermediate-risk nodal disease. Prophylactic central neck dissection may be considered in the presence of PTC with BRAFV600E mutation.

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Assessment of attainment of recommended TSH target levels in thyroid cancer patients following in Dubai hospital

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Objectives
Thyroid cancer long-term treatment requires suppression of thyroid stimulating hormone (TSH) levels to below normal range based on risk stratification of the patient at time of diagnosis. This audit aimed to assess the practicality of implementation of the guideline recommendations of the American Thyroid Association (ATA) for target TSH levels in high, intermediate and low risk thyroid cancer patients. It also aimed to identify whether lack of implementation of the guidelines will affect patient outcomes in form of increased thyroglobulin levels.
Methods
Health records of 100 adult patients with a diagnosis of thyroid cancer were reviewed by selecting patients who visited the Thyroid Clinic at Dubai Hospital in 2017–2018. Baseline characteristics were recorded as well as the last 3 TSH values of each patient as a mean TSH per patient. We also recorded the most recent thyroglobulin level. Risk stratification was documented from medical notes and histopathology reviews. TSH targets were below 0.1uiu/ml in high-risk

thyroid cancer patients, below 0.5 uiu/ml in intermediate-risk patients and TSH of 0.5–2 uiu/ml in low-risk thyroid cancer patients.
Results
A total of 100 patients were included in the study. 87% female and 45% UAE nationals. The mean age was 47.35 years. Low-risk and intermediate-risk patients achieved target TSH values, with a mean TSH of 0.66ng/ml in the former and a mean TSH of 0.26 ng/ml in the latter. Thyroglobulin levels in both groups was acceptable (target <1 ng/ml) at 0.3 and 0.5 ng/ml, respectively. High-risk thyroid cancer patients did not achieve target TSH. The mean level was 0.4 uiu/ml. The mean thyroglobulin level was significantly elevated in this group at 13.95 ng/ml. Half of the patients included did not have any written data available in their electronic records to accurately classify them into an appropriate risk category. This does not facilitate in the selection of appropriate therapeutic targets. Despite this issue, patients in this group have reasonable control with a mean TSH value of 0.80 uiu/ml and a thyroglobulin level of 0.68 ng/ml.
Conclusion
We report difficulties in applying the 2015 ATA Guidelines in risk stratification of thyroid cancer patients, as accurate classification relies on clear documentation of the history, including type of surgery and histopathology, which is not always readily available in follow up patients. Target TSH value ranges cannot be determined in these patients. We also note that high-risk thyroid cancer patients are not achieving target TSH or thyroglobulin levels, possibly due to a heavy burden of disease.

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P398

Intellectual outcome in children with subclinical hypothyroidism: effects of two years of levothyroxine treatment

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Introduction
Subclinical hypothyroidism (SH) is characterized by serum TSH levels above the upper limit of the reference range, in the presence of normal serum concentrations of total T4 and free T4. Associ-ation between SH in childhood and adverse neurocognitive outcomes remains controversial.
Objective
To evaluate the intellectual outcome of children with SH before and after 2 years of treatment with levothyroxine (L-T4).
Methods
Thirty-five children (18 males and 17 females) aged 8.8 ± 0.5 years with persistent, idiopathic and mild SH (TSH serum levels between 4.5 and 10 mUI/L) were enrolled in the study. Thirty-five age- and sex-matched healthy children were enrolled as controls. Twenty-one children underwent a 2 year-course of L-T4 treatment (SH-group 1) whereas 14 refused any treatment (SH-group 2). Intellectual quotient (IQ) was evaluated through the Wechsler Intelligence Scale-revised for children in all subjects at study entry and after two years of therapy in SH-group 1 and two years of clinical observation in SH-group 2.
Results
At baseline, no significant differences were observed between SH children and controls as regards to verbal (VIQ, 98.89 ± 2.43 vs 97.03 ± 2.93) performance (PIQ, 100.91 ± 1.75 vs 106.23 ± 1.82), and full-scale (FSIQ, 99.80 ± 1.98 vs 102.34 ± 2.44) IQs. Moreover IQs at baseline were comparable in both SH-group 1 and SH-group 2 (VIQ 100.76 ± 2.96 vs 96.07 ± 4.03; PIQ 102.19 ± 2.33 vs 99.00 ± 2.63; FIQ 101.52 ± 2.61 vs 97.21 ± 3.00, respectively). Two years of L-T4 treatment in SH-group 1were associated with a normalization in TSH values as compared to baseline (6.21 ± 0.21 vs 3.19 ± 0.40 mUI/L, $P<0.0001$) but not with an improvement in IQ scores (VIQ 100.33 ± 3.52, PIQ 105.86 ± 3.04, FSIQ 103.67 ± 3.30) as compared to both baseline and untreated SH-group 2 IQ values (VIQ 96.86 ± 3.93, PIQ 99.29 ± 2.60, FSIQ 97.50 ± 2.92).
Conclusions
Our data suggest that persistent, mild SH in children is not associated with intellectual impairment, and that a 2 year-course of L-T4 treatment does not induce any significant improvement in IQ scores.

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P399

Cardiac size and function in children with subclinical hypothyroidism

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Background
The management of subclinical hypothyroidism (SH) is still challenging in particular for mild forms with TSH levels ranging between 4.5 and 10 mU/L. Although SH in children seems to be a bening condition, ongoing scientific investigations have highlighted the presence of subtle proatherogenic abnormalities among children with modest elevations in their TSH levels. Data on cardiac performance in children with SH are still scanty.
Aim
To compare left ventricular (LV) geometry and function of SH subjects in comparison to healthy comparable controls before and after a trial with levothyroxine ($L\text{-}T_4$) therapy.
Methods
Thirty-six (36) children (19 females and 17 males), aged 8.5 ± 0.6 years, with persistent SH (at least 2 years) and 36 euthyroid matched controls were enrolled in the study. At study entry height, BMI, heart rate (HR), systolic (SBP) and diastolic bloody pressure (DBP) were assessed and Doppler echocardiography was performed in all subjects. Twenty-two SH children, who accepted to start $L\text{-}T_4$ therapy, were reevaluated after 2 years of treatment and 22 matched controls were observed throughout the same period.
Results
LV size and systolic function were comparable between SH subjects and controls at baseline and increased similarly over time, whereas SH children showed a significant prolongation of isovolumic relaxation time (IVRT) (85.95 ± 2.72 msec) compared to controls (78.82 ± 2.27 msec, $P<0.05$), even-though still within normal values for age. In the 22 SH children who underwent L-T4 therapy, the IVRT significantly decreased (74.61 ± 3.25 msec) versus baseline value (85.47 ± 2.89 msec, $P<0.05$) and became similar to controls (74.92 ± 1.18 msec). No significant differences in HR, SBP and DBP were detected between SH subjects and controls.
Conclusions
Long lasting mild SH in children seems to be associated with mild subclinical diastolic dysfunction, which improved with $L\text{-}T_4$ therapy. Whether this subtle alteration may lead to clinical consequences should be further investigated.

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P400

Bone homeostasis in children with Subclinical hypothyroidism: effects of two-years treatment with levothyoxine

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Background
Thyroid hormone plays a key role in bone mineral homeostasis and significant alterations in its circulating levels has been associated with impairment in skeletal growth during childhood. To date, bone effects of subclinical hypothyroidism (SH) has not been demonstrated yet, therefore the management of this condition is still debated.
Aim
To evaluate bone mineral density (BMD) in children with mild, persistent SH and the effects of two-years treatment with levothyroxine (L-T4) on their skeletal homeostasis.
Methods
Seventeen children (8 males), aged 8.7 ± 1.03 years with mild (TSH levels between 4.2 and 10 mU/l), persistent (≥2 years from the diagnosis) and idiopathic SH were enrolled in the study, togheter with 17 age-, sex- and BMI-matched controls. At study entry, both groups underwent a complete clinical, laboratoristic and radiographic evaluation, by using the dual-energy X-ray densitometry (DXA) to evaluate their lumbar spine BMD. In the second phase of the study, SH children were treated for two years with L-T4 and then reassessed to evaluate possible changes in bone mineral status.

Results
At study entry, mean BMD Z-score was normal in SH subjects and comparable to controls (-0.41 ± 0.42 vs -0.12 ± 0.25, respectively, p ns). After two years of L-T4 therapy, a mild, but not significant, increase in BMD z-score was observed in SH children versus basal values (0.81 ± 0.56, $P = 0.08$).
Conclusions
Bone health, evaluated by lumbar spine DXA, is not impaired in SH children, despite long-term duration of idiopathic SH and two-years treatment with L-T4 did not change significantly their skeletal homeostasis.

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P401

Jejunum metastasis and perforation from anaplastic thyroid cancer

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Introduction
Anaplastic thyroid carcinoma (ATC) accounts for 1.7% of all thyroid cancers with poor prognosis and a median survival of 4 to 12 months. We report a case of ATC with small intestine perforation due to metastasis in the jejunum.
Case report
A 57-year-old woman was referred to our department for a rapidly enlarging goiter and dyspnea. Her latest thyroid ultrasound was performed about a month ago and demonstrated 2 nodules measuring 21×16 mm and 10 mm respectively, with calcifications present. The fine-needle aspiration revealed Bethesda III cytology. A new cytologic test was performed to a 4,5 cm nodule and showed neoplastic cells with characteristics of poorly differentiated thyroid cancer. The CT scans revealed a soft tissue mass with calcifications, extending from the thyroid gland to the upper half of the mediastinum and distant metastases to lung, brain and intestine. The patient underwent a partial thyroidectomy and tracheotomy to relieve her respiratory distress and the histological report showed anaplastic thyroid cancer. Brain CT that was performed due to altered levels of consciousness revealed metastatic sites in the semioval center. A few days later the patient presented an acute abdominal symptomatology and a CT scan revealed enlarged periportal lymph nodes, a regional increase in mesenteric fat density, small amounts of free intraabdominal fluid, small air bubbles in the abdomen and thickening of a small bowel fold and peritoneal fluid in the pouch of Douglas. The patient underwent surgery and histology revealed 6 metastatic foci of 2-15 mm in diameter dispersed within an 8 cm in lenth jejunal wall. One of these foci caused a 12 mm long perforation of the intestine. The patient, despite the supportive treatment, died on the 26th day of hospitalization.
Conclusion
All ATCs are considered as TNM stage IV. The 1-year survival rate is 20%. About 10-50% of all patients will have extensive disease at diagnosis. Most common metastases involve lung and pleura. Brain metastases account for 1-5% and are associated with a poor prognosis, while the jejunum metastases are extremely rare ($< 2\%$).

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P402

FNAB results of 520 patients in a mild-to-moderate iodine deficient city in Turkey

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Introduction
Thyroid nodules are common in population. High resolution ultrasound and fine needle aspiration biopsy (FNAB) are advised as the first line diagnostic methods. Bethesda classification system is used to provide standardization of cytologic reports. We aimed to evaluate ultrasound guided FNAB results in a mild-to-moderate iodine deficient city of Turkey.

Methods
The patients ($n = 520$), who underwent FNAB between December 2011 and December 2012 in an endocrinology unit of Batman District Hospital, were enrolled to the study. Nodules that were at least 1 cm diameter in size or smaller than 1 cm with suspicious ultrasonographic features were biopsied ($n = 635$). Among the recruited subjects, 89 had simultaneous biopsies from 2 nodules and 13 had simultaneous biopsies from 3 nodules. FNAB was executed by using ultrasound guided 22 gauged needles. Sample adequacy and cytopathological definition was determined according to the Bethesda system for thyroid cytopathology. Nodules were divided into five groups according to the largest diameter.
Results
Four hundred and forty-three women and 77 men, 520 patients in total were aged 43.9 ± 14.6 years, including, were enrolled into the study. Underlying pathology were multinodular goiter in 450 (86.5%) patients and solitary nodule in 70 (13.5%). 35 patients underwent thyroidectomy in our hospital and one patient had papillary thyroid cancer and one had follicular cancer. The remaining had benign pathology. Cytopathological results and distribution according to nodule size are shown in Table 1–2.

Table 1 Cytopathological results of 635 biopsies.

Subtypes	Frequency	Percent
I. Nondiagnostic or Unsatisfactory	165	25.9
II. Benign	443	69.7
III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	19	3.0
IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm	3	0.5
V. Suspicious for Malignancy	5	0.9
VI. Malignant	0	0.0

Table 2 Distribution of cytopathological results according to nodule size.

Subtypes	Group ≤10mm	Group B 11-19 mm	Group C 20-29 mm	Group D 30-39 mm	Group E ≥40 mm
I. Nondiagnostic or Unsatisfactory	18	76	50	16	5
II. Benign	15	155	167	69	37
III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	0	8	6	5	0
IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm	0	0	0	2	1
V. Suspicious for Malignancy	0	2	2	1	0
VI. Malignant	0	0	0	0	0

Discussion
Batman District Hospital is localized in a mild-to-moderate iodine deficient part of Turkey. Therefore multinodular goiter disease was much more prevalent than solitary nodules. Benign cytology was evident in most of the nodules biopsied. Although cytopathological evauation was made by 2 general pathologists, our rates were similar to current literature. More than half (56.5%) of the nodules were 2 cm or larger in size. Therefore large nodules requiring FNAB was a common clinical setting in case of multinodular goiter.

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P403

Thyroid lesions in patients with acromegaly: Experience of diabetology-endocrinology department of Oujda's Mohammed VI university hospital

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Introduction
Acromegaly is a quite rare and insidious disease caused by the oversecretion of growth hormone and subsequently insulin - like growth factor 1. Recent studies have demonstrated an increased co-existence of different thyroid lesions with acromegaly. However the data concerning this co-occurrence remains a matter of debate. The purpose of this study is to shed light on the different thyroid lesions concerning the patients with acromegaly who are followed up in the endocrinology department of Oujda's Mohammed VI university hospital to offer an optimal management.
Materials and methods
This is a retrospective data analysis of 10 acromegaly patients followed up in in the endocrinology department of Oujda's Mohammed VI university hospital.

Results
Mean age at diagnosis was 49 years with a female predominance. The median diagnosis delay was 5 years. 70% of the patients underwent transsphenoidal pituitary surgery and 44% were coupled to radiation therapy. Furthermore, 80% have been treated by Somatostatin analogs. Thyroid ultrasound showed a multinodular goiter in 50% of patients; homogeneous parenchyma in 10% and a thyroid nodule also in 10%. Blood tests revealed a toxic goiter in 20% of cases; central hypothyroidism in 20%, and central hyperthyroidism in 1 patient. A total thyroidectomy was proceeded in 30% of cases due to compressive symptoms. According to pathology lab report only 1 papillary thyroid carcinoma was recognized.
Conclusion
Although the data concerning the co-occurrence of acromegaly and thyroid lesions still remain controversial, systematic thyroid exploration should not be neglected either when the acromegaly diagnosis is made or during further observation and treatment. Nevertheless, it's particularly important to rule out thyroid cancer.

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P404

Pancytopenia and reversible cardiomyopathy - complications of thyrotoxicosis: case report

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Introduction
Grave's disease is frequently associated with cytopenia. Pancytopenia, however, is rare. Thyroid hormones have a direct effect on myocardial contractility and left ventricle (LV) diastolic function. Only less than 1% of the patients with hyperthyroidism develop cardiomyopathy with impaired left ventricular systolic function.
Case
A 51-year old woman was admitted to the Hospital of Lithuanian University of Health Sciences, Kaunas clinics with 6 months history of tachycardia, bilateral leg oedema and progressive dyspnea. For 9 years, the patient was treated with Thiamasole for thyrotoxicosis. Physical examination demonstrated enlarged thyroid, pale skin, cyanotic lips. Both legs were swollen below the knee down to the feet. There was no endocrine ophthalmopathy. Cardiac auscultation revealed an irregular heartbeat with rate of 128 bpm. Laboratory tests: TSH <0.001 mIU/l (0.27–4.2), FT4 34.38 pmol/l (12–22), FT3 7.38 pmol/l (3.34–5.14), anti-TSH-R 180 U/l (<9), anti-TPO 307.4 kU/l (0–12), anti-Tg 12 kU/l (0–100). Pancytopenia was diagnosed by haemoglobin 60 g/l (135–169), neutrophils 1.30×10^9/l (1.8–7.4), platelets 64×10^9/l (166–308). An electrocardiogram showed atrial fibrillation with heart rate of 128 bpm. Thyroid ultrasonography revealed enlarged thyroid gland with bilateral hypoechogenic zones. Color Doppler showed a highly increased vascularisation. Chest X-ray showed hydrothorax (12.3 cm liquid in the right pleura). Therapeutic thoracocentesis was performed. 5.6 cm of free abdominal fluid were observed in the peritoneal cavity by abdominal US. A transthoracic echocardiogram (TTE) was performed after intensive treatment (after 1 month), when clinical symptoms regressed. TTE showed moderately reduced systolic LV function (ejection fraction 50%), normal LV diastolic function; mild pericardial effusion, moderate aortic regurgitation, expanded mitral valve ring and severe mitral regurgitation. Red blood cells were transfused to treat anaemia. Prednisolone 40 mg/d were prescribed while gradually reducing the dose. Treatment with Thiamasole was continued and the dose was increased to 30 mg/d after adjusting the amount of the leukocytes. In order to relieve the symptoms, diuretics were prescribed, B-blocker and anticoagulation therapy was also started to prevent embolisms due to atrial fibrillation. Pancytopenia were no longer observed when we reached euthyrosis and the condition of the patient significantly improved. Before patient's discharge we got information about positive M. tuberculosis culture in the pleural puncture. It is likely due to immunosuppression. The patient was referred to specific treatment.
Conclusion
Pancytopenia and reversible cardiomyopathy are the rare complications of Grave's disease and conventional treatment for hyperthyroidism usually reverses.

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P405

Radiofrequency ablation in the treatment of benign thyroid nodules: a good alternative to surgery

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Introduction
To date, benign thyroid nodules complainig of symptomatic or cosmetic problems and autonomous functioning thyroid nodules (AFTN) have generally been treated with surgery or I131. Radiofrequency ablation (RFA) is a novel technique that has demonstrated safety and efficacy in the treatment of these nodules. We describe the clinical experience at our hospital.
Material and method
We include 33 patients (28 women, 5 men) from January 2013 to September 2018. The mean age was 50.1 years (range 20-83) and TSH 1.17 mUI/L (0.041-4.31). Malignancy was previously ruled out with core needle biopsy (CNB). 55% were located in the left thyroid lobe, 40% in the right and 6% in the isthmus. The content of the nodules was: 51.5% solids with an initial volume of 32.10 ml ($\pm$25.23), the 36.5% mixed with a volume of 27.25 ml ($\pm$25.16) and 12% cystic with volume of 17.48 ml ($\pm$13.06). The patients had a minimum follow-up of 6 months and maximum of 2 years. The indications of the technique were: 12 AFNT, 10 cosmetic problem, 9 pressure clinic and 2 for great size.
Results
100% of the nodules underwent a decrease in size with an average reduction of 64% at 12 months. The maximum reduction occurred at 12 months in solids (64%), at 18 months in mixed (83.65%) and at 24 months in cystic (79.27%). Of the 12 AFTN, 100% normalized TSH at 3 months. Of the patients with local clinic, 50% underwent partial improvement and the other 50% experienced disappearance of the symptoms. As complications there were 1 local 2-week pain, 1 self-limiting perinodular hemorrhage, 2 temporal recurrence dysphonia and 3 mild and self-limited hyperthyroidism. 2 solid nodules experienced regrowth at 18 months. There was no case of hypothyroidism.
Conclusiones
ARF is an effective technique for the decrease in size of thyroid nodules, especially those of mixed content. It is very useful for AFTN with normalizationof thyroid function in all cases. This technique presents few complications and prevents hypothyroidism so it is a good alternative to I131 or surgery.

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P406

Exacerbation of thyrotoxicosis following radioiodine therapy in benign thyroid diseases: can it be predicted?

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Introduction
Radioactive iodine (RAI) is an effective and widely used treatment for thyrotoxicosis. Post-radioiodine thyrotoxicosis is a well-known side effect of RAI. This is usually mild and easily controlled mostly with beta blockers but sometimes needs anti-thyroid drugs (ATD).
Aim of the study
To assess the incidence and predictors of post-radioiodine thyrotoxicosis.
Methods
Retrospective analysis of 86 patients who had RAI treatment in 2017 for hyperthyroidism in Mid-Yorkshire Hospitals, UK. Thyroid function tests were checked at diagnosis, immediately before RAI treatment and 4-6 weeks following RAI treatment. Post-radioiodine thyrotoxicosis was defined by undetectable TSH and high free T4 level 4–6 weeks after RAI. Multiple logistic regression analysis was conducted to assess for the presence of any predictor of post-radioiodine thyrotoxicosis.
Results
Mean age was 52.53 years and 73% were female. Thyrotoxicosis was caused by Graves' disease in 65.1% of the patients. 93.1% were pre-treated with antithyroid drugs prior to RAI. Mean TSH, free T4 and free T3 prior to RAI treatment was 1.36 mu/L, 17.29 pmol/L and 5.96 pmol/L, respectively. RAI dose of 385 MBq was given in 72.1% while 539 MBq was given in 27.9%. Post-radioiodine thyrotoxicosis occurred in 20 (23.3%) patients. Mean free T4 and free T3 was 44.73 pmol/L and 15.09 pmol/L, respectively. Two (2.3%) patients showed classic radiation thyroiditis (thyrotoxicosis with neck pain and tenderness). In 8 (9.3%) patients, this was associated with thyrotoxic symptoms (none of them developed thyroid storm). In 7 (8.14%) patients, free T4 was 2 times above the

upper limit of normal (free T4 >50 pmol/L) and Carbimazole (median dose 35 mg) was restarted to control thyrotoxicosis. Six months following RAI, 13 (65%) patients become hypothyroid. On the other hand, 6 (30%) patients remained thyrotoxic. Multiple logistic regression analysis showed that none of the independent variables (age, sex, cause of thyrotoxicosis, free T4 at diagnosis, TSH receptor antibody titre, goitre size, highest dose of Carbimazole, duration between diagnosis and RAI treatment, RAI dose and immediate restart of ATD following RAI) was significantly associated with post-radioiodine thyrotoxicosis (P value >0.05 for all independent variables). However, TSH receptor antibody was measured in only 44% of patients.
Conclusion
Exacerbation of thyrotoxicosis following radioiodine treatment is common and usually easy to control. However, it cannot be predicted. Patients need to be prepared for the likelihood of requiring antithyroid medications post radioiodine.

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Adrenal and Neuroendocrine Tumours 2

P407

ACTH-dependent hypercortisolism: always follow your nose

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A 41-year-old woman presented with a puffy face since five months. She experienced alopecia, hirsutism, easy bruisability, amenorrhea and proximal muscle weakness. Clinical examination revealed a moonface, centripetal obesity, proximal muscle atrophy, thinned scalp hair, hyperpigmentation in sun-exposed neck region, ecchymosis and arterial hypertension grade 1. Blood analysis showed elevated morning cortisol, elevated morning ACTH of 66.1 pg/ml (normal 10–60), hypokalemic metabolic alkalosis (potassium 2.6 mmol/l, bicarbonate 34 mmol/l) and hypernatremia (149 mmol/l). Cushing's syndrome was diagnosed with elevated 24-hours urinary cortisol excretion of 963 µg/24 hours (normal 21–292) and elevated late-night salivary cortisol of 0.437 µg/dl (normal <0.107). Loss of circadian rhythm and high ACTH and cortisol values at midnight confirmed ACTH dependency. No adenoma could be visualised on MRI of the pituitary gland. Inferior petrosal sinus sampling (IPSS) displayed a central-to-peripheral ACTH gradient of 2.8: clearly above the cut-off of 2.0. Surprisingly, we did not observe the expected rise in ACTH gradient after CRH-stimulation, with a gradient below 3.0 (1.4 after 5 min and 1.2 after 10 min). Additional PET-CT showed intense metabolic activity in the left anterior ethmoidal sinus and left upper nasal turbinate, extending to the middle and lower left nasal cavity. Biopsy of this polypoid lesion revealed an olfactory neuroblastoma (ONB) with positive immunostaining for ACTH. Our patient underwent endoscopic resection of the tumour as far as the lamina cribrosa, including resection of the entire middle turbinate. The exposed dura mater and the nasal septum showed no signs of tumour invasion. Postoperative values of cortisol and ACTH were undetectable, suggestive for successful resection. Anatomopathological analysis confirmed our previous diagnosis. Olfactory neuroblastoma (syn. esthesioneuroblastoma) is a rare neoplasm originating from neuroectodermal olfactory cells situated in the upper nasal cavity, representing about 3% of all sinonasal malignancies. ONB presenting with ectopic ACTH syndrome (EAS) is extremely rare. To our knowledge, only 18 cases have been published. Clinicians should be aware that inconsistent IPSS results might be due to an ACTH-producing tumour in the sinonasal region, which can be explained by the anatomical proximity to the venous drainage of the pituitary gland. In case of EAS, especially with inconsistent IPSS results, one should always follow one's nose and look at the sinonasal region.

Keywords: Cushing's syndrome, ectopic ACTH syndrome, esthesioneuroblastoma, olfactory neuroblastoma, IPSS

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P408

Metyrapone test in secondary adrenal insufficiency – is ACTH measurement alone sufficient for a proper diagnosis?

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In secondary adrenal insufficiency (SAI), the Synacthen test can give a false negative result. If disease is strongly suspected, an insulin hypoglycaemia test or Metyrapone (Metopirone) test should be carried out. Insulin test could be hazardous for patients with adrenal insufficiency (due to high risk of severe hypoglycaemia), so in our clinic we use overnight single-dose Metyrapone test. Although this test is easy to perform, measurement of 11-deoxycortisol concentration is not a standard procedure in most laboratories. Since the essence of Metyrapone test in secondary adrenal insufficiency is to evaluate the corticotropin reserve of hypophysis, the assessment of ACTH increment would be the ideal single measurement to state the diagnosis. However, recommendations in different guidelines are inconsistent about interpretation of ACTH results in this test. Proposed cut-off values for post-metyrapone ACTH response vary from >75 ('Endocrine testing protocols' in 'Endotext') to >200 pg/ml (Summary of Product Characteristic). The aim of the study was evaluation of ACTH response to single-dose Metyrapone administered at midnight and comparison of ACTH and 11deoxycortisol concentrations achieved during the test. In 110 persons (101 women and 9 men) referred to our clinic with suspicion of secondary adrenal insufficiency, the overnight single-dose Metyrapone test was done. On the basis of low post-metyrapone 11deoxycortisol concentration (<7 µg/dl) the diagnosis was confirmed in 38 patients (6 men and 32 women). The post-metyrapone ACTH values were 2-327 pg/ml (120.7±94.3) in patients with confirmed SAI and 110–645 pg/ml (270.6±156.7) in healthy subjects. There was no correlation between post-metyrapone ACTH and 11deoxycortisol levels in neither group (r=0.36 and 0.16 respectively). Using the lower ACTH cut-off value (75 pg/ml) 20 patients with SAI would be missed. Using the higher ACTH cut-off value (200 pg/ml) the diagnosis would still be false-negative in seven patients. Even though it seems logical that single ACTH measurement should be sufficient to establish the proper diagnosis of SAI, our results don ot support this hypothesis. Therefore, the concurrent assessment of 11deoxycortisol concentration is necessary. Moreover, proposed cut-off values for this test should be revised.

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Diagnostic accuracy of the aldosterone to active renin ratio in detecting primary aldosteronism: the graz endocrine causes of hypertension (GECOH) study

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Context
The aldosterone to active renin ratio (AARR) is the recommended screening test for primary aldosteronism (PA), but prospective study data on its sensitivity and specificity are sparse.
Objective
We investigated the diagnostic accuracy of the AARR for detecting PA.
Design
This is a prospective diagnostic accuracy study.
Setting
This study was conducted from February 2009 to August 2015 at the outpatient clinic of the Department of Endocrinology and Diabetology of the Medical University of Graz, Austria.
Participants
We included 400 patients with arterial hypertension who were referred to our tertiary care center for screening for endocrine hypertension.
Intervention
Participants had a determination of the AARR (index test) and a second AARR determination followed by a saline infusion test (SIT) after 2 two 6 weeks. PA was diagnosed in individuals with any AARR of ≥3.7 ng/dl/µU/ml (including a plasma aldosterone concentration [PAC] of ≥9 ng/dl) who had a PAC of ≥10 ng/dl after the SIT. We did not substantially alter antihypertensive drug intake.

Main outcome measures
Primary outcome was the receiver operating characteristic (ROC) curve of the AARR in diagnosing PA.
Results
Eligible for analyses were 382 participants and PA was diagnosed in 18 patients (4.7%). The area under the ROC curve of the AARR in detecting PA was 0.973 (95% confidence interval [CI]: 0.956–0.990). Sensitivity and specificity for a positive AARR in diagnosing PA was 100% (95% CI: 81.5–100.0) and 89.6% (95% CI: 86.0–92.5), respectively.
Conclusions
The AARR has a good diagnostic accuracy for detecting PA.

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Large adrenal incidentalomas require a dedicated diagnostic procedure

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Introduction
The management of large non secreting adrenal tumors (at least 4 cm) is still a matter of debate as it is unclear whether imaging, especially 18F-FDG, can be used to characterize their potential malignancy. Moreover, the risk of new hypersecretion in non-operated tumors is uncertain. Our aim was to better characterize these large adrenal incidentalomas.
Methods
Patients followed in our Center for a non-secreting large (at least 4 cm) adrenal incidentaloma, with an initial CT and 18F-FDG PET CT, were retrospectively included. Patients who were not operated after initial diagnosis had to be followed with clinical, biological and imaging evaluations for at least 3 years or till delayed surgery.
Results
81 patients were included in the study: 44 patients (54.3%) had initial surgery while 37 were followed, including 21 (25.9%) who were operated after a mean of 19 months. Among the 65 operated patients, 13 (20%) had a malignant lesion (3 with metastasis, and 10 with adrenocortical carcinoma): unenhanced CT <10 showed 85.6% sensitivity and 78.8% specificity; all had a 18F-FDG uptake ratio >1.5. Among the 24 patients who were followed for at least 3 years, 5 (20.8%) finally presented hypercortisolism (4 subclinical).
Conclusions
As expected, large adrenal tumors are at higher risk of malignancy. The combination of unenhanced CT <10 and 18 F-FDG PET ratio <1.5 prove to be reassuring and might lead to a close follow-up rather than immediate surgery. Hormonal follow-up should be focused on the risk of hypercortisolism.

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Necessity of educational programs for healthcare givers in preclinical settings of acute adrenal insufficiency in patients with chronic hypocortisolism

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Adrenal crisis is a life-threatening complication in patients with adrenal insufficiency. In order to prevent critical situations, patients are supposed to increase their glucocorticoid dose in distressing situations. If dose adjustment is not sufficient, sooner or later patients will fall into a coma, followed by death. While health condition worsens patients usually call paramedics, followed by a decision for primary therapy and transportation to the nearest hospital. We assessed whether paramedics and emergency physicians had ever suspected an acute adrenal crisis and initiated a steroid treatment in a preclinical setting. Furthermore, we wanted to know whether they feel confident in recognizing patients with acute adrenal crisis. To conclude, we asked them to estimate their respective need of further educational programs. We sent 1000 questionnaires to paramedics and emergency physicians in the region of Hanover containing questions about topics mentioned above. We received 19.6% ($n=196$) completed questionnaires of which 23% ($n=46$) were answered by emergency physicians and 68% by paramedics. All in all, questionnaires were answered by very experienced care givers with 70% having more than 500 responses to emergencies. Two thirds of emergency physicians had already completed their residency. Twenty percent of all participants had suspected an acute adrenal crisis at least once. Nevertheless, 66.6% of these participants had not asked or searched for an emergency card. Emergency physicians were asked whether any preclinical therapy besides volume infusion is necessary. Only 52% considered an additional therapy with no difference between residents and specialists ($P=0.52$). Specialists for internal medicine suggested an additional therapy significantly more often than specialists for other professions ($P=0.01$). There was no correlation between the number of emergency calls and considering additional therapy. Furthermore 94% of participants described insecurities about recognizing an acute adrenal crisis with only 67% asking for additional educational programs concerning acute adrenal crisis and its therapy. In summary, neither emergency physicians nor paramedics feel confident in recognizing patients with acute adrenal crisis. When suspecting an acute crisis two out of three did not ask or look for an emergency card (containing life-saving instructions). Half of the physicians did not consider any additional therapy besides volume infusion. Only specialization in internal medicine is associated with higher rates of specific additional therapy. We could show similar data for general practitioners in the past. We recommend additional education for the preclinical setting.

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Challenges in diagnosing and treating a glucagon secreting tumor – case report

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Introduction
Glucagonoma is a rare pancreatic neuroendocrine functional tumor, with an estimated incidence of 1 in 20 million people. At the moment of diagnosis, the majority of patients present locoregional and liver metastases.
Case report
We present the case of a 46 years old male patient, diagnosed with glucagon secreting pancreatic neuroendocrine tumor in February 2018. As part of the glucagonoma syndrome, the patient was also suffering from insulin treated diabetes mellitus, necrolitic migratory erythema, deep venous thrombosis, iron deficiency anemia, hypoalbuminemia, diarrhea, weight loss, cheilitis, stomatitis. Furthermore, he presented glucocorticoid osteoporosis with left pertrochanterial fracture and vertebral fractures, because he was treated with methylprednisolon for the skin lesions initially diagnosed as disseminated pustular psoriasis. Serum glucagon $=2138$ pg/ml (NV <209), chromogranin A $=462$ µg/l (NV $=27$-94), and thoraco-abdomino-pelvic CT scan revealed 3.5/4.4 cm solid tumor located in the caudal part of the pancreas, with no visible metastases. The screening for MEN1 syndrome was negative. A somatostatin receptor-based imaging was not available. Endoscopic ultrasound with fine needle aspiration and biopsy were performed, confirming the diagnosis of well-differentiated neuroendocrine tumor (ki67 $=2\%$). Due to the increased surgical risk at that moment, the surgical intervention (distal pancreatectomy, peripancreatic lymph node dissection, en-bloc splenectomy) was postponed and treatment with somatostatin analogs (SSA) was initiated. Intravenous zolendronic acid was administered as treatment for osteoporosis. One month after initiating the SSA treatment, there was a significant clinical improvement, with remission of diarrhea and almost complete cure of skin lesions. Chromogranin A level was within the normal range. Bone scintigraphy revealed multiple spots with increased radiotracer uptake, suggestive for metastases, while the 18F-FDG PET-CT scan performed afterwards showed no signs of metastases. On the other hand, although the pancreatic tumor had a low proliferative index, PET-CT scan revealed very intense FDG uptake in this

area, suggesting that, if present, the metastases would have been detected by this investigation. Since the therapeutic approach is different depending on the presence or absence of metastatic disease, octreoscan was recommended in order to decide if the patient would benefit from the tumor resection.

Conclusions

Due to its low incidence, the diagnosis of glucagonoma is very rarely taken into account. This case report emphasizes the importance of an early diagnosis, thus allowing initiation of treatment in the incipient stages of the disease. While the medical treatment with SSA usually lead to a significant clinical improvement, the surgical therapy is the only one that may allow complete disease remission.

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Phenotypic variability within a family with multiple endocrine neoplasia type 1 (MEN1) syndrome

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MEN1 is an autosomal dominant endocrine tumour syndrome, caused by inactivating mutations of the *MEN1* tumour suppressor gene at 11q13 locus and characterised by occurrence of hyperparathyroidism, pancreatic tumours and pituitary adenomas. We describe a family with MEN1 syndrome. The index case was a 71-year-old man, referred to Endocrinology clinic in Midland Regional Hospital Portlaoise for hypercalcemia (calcium 3 mmol/l, phosphate 0.5 mmol/l, PTH 350 pg/ml, creatinine 120 μmol/l) and diagnosed with primary hyperparathyroidism (PHPT). He was treated with cinacalcet for hypercalcaemia as he had multiple comorbidities such as ischaemic heart disease with a history of coronary artery bypass grafting and prosthetic aortic valve replacement, heart failure, chronic obstructive pulmonary disease and abdominal aortic aneurysm. CT thorax for respiratory symptoms demonstrated a bulky pancreas with a 4×3 cm heterogenous lesion in the pancreatic tail. Due to the presence of PHPT and the pancreatic lesion, he underwent *MEN1* genetic testing. In the meantime, his eldest son presented at 40 years with hypercalcaemia due to PHPT (calcium 3.29 mmol/l, phosphate 0.75 mmol/l, PTH 174 pg/ml). He was referred to St. Vincent's University Hospital neuroendocrine multidisciplinary clinic and underwent subtotal parathyroidectomy, which showed parathyroid adenoma on histology. On screening, he had a non-functioning pituitary macroadenoma which was resected, bilateral adrenal adenomas with low-grade hypercortisolism and pancreatic neuroendocrine tumours (pNETs). The second son also presented with hypercalcaemia secondary to PHPT. On further screening, he had pNETs but no evidence of pituitary tumour or adrenal lesions. Genetic testing of all three patients revealed a heterozygous mutation in *MEN1* gene, Exon 9, c.1348C>T, pGln405Ter. In conclusion, this report of MEN1 family highlights the phenotypic variability of MEN1 syndrome within one family having the same *MEN1* gene mutation. Careful phenotyping of patients with PHPT can reveal additional diagnoses of endocrine tumours.

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High levels of chromogranin A in connection with proton pump inhibitors

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72 years old patient was send to endocrinological outpatients clinic with suspect to nevroendocrine tumor (NET) with chromogranin A (CgA) level 379 μg/l (range 19.4–98.1). She described abdominal colic and diarrhoea lasting 2–3 hours after meals accompanied by dizziness, drenching sweat and lower blood pressure for the last 2 years. Comorbidities: arterial hypertension, chronic gastritis, heart failure and osteoporosis. Medications: omeprazole, losartan, pravastatin, torasemid, acetylsalicylic acid, paracetamol, diclofenac occasionally and ibandronic acid. At inspection clinical status were normal except pain on right abdominal site at deep palpation. Complete blood count, biochemical tests (except creatinine 115 μmol/l, (eGFR 41 ml/min/1.73 m^2)) and tumor markers were normal. The hormonal axis of thyroid, glucocorticoid, somatotropic, gonadotropic and prolactin was normal. A pheocromocitoma was excluded. 5-hydroxyindoleacetic acid (5HIAA) levels were elevated (109.0 and 159.2 μmol/l (range 10–47)). Secondary hyperparathyroidism was found and treated. Abdominal US and jejunoileography were normal. The EGDS showed a hiatal hernia. The colonoscopy revealed plain chronic colitis. The endoscopic US revealed 1 cm hyposonic areal in pancreas. Thorax CT, abdominal CT, and MR were normal. Octreoscan and PET-CT were negative. We followed CgA: 543.1, 994.2, 1365 μg/l. No reasonable organic cause for high CgA was found. Additionally, control 5HIAA were in normal range (27.9 and 20.5 μmol/l). The patient was on omeprazole 20 mg/d with a change to pantoprazole 40 mg/d within the 4 month of our evaluation. Pantoprazole was discontinued for 3 weeks and CgA fell to normal range (77.6 μg/l). She was tested with pantoprazole for 2 months and CgA rose to 479.3 μg/l. After discontinuation of proton pump inhibitor (PPI) CgA was again in normal range (66.9 μg/l).

Conclusion

Increase of CgA to such high levels was related to PPI. Control of 5HIAA and all morphological diagnostics were negative. A steep increase of CgA in a relatively short time could show other reasons than NET. Levels of creatinine were stabile. Other possible reasons of falsely elevated CgA are untreated hypertension, glucocorticoid excess, chronic atrophic gastritis, Parkinson disease and presence of heterophile antibodies.

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A case of pheochromocytoma left untreated for twelve years: Role of the endocrinologist

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Pheochromocytomas are rare chromafin, catecholamine-producing neuroendocrine tumors that arise from the adrenal medulla. Nearly half of these tumors are presented as an unexplained death and autopsy reports indicate higher incidence than it is proposed. We report the case of patient with pheochromocytoma treated only with minimal dose prazosin for twelve years. The operation was cancelled twice, on the day of surgery because the patient was not prepared with alpha-blockers and paroxysmal high blood pressure had happened. The patient was treated with 1 mg prazosin per day, and was not refer to an endocrinologist. He experienced episodic and sudden onset of high blood pressure that exceeds 270/130 mmHg, with dizziness, severe headache, tachycardia and sweating. The paroxysms have occurred two-three times a month. Diagnoses of diabetes mellitus and CKD were set in the meanwhile. The patient was admitted to the Department of Endocrinology of University Clinical Center of Republic of Srpska at the beginning of 2019. CT evaluation showed big, heterogeneous tumor mass, approximately 12×13×10 cm with 140 HU after i.v. contrast administration. In 24-h urinary collection adrenaline was five fold higher and noradrenaline was three times above the upper reference limit. Excretion of dopamine in 24-h urinary collection was in reference range. Phenoxybenzamin was initiated as starting dose of 10 mg and was gradually increased to 40 mg/day prior the operation. Also, 0.9% NaCl was gradually increased up to maximal 3.5 l/day to avoid the orthostatic hypotension. Two units of blood transfusion were given 48h before surgery and Low dose of bisoprolol was introduced in the therapy. Open resection was performed 15th. Any anaesthesia-related complications were recorded during surgery. The real tumor size was 16×14×12 cm. Postoperative, blood pressure was stabilized with noradrenaline.

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High prevalence of autonomous aldosterone secretion in patients with type 2 Diabetes Mellitus and arterial hypertension. The effect of SGLT2 inhibitors on renin-angiotensin-aldosterone system

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Introduction
The causes of arterial hypertension in diabetic and non-diabetic hypertensive patients are still not clear. However, in recent studies in non-diabetic hypertensive patients (NDHP) we observed dysregulation of aldosterone (ALD) secretion either in the form of autonomous secretion or as hyperesponse to stress. To the best of our knowledge, a similar study in hypertensive patients with type 2 Diabetes Mellitus (DHP) has not been conducted yet.
Objectives
The main aim of this study was to investigate ALD secretion in DHP. Furthermore, to investigate the effect of a sodium-glucose co-transporter type 2 inhibitor (SGLT2i) on renin-angiotensin-aldosterone system (RAAS).
Patients and methods
We included 71 DHP and 60 NDHP who served as controls, with normal renal function. Autonomous ALD secretion was tested using a diagnostic test (DCVT) for both groups, based on the pharmacological blockage of RAAS: midnight administration of dexamethasone (2 mg), captopril (50 mg) and valsartan (320 mg); blood sampling in the next morning for ACTH, cortisol, active renin, ALD and ALD/active-renin-ratio (ARR) estimation. An extra dose of 50mg captopril was given one hour before venipuncture. In addition, 10 mg empagliflozin (SGLT2i) was granted in diabetic patients for a month and active renin, ALD, ARR, ACTH and cortisol levels were estimated before and after treatment initiation. To establish the diagnosis of autonomous aldosterone secretion we used both post-DCVT ALD and ARR simultaneously. Their upper normal limits (UNL) were calculated based on the results of NDHP (control group) as Mean + 2SD (ALD: 110 pmol/l and ARR: 10 pmol/mU, sensitivity and specificity: ALD: 100 and 98%, ARR: 10 and 96% respectively).
Results
Autonomous ALD secretion was found in 27.7% (19/71) of DHP. No statistically significant difference in age, systolic/diastolic pressure, basal ARR and potassium/sodium concentrations in serum and 24h-urine, between the two groups (DHP vs NDHP) was found. In contrast, statistically significant difference in the post-DCVT ALD and ARR (Mean $\pm$ S.E.: ALD:132.2 $\pm$ 22.71 vs 51.87 $\pm$ 4.54, $P < 0.0001$ and ARR:20.63 $\pm$ 10.88 vs 3.74 $\pm$ 0.42, $P = 0.001$) between groups was observed. Finally, no effect on RAAS after empagliflozin administration in DHP (ARR:25.59 $\pm$ 6.3 vs 27.95 $\pm$ 5, $P = 0.2$) was found.
Conclusions
The prevalence of autonomous ALD secretion in diabetic hypertensive patients was found to be particularly high, similar to what was found in non-diabetic hypertensive patients using the same methodology.

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Extreme improvement in metabolic status with remarkable weight loss of 64 kg after adrenalectomy due to Cushing syndrome, and development of rheumatoid arthritis eight months later

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A 48-year - old woman was admitted in september 2015 for Cushing clinical sings obesity, weight was 120 kg, BMI 44,4 kg/m^2, arterial hypertension 160/120 mmHg, hyperlipidemia, moon face, purplish abdominal strie, amenorrhoea, marked swelling of bouth lags, more right leg with varices. Because high D dimer and factor VIII there was suspicion of deep venous thrombosis, Doppler of veins was done immediately wich excludes deep vein thrombosis, and as part of preoperative preparation, the patient was on low molecular weight heparin. She had high 24-h urinary cortisol, plasma cortisol not suppressed by 1 mg dexamethasone overnight (784.7 nmol/l), ACTH less then 1 pg/ml, OGTT test confirmed diabetes mellitus, plasma aldosteron, plasma renin activity and metanephrines were normal, as well as LH, FSH and thyroid hormons. PRL was also low, which significantly cinsidered because patient was treated with bromocriptin from 2004 to 2014 year, after which prolactinoma disapperaed, osteodensitometry has shown osteopenia. Abdominal computed tomography demonstrated a nodule 3.8 cm in the right adrenal gland. She anderwent right adrenalectomy, and histological examination confirmed an adrenal adenoma. Three weeks after the adrenalectomy there was an entrocolitis caused by Clostridium difficile, and she was admitted in state of prostration, febrile, with frequent water diarrhoea, which led to the Addison crisis. Recovery after that was slow, patient was on replacement therapy for next six months. Total colonoscopy was normal, and on gastroscopy gastroduodenitis is found. Eight months after biochemical and clinical resolution of hypercortrisolism blood pressure fell on 120/80 mmHg, cushingoid features regressed completely, she lost 64 kg of body weight, and kept the same weight until 2019 year, the lipid profile was normalised, and remaind normal, blood sugar has normalized, edema and enlarged veins disappeared, the menstruial cycle again became regular, only depression has occurred and patient is constantly under therapy. Two months after termination of replacement therapy she complained of back pain, pein on motion, marked tenderness, swelling of fingers and pain of the first and second metacarpophalangeal joint. Rheumatological exam suggest a rheumatoid arthritis with highly positive rheumatoid factor and C reactive protein, cystic erosiones of PIP and DIP joints, ANA were negative, terapy with Metotrexat 7.5 mg weekly is still in progres, without corticosteroids, and have a very good effect at joint level. In conclusion after treatment of Cushing syndrom patients shoud be evaluated for development of autoimmune disorders in order to obtain early diagnosis and proper treatment.

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Contribution of morphological and functional liver imaging to differentiate liver metastases of adrenocortical carcinoma from those of neuroendocrine tumors in a woman with a final diagnosis of multiple endocrine neoplasia type 1

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A 44-year-old woman was admitted for diabetic ketoacidosis and severe hypertension. She had aggressive clinical features related to Cushing's syndrome (CS). ACTH-independent CS was diagnosed based on undetectable ACTH (0.65 pmol/L) and unsuppressed cortisol levels by dexamethasone (6363 nmol/L). Adrenal contrast-enhanced computed tomography (CT) scans showed a 15x12x20 cm heterogeneous mass of the left adrenal that pushed back the spleen and the left kidney with thrombosis of the left ovarian and renal veins. The unenhanced density of the mass was >10 Hounsfield Units with a $<50\%$ absolute percentage washout. Multiple liver nodules (from 35 to 80 mm) were identified with a hyper vascularized pancreatic nodule compatible with a neuroendocrine tumor (NET). A well differentiated Grade 1 NET was diagnosed after liver biopsy. Laboratory testing found increased levels of pancreatic polypeptide >2000 pmol/L. Somatostatin receptor scintigraphy showed positive findings only in one liver metastasis. (18)F-FDG PET/CT showed an increased FDG uptake by the left adrenal mass (SUV max: 12.3) and the liver metastases (SUV max from 4 to 11.4) and also by thoracic and lumbar vertebras. As she had hypercalcemia, we looked for a primary hyperparathyroidism that was biologically and morphologically confirmed. Because of the occurrence of tumors involving several endocrine glands, we suspected a Multiple endocrine neoplasia type 1 (MEN1). A pituitary prolactin adenoma was also found. Genetic diagnosis allowed us to identify a germline MEN1 mutation. Given the liver discrepancy of morphologic and functional imaging about the origin of the liver metastases, we performed a liver MRI which characteristics confirmed a double origin of liver metastases: hyperintense lesions on T2-weighted and diffusion-weighted imaging with a strong hypervascularization were rather for the diagnosis of neuroendocrine liver metastases, while hyperintense lesions on T2-weighted associated with a heterogeneous enhancement were rather for the diagnosis of metastases of adrenal carcinoma. Adrenal steroidogenesis blockade was started using ketoconazole and mitotane, then metyrapone. Chemotherapy with carboplatin and etoposide was performed because of disease progression. After 2 months, the size of some liver metastases was decreased by 10%. Unfortunately, this woman returned to her country and she has not been seen since her departure. In conclusion, this case allowed us to diagnose a MEN1 from an association of liver metastases with a double primary tumors' origin: adrenal

carcinoma and pancreatic neuroendocrine tumors. Morphological (CT, MRI) and functional (PET-CT) imaging's were complementary to help us to better manage this patient.

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Prolonged hypoaldosteronism after unilateral adrenalectomy for primary aldosteronism: a report of two cases

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Introduction
Prolonged hypoaldosteronism is an uncommon complication following unilateral adrenalectomy for primary aldosteronism. There are only 5 case reports in literature. However, a retrospective series involving 110 patients found that it occurred in 5% of patients. We present our experience with two patients.
Case presentation
Patient 1 was a 51-year-old male presenting with a 7-year history of difficult-to-manage hypertension. He was intolerant to many antihypertensives and had undergone bilateral renal denervation. Despite this intervention, blood pressure remained poorly controlled. He was found to have primary aldosteronism. No adenoma was detected on CT, but adrenal venous sampling lateralized to the left gland, with contralateral suppression. He underwent left adrenalectomy where primary adrenal hyperplasia was found. Postoperatively, blood pressure was good requiring no medications. However he developed hyperkalemia and doubling of his baseline creatinine. Renin was undetected at 2 months. Subsequent renin levels were detectable but low. Aldosterone levels monitored until 30 months postop were borderline low, and hyperkalemia and raised creatinine levels persisted. Mineralocorticoid replacement was initiated, but then discontinued by the patient who remained well. Patient 2 was a 50-year-old male with 16 years of hypertension. Blood pressure was poorly controlled on 3 agents and he had severe spontaneous hypokalemia. Workup confirmed primary aldosteronism. CT showed a 3.0 cm hypodense adenoma in the right adrenal with nodular thickening of the left gland. Adrenal venous sampling lateralized to the right, with contralateral suppression. Immediately following right adrenalectomy, blood pressure improved. However at 2 months, he had to restart nifedipine. He was also noted to have hyperkalemia, elevated creatinine with borderline low renin and aldosterone levels. This persisted at 9 months postop. He was initially treated with salt tablets. As the patient was asymptomatic, mineralocorticoid therapy was not instituted.
Discussion
The etiology of prolonged post-adrenalectomy hypoaldosteronism is unclear. It has been proposed to be due to atrophy of the zona glomerulosa resulting in suppressed aldosterone synthesis and insufficiency—a functional primary hypoaldosteronism. Conversely, hyporeninemic hypoaldosteronism which both our cases had is very rare, occurring in only 1.8% of cases in the above series. Interestingly, impaired renin response following renal denervation may play a role in our first patient.
Conclusion
Post-adrenalectomy hypoaldosteronism may be more common than appreciated. Monitoring of patients' wellbeing, blood pressure, electrolytes, renal function and recovery of the renin-aldosterone system is important as the entity may result in hypotension and hyperkalemia with potentially severe consequences.

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Premature ovarian failure in a patient with schmidt syndrome

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Introduction
Premature ovarian failure (POF) may be a part of autoimmune polyglandular syndromes that involves multiple endocrine and systemic conditions due to autoimmunity.
Material and methods
We aim to present the case of a young women diagnosed with POF and Schmidt syndrome. The patient was followed in different tertiary centers of endocrinology. The informed consent was obtained.
Case report
A 31-year old patient with no prior significant medical history was admitted for further investigations presenting asthenia, fatigue, decreasing muscle strength, irritability and muscle pains. The clinical examination revealed normal weight (BMI- Body Mass Index of 21.33 kg/m^2), generalized hyperpigmentation of skin, darkened gums, low blood pressure with postural hypotension. The biochemical parameters revealed low sodium and clor serum levels, potassium in the upper limit range, normal glycemia. Hormonal profile showed low serum cortisol of 18.3 nmol/L (normal: 172–497 nmol/L), increased serum ACTH (Adrenocorticotropic Hormone) of 729.7 pg/mL (normal: 7.2–63.3 pg/mL, increased TSH (Thyroid Stimulating Hormone) of 15.92 μUI/mL (normal 0.4–4 μUI/mL), FT4 (Free Thyroxine) in the lower limit range of 13.5 pmol/L (normal: 10.6–22.7 pmol/L), raised anti-thyroid antibodies. Thyroid ultrasound revealed normal volume with a heterogeneous echogenicity. The diagnoses of Schmidt syndrome was established and replacement therapy with glucocorticoid analogue and thyroid hormones was introduced. Two years later the patient presented oligomenorrhea and secondary amenorrhea with negative progesterone test. The gynecological examination revealed low ovarian volume and linear endometrium of 3 mm. Hormonal profile showed normal prolactin, low estradiol and progesterone levels and slightly elevated levels of FSH (Follicle Stimulating Hormone) of 17.8 mU/mL (normal: 1.79–5.12 mU/mL) and LH (Luteinizing Hormone). Once confirmed POF, specific oestroprogestative therapy was added.
Conclusion
Loss of regular mentrual cycles in a young women with two pre-existing endocrine conditios due to autoimmunity is suggestive for POF. Treatment is necessary due to increased risk of osteoporosis and cardiovascular complications.

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P421

RET Y791F carriers' medical history – experience from one center

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Introduction
Germline mutations of *RET* oncogene result in development of multiple endocrine neoplasia type 2 (MEN 2). There is a strong correlation between type of the *RET* sequence changes and the aggressiveness of main syndrome feature, medullary thyroid carcinoma (MTC), and the incidence of remaining manifestations, mainly pheochromocytoma (PHEO). For many of the *RET* germline mutations, the clinical risk have been precisely defined, but there are still *RET* sequence changes of unknown significance, among which RET Y791F is the most controversial variant.
Material and methods
We retrospectively studied clinical data of 90 patients (28 index cases and 62 relatives) with *RET* Y791F variant, registered in our Department. In each patient with diagnosed PHEO additional predisposing genes (VHL, SDHx, TMEM127, MAX) were sequenced.
Results
In a group of index cases, in 5 patients pheochromocytoma (3 benign and 2 malignant with confirmed metastases) and in 23 medullary thyroid cancer were the first clinical manifestation with the mean age of revealing 35.8 years in case of PHEO and 58.6 years in case of MTC. Among 62 screened relatives, mean age 37.7 years, in 12 cases lack of data made determination of clinical status impossible, 50 from 62 relatives remained under close surveillance for mean time of 6 years. During follow up period MTC was diagnosed in 1 patient, 23 patients were subjected to prophylactic total thyroid excision with no MTC and 9 cases of C-cell hyperplasia on histological analysis. 26 patients, mean age 30.6 years, are still being observed with no clinical, biochemical or ultrasonographical symptoms of MTC. In the whole group of screened relatives there were no pheochromocytoma. There were also no coincidence of MTC and PHEO in *RET* Y791F carriers.

Conclusions
The controversy over the importance of *RET* Y791F variant, prompted us to retrospective analysis of *RET* Y791F carriers medical history. Only one casee of MTC revealed in our cohort of screened relatives, occasional pheochromocytoma cases reported in RET Y791F carriers, recent reports from other centers suggesting no causative role of this variant in MEN 2 development, induce the question about surveillance in this group of patients and moreover the legitimacy for prophylactic thyroidectomy in asymptomatic subjects. On the other hand, low mean age of followed up relatives may raise doubts, whether the clinical manifestation will not appear in the later age, typical for low risk *RET* oncogene mutations.

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P422

Association between new anthropometric parameters and new inflammation indicators in non-functioning adrenal incidentalomas

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Introduction
Studies demonstrate that non-functioning adrenal incidentalomas are assosiated with increased risk of diabetes mellitus and cardiovascular diseases. Chronic inflammation plays key role in developing type 2 diabetes, as well as cardiovascular diseases.
Aim
The purpose of the study was to evaluate new anthropometric parameters (BAI, LAP, VAI, BRI, ABSI, RFM) and its relationship with inflammation indicators (PLR, MPVLR, SII) among patients with non-functioning adrenal incidentalomas.
Material and methods
63 patients hospitalized in Endocrinology City Hospital in Piekary in 2014–2017 with non-functioning adrenal incidentalomas were inclued to the study. The exclusion criteria were mainly: other adrenal disorders, decompensated diabetes defined as HBA1C% >7, kidney failure as eGFR <60 ml/min/1.73 m^2, liver failure as bilirubin >2 mg/dl, INR >1.5 and albumins <3.5 g/dl, severe inflammation, treated cancer disease. Anthropometric parameters were measured in morning hours, biochemical parameters were taken from the patient's medical record.
Results
The average age was 60 years ($\pm$9.9), waist circumference in women was 99.9 cm ($\pm$15.3), in men 109.2 cm ($\pm$11.2), cortisol concentration at 8 a.m. was 10.7 ug/dl ($\pm$3.2), CRP was 2.5 ($\pm$4.0). In the studied group, PLR correlated negatively ($P<0.05$) with VAI ($r=-0.4$) and LAP. There was also negative correlation observed between VAI and MPVLR ($r=-0.3$) and VAI and SII ($r=-0.3$). There was no signifficant correlation ($P>0.05$) demonstrated between analyzed inflammation indicators and BAI, BRI, ABSI, RFM in the studied group, and no signifficant difference ($P>0.05$) betweeen analyzed inflammation indicators in group of patients with and without compensated diabetes.
Conclusion
The study indicated that the measurment of VAI and LAP could reflect new inflammaltion indicators in analyzed group of patients with non-functioning adrenal incidentalomas. It is worth to enlarge the studied group to confirm obtained results.

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P423

Comparison of visualization methods in ACTH-ectopic lung tumor: a case report

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Background
ACTH-ectopic syndrome is a rare cause of endogenous hypercortisolism and may pose serious difficulties in topical diagnosis.
Case description
Clinical features of hypercortisolism manifested at the age of 18 years (2012). A year later he was referred to an endocrinologist: ACTH 113 pg/ml (0–46), cortisol in 24-h urine 2915 µg/day (4.3–176), 1 mg DX test cortisol 1020 nmol/l, 8 mg DX test 764 nmol/l, intact pituitary MRI with contrast, abdominal and retro-peritoneum contrast-enhanced CT scan revealed no sighs of mass lesion. Chest CT showed nodular formation in the lingual lobe of the left lung and single enlarged paraaorthic lymph node. Octreoscan was negative. Atypical resection of the left lung was performed (07.02.2014), histological and immunohistochemical study showed typical lung carcinoid with negative expression of ACTH. Due to persistence of the symptoms of hypercortisolism in postoperative period, bilateral adrenalectomy was subsequently performed (24.02.2014) with a slight positive clinical effect. In September 2014 therapy with somatostatin analogues (long-acting octreotide 30–40 mg/month) was initiated with a moderate positive effect in ACTH levels, which remained elevated and continued to increase even in the setting of high-dose dexamethasone treatment. In February 2015 MSCT showed bilateral single enlarged hilar lymph nodes, whole-body diffusion MRI showed no signs of an ectopic tumor. In May 2016 we repeated diffusion MRI which revealed fibrous tissue formation in the apex of the left lung with a size of 9x8 mm and enlarged left hilar lymph nodes. The patient was consulted by a surgeon: due to absence of absolute indications surgical treatment was delayed and follow-up examination was recommended in order to specify the nature of the revealed changes. In December 2016 we observed same changes on chest MSCT scan. In May 2017 we conducted PET-CT with ^{68}Ga DOTA-TATE in the setting of octreotide withdrawal and observed radiotracer uptake in previously described findings. The same visualization was obtained by performed whole-body scintigraphy with Tc-99 tetracozactide. The patient underwent surgery (left thoracotomy, upper lobectomy, lymphadenectomy from the root of the left lung and mediastinum) with following course of chemotherapy and entered remission in the postoperative period. Histological and immunohistochemical study showed atypical lung carcinoid with ACTH expression and lymph node metastases.
Conclusion
Described case confirms complexity of topical diagnosis in ACTH-ectopic syndrome, leading to substantial delay in surgical treatment.

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P424

Paraneoplastic Cushing's syndrome related to recurrence of a malignant ovarian teratoma

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A 38-year-old woman presented with symptoms suggesting Cushing's syndrome. She has a history of surgery of mature ovarian teratoma (hysterectomy, ovarectomy) associated to radio and chemotherapy 15 years ago. The malignant teratoma relaps with hepatic and grelic metastases, and was *unresectable.* Main complaints were weight gain with centripetal fat distribution, muscle weakness, melanodermia and purpule striae on the skin of the abdomen, thighs, breasts and arms. She has a history of uncontrolled diabetes mellitus type 2 on insulin therapy and hypertension. Investigations: Cortisol failed to suppress after low dose and high dose on Dexamethasone suppression test. Plasma ACTH was 180 pg/ml (normal <60 pg/ml). A brain MRI confirmed the absence of any pituitary abnormality. Therefore, a diagnosis of ectopic Cushing syndrome was established. Computed tomography (CT) chest and abdomen showed multiple hepatic and intraabdominal and intraperitoneal masses, suspected radiologically to be a hamartoma. In-111 ***OctreoScan revealed suspected*** lesions located in the liver. The review and the re-reading of ***slides from ovarectomy showed a*** a focus of 3 mm with endocrine cell proliferation. Patient received ketoconazole treatment during 3 years with a moderate regression of the symptoms, then she received ***somatostatin analog*** therapy during 3 months. Conclusion: Ectopic cause of ACTH-secretion should be always included in differential diagnosis of Cushing's syndrome especially with malignoma in patient's history. Remarkable in this case is the delay of teratoma recurrence with paraneoplastic ACTH-secretion after 15 years of tumor-free interval.

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P425

Insulinoma: a case series of a tertiary care center

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Introduction
Insulinoma is rare tumor with an incidence of 1 in 250,000 patient-years. It presents with repeated episodes of hypoglycemia due to endogenous hyperinsulinemia, which occurs mostly in the fasting state. Insulinomas are usually sporadic, solitary, benign and encapsulated small lesions and majority of them measure <2 cm in diameter. They pose a challenge for pre-operative localization.
Materials and methods
A retrospective study of patients diagnosed with insulinoma during the period 1999–2018 (19 years) was done. Biochemical diagnostic criteria used were plasma concentrations of glucose <0.5 g/L with corresponding insulin level >3.0 µU/ml and C-peptide of >0.6 ng/ml. The localization of the tumor was done by various modalities namely computed tomography (CT), magnetic resonance imaging (MRI) and intra-operative ultrasonography (IOUS).
Results
Seven cases of insulinoma were included in the analysis, aged between 26 and 80 years, with a median age of 50.7 years. There were 3 males and four females (sex ratio 75%). All of them presented adrenergic features (sweating, shakiness, tachycardia, anxiety, and a sensation of hunger) and only one presented neuroglycopenic signes. Eighty-five percent of patients presented with pre-prandial hypoglycemia. There was weight gain in 57%. Hypoglycemia was spontaneous in 4 cases and 72-hour fasting plasma glucose test was necessary in other 3 cases. The average Plasma concentration of glucose was 0.42 g/l with corresponding insulin level 18.33.0 µU/ml(4.2–380 µU/ml) and C-peptide of 4.63 ng/ml (1.6–9.55 ng/ml). Different modalities were employed for pre-operative localization of these patients out of which 1 (14.2%) cases were localized with CT, 2 (28.5%) cases with MRI and 4 (57%) of them could not be localized out of which 2 were localized by IOUS. Among 7 cases, 4 underwent surgery out of which one patient underwent distal pancreatectomy as tumor was not localized and 3 underwent enucleation. In all the cases, the size of the insulinoma ranged between 1 and 2 cm. All patients were cured after surgery with no complications except 1 patient presented a transient pancreatitis.
Conclusion
In a non-diabetic patient with hypoglycemia, the diagnosis of insulinoma should be kept in mind. The commonest presentation in our series was pre-prandial hypoglycemia. A proper diagnosis and management can have a great impact on outcome and survival so it is important to address this.

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P426

Validation of 24-hour human adrenal steroid rhythms measured by ULTRADIAN interstitial automated microdialysis: Comparison with plasma

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Background
Hormones oscillate in circadian and ultradian rhythms. Consequently, single time point measurements are very difficult to interpret. To address this, we developed an automated system of 24-hour ambulatory microdialysis. This allows measurement of free hormone concentrations in subcutaneous interstitial fluid collected while participants continue normal daily activities. To validate the technique for adrenal steroid hormones, we simultaneously sampled interstitial fluid and blood plasma over 24 hours in a cohort of healthy women and men.
Methods
Participants (age 18–68, no regular medications, no active medical conditions, BMI 16-29) were recruited for hormone profile analysis. A 20 kDa linear microdialysis sampling catheter was inserted in abdominal subcutaneous tissue. Catheters were perfused at 1 microl/min using a portable CMA107 microdialysis pump attached to our novel fraction collector (U-RHYTHM) worn in an elasticated waist band. Microdialysate samples within the fraction collector were separated by air bubble every 20 minutes. Simultaneous blood samples were obtained from peripheral venous blood using an automated blood sampling system (HABS). A standard routine with respect to food, light exposure and sleep was maintained throughout the 24-hour sampling period. Multiplex analysis of steroid concentrations in both blood and microdialysate was achieved using triple quadrupole mass spectrometry. Plasma adrenocorticotropic hormone was measured using the IMMULITE 2000 Immunoassay System.
Results
We will present data from the first 5 recruited participants. 72 consecutive samples of blood and microdialysate were analysed for each participant. Analyte profiles detected in both compartments include cortisol (F), cortisone (E), tetrahydrocortisol (THF), tetrahydrocortisone (THE), corticosterone (CCS), 18-OH-cortisol (18-OHC), 18-OH-corticosterone (18-OHCCS), and aldosterone. All 24-hour profiles demonstrated circadian and/or ultradian rhythms.
Conclusions
U-RHYTHM interstitial microdialysis reliably and accurately detects dynamic fluctuations in steroid physiology. Measurements in interstitial fluid are highly correlated with plasma. Therefore we propose that U-RHYTHM ambulatory microdialysis is a more powerful, credible and accurate alternative to traditional single-time point assessments of adrenal function. U-RHYTHM therefore has broad potential as a clinical tool in the diagnosis and monitoring of adrenal disorders, including Cushing's syndrome and adrenal insufficiency.

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P427

Genetic mutations in bladder paragangliomas - not just SDHB-related disease

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Bladder Paragangliomas (PGLs) are rare forms of neuroendocrine tumours arising from sympathetic paraganglionic tissue. They account for $<1\%$ of all Pheochromocytomas and Paragangliomas (PPGLs) and $<0.06\%$ of all bladder tumours. All patients with PPGLs are recommended to be considered for genetic testing as $\sim 40\%$ of PPGLs are associated with a germline mutation, even if there is no prior family history of disease. Identifying an inherited PPGL predisposition has important implications for ongoing care and surveillance of the index case and provides the opportunity for cascade targeted genetic screening in the family. Bladder PGLs often display aggressive phenotypes with metastatic disease particularly if a germline SDHx mutation is identified thus requiring closer long term follow-up. Bladder PGLs can either be secretory or non-secretory and elevated normetadrenaline levels are often found in those with inherited SDHx mutations. We report six cases of bladder PGLs - 2 female and 4 male patients. Patients were aged 14–64 at the time of diagnosis, with a mean age of 36. Five presented with haematuria and 1 PGL was found incidentally following radiological imaging. Other reported symptoms were headaches, sweating and palpitations which were relieved by passing urine. Only 1 patient reported a family history of PGLs. Five patients had elevated plasma normetadrenaline levels and one patient was asymptomatic with plasma metanephrines within the reference range. Metastatic disease has been detected in two patients so far, one of whom had elevated Dopamine metabolites. Five patients had genetic testing. Pathogenic mutations were identified in four patients (FH, SDHA, SDHB*2 genes) and no mutation was identified in one patient from our genetic panel. All tumours demonstrated MIBG avidity. SDHB immunostaining on resected histology was available for two cases - absent staining in the patient with SDHA mutation and strongly positive SDHB immunoreactivity in the patient with FH mutation. Elevated plasma normetadrenaline together with negative SDHB immunostaining is a strong predictor of mutations affecting the SDHx genes. Elevated Dopamine and its metabolites in the context of Bladder PGLs (as in any sympathetic PGLs) should raise suspicion of metastatic disease warranting rigorous surveillance with multi-modal imaging. Hence it is important to undertake genetic testing in all patients diagnosed with bladder PGL with an extended panel as we have identified FH and SDHA mutations in our cohort. The genetic panel may need to involve further genes in the citric acid cycle to guide better surveillance strategy for this particular tumour group.

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P428

PAI-BEL: the Belgian registry on Primary Adrenal Insufficiency

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Introduction
Primary Adrenal Insufficiency (PAI or Addison's disease) is a rare disease with an increasing prevalence that may be complicated by life-threatening acute adrenal crisis. Valid epidemiological data are difficult to obtain. In Belgium, a national PAI registry had not been established yet.
Objective
We collected epidemiological and clinical data in a large cohort of adult patients with a known Addison's disease to have a better knowledge of epidemiology and management of PAI in Belgium.
Design
A nationwide multicentric study on PAI was designed to collect data on epidemiology, etiology, diagnostic circumstances, tests used for diagnosis, current substitution treatments, side effects of treatment and incidence of acute adrenal crises.
Results
One hundred eighty six patients with PAI were included in the registry between 2015 and 2018. The mean age at diagnosis was 37 ± 18 years with a higher prevalence in women (sexe ratio F/M = 1.45). The mean duration of the disease was 17 ± 14 years (1–67 years). Auto-immune disease was the most common cause of PAI (61%), followed by bilateral adrenalectomy (26%), genetic causes (8%), adrenal hemorrhage (2%), tuberculosis (2%) and mitotane chemotherapy (1%). Bilateral adrenalectomy was performed for Cushing's syndrome, bilateral pheochromocytoma and bilateral adrenal metastases. Type 2 polyglandular autoimmune syndrome was more prevalent in women (sexe ratio F/M = 3.14). After exclusion of non-autoimmune causes, clinical presentation was mostly progressive with non-specific symptoms at diagnosis: asthenia in 85%, weight loss in 83%, anorexia in 72% and digestive symptoms in 56% of patients. Melanodermia was found in 79% of patients. On average, baseline morning plasma cortisol was decreased to 50% of the lower limit of the normal range whereas baseline ACTH was increased to 22-fold the upper limit of the normal range. All patients were substituted with glucocorticoids, mostly with hydrocortisone (97% of patients) at a mean daily dose of 25 ± 7 mg or 13 mg/m^2. 88% of patients received mineralocorticoid substitution (fludrocortisone) at a mean daily dose of 100 ± 50 µg. Thirty percent of patients experienced at least 1 acute adrenal crisis. There was no difference in age, hydrocortisone daily dose or etiology between patients having single or multiple crisis. Acute adrenal crisis were more prevalent in women than in men (sexe ratio F/M = 1.9).
Conclusion
These data provide the first epidemiological data on primary adrenal insufficiency in Belgium that may help physicians to implement strategies to decrease the risk of overtreatment and to prevent acute adrenal crisis.

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P429

Urinary steroid profiling by gas chromatography-mass spectrometry (GC-MS) in Cushing's syndrome

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Introduction
Steroid profiling by mass spectrometry approaches consists in the simultaneous measurement of several steroid molecules in a biological sample, allowing an optimal characterization of steroidogenesis alterations, particularly in the context of adrenal tumors. Twenty-four hours urine samples have the advantage of being non-invasive and of giving an integrated view of steroidogenesis. Urinary steroid profiling has thus been shown to be particularly useful in the diagnosis of adrenal unilateral tumor (Weykamp, 1989; Arlt, 2011; Honour, 2018). We describe here the optimization and validation of a gas chromatography-mass spectrometry (GC-MS) approach, allowing the determination of a profile of 19 steroid urinary metabolites.
Material and methods
Urinary samples preparation required several steps including enzymatic hydrolysis, liquid-liquid extraction and derivatization of steroid metabolites. Retention time and mass spectrum of each steroid metabolite were determined by injection of the corresponding external standard in fullscan mode. Calibration curves were obtained by the sequential injection of a growing amount of each steroid external standard from 0.05 to 5 µg. A fixed amount of 8 internal standards was added to each sample and calibration point to normalize the results. Linearity, repeatability and reproducibility of the method were further evaluated.
Results
Optimized conditions of urine samples (U) preparation were as follows: enzymatic hydrolysis with arylsulfatase/glucuronidase for 4 hours at 55°, first derivation in methoxyamine/pyridine for 4 hours at 55° and second derivation in trimethylsilyimidazole for 5 hours at 100°. R^2 of the 19 calibration curves ranged from 0.983 to 0.998. Coefficient of variation (CV) of repeatability and reproducibility ranged respectively from 2.4% to 14.4% and from 3.2% to 13.6%. As previously described (Arlt, 2011), we confirmed with this approach, the increase in steroid precursor metabolites (including THS, 5-PT and 5-PD) in urinary samples from patients with adrenocortical carcinoma. This method was applied for the first time to urinary samples from 5 patients with Cushing disease and 10 control subjects matched on age and sex, highlighting a global activation of steroidogenesis in Cushing disease, characterized by an increase of both glucocorticoid (THF, ALLO-THF, THE), androgen (Etio, An), glucocorticoid and androgen precursors (PT, 5-PT, 5-PD) urinary metabolites.
Conclusion
We propose here a complete methodology of urinary steroid profiling by GC-MS, validated on samples from patients with adrenal carcinoma. This approach will give new insights into the characterization of steroidogenesis alterations, including in Cushing disease.

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P430

Efficacy of DHEA in improving Quality of Life in prolonged HPA axis suppression from exogenous steroids

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Dehydroepiandrosterone (DHEA) has been a subject of controversy for more than a decade being called 'a miracle hormone', the 'elixir of life' and 'an anti-aging supplement'. However, recent literature has proven mild to moderate benefit in selected group of patients. Data is mostly limited to primary adrenal failure patients with adequate glucocorticoid and mineralocorticoid replacement and in hypopituitarism from variable aetiology associated with severe disabling quality of life. We present here a small study of four patients with prolonged hypothalamic-pituitary-adrenal (HPA) axis suppression from high dose glucocorticoids who were prescribed DHEA. All 4 patients had been diagnosed with adrenal insufficiency following long-term steroid use for a variety of conditions; Asthma, Polymyalgia Rheumatica and Allergic Bronchopulmonary Aspergillosis. The age range of our patients was 45 to 70 years on commencement of DHEA with a mean age of 62.5 years. Despite adequate steroid replacement as evidenced by Cortisol day curves, our patients continued to suffer from poor quality of life with symptoms of extreme lethargy, nausea, dizziness, muscle aches and reduced productivity. Longer acting steroid preparation in the form of Plenadren was tried in one of the patients with little benefit. All 4 patients had Dehydroepiandrosterone Sulphate (DHEA-S) levels which were undetectable at <0.4 µmol/l (0.9–11.6 µmol/l) prior to commencement of DHEA. Considering significant impact on quality of life, DHEA was trialled in doses 25 mg to 50 mg. AddiQoL-30 questionnaire (a validated assessment tool used to assess the impact on quality of life in patients with Addison's disease) was used pre and post treatment to assess efficacy of treatment. All patients showed significant improvement in quality of life scores ranging from 13 to 42 points, with a significant mean improvement of 23 points. Our study has explored benefits in a relatively new cohort of patients with prolonged HPA axis suppression from glucocorticoid use. Widespread use of high dose steroids have increased such presentations to Endocrine clinics and hence, we highlight the need for further large group randomized controlled trials including these subgroups for future studies. The limitations of this study are the small number of cases without a control group however, this will be addressed in the future from our large cohort of selected patients with HPA axis suppression due to exogenous steroids.

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P431

Residual adrenocortical function in autoimmune addison's disease: interim results of a cross-sectional study

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Background
Current dogma states that in autoimmune Addison's disease (AAD), all adrenocortical function eventually is lost. Yet growing evidence suggests that a subgroup of patients retain some self-production.
Aim
To explore whether residual production of adrenocortical steroids is present in a subgroup of AAD patients.
Material and methods
In an open non-randomized cross-sectional study, an interim of 22 AAD patients delivered a medication-fasting morning blood sample for analysis of adrenocortical steroids by the highly sensitive and specific liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Before sampling, patients abstained from cortisone acetate or hydrocortisone and fludrocortisone for at least 18 and 24 hours, respectively. Residual function was defined as morning serum cortisol (s-cortisol) and/ and or aldosterone (s-aldosterone) above their corresponding lower limit of quantification (LLOQ). Dehydroepiandrosterone (DHEA) and corticosteroid precursors were also measured.
Results
Twenty-two patients (8 males, 14 females) aged 49.7 ($\pm$14.3) years with verified autoimmune adrenal insufficiency were included. Mean disease duration was 18.1 ($\pm$13.9) years. Twelve of 22 (54%) patients had morning s-cortisol exceeding the LLOQ of 0.91 nmol/l. Median s-cortisol was low (3.19 nmol/l [0.92–339.6]), but three patients presented with s-cortisol 71, 204 and 339 nmol/l. They had disease durations of 44, 5, and 5 years, respectively. There was no significant correlation between measurable s-cortisol and age ($P<0.899$), sex ($P<0.254$) or disease duration ($P<0.350$). S-aldosterone surpassed the LLOQ of 2.3 pmol/l in three patients (3, 14 and 217 pmol/l, respectively) in which all had detectable s-cortisol as well. Seven patients (32%) had measurable levels of DHEA (median 0.86 nmol/l [0.65–1.65]). Corticosteroid precursors were detected in 5 patients (23%) for 11-deoxycorticosterone (median 0.11 nmol/l [0.03–0.92]), 5 (23%) for 18-hydroxycorticosterone (median 0.25 nmol/l [0.07–3.40]), 5 (23%) for corticosterone (median 4.00 nmol/l [0.17–50.84]), and 4 (18%) for 11-deoxycortisol (median 1.96 nmol/l [0-18–2.15]). All precursors were present in the three patients with the highest fasting s-cortisol. In seven patients (33%) with measurable s-cortisol less than 3.5 nmol/L, none of the precursors were detected.
Conclusion
More than half of the patients had detectable levels of adrenal steroid hormones even years after the diagnosis; three had clinically significant levels of cortisol as well as detectable precursors. Patients with preserved steroid producing-capacity could be candidates for therapy aimed at regenerating and restoring adrenocortical function.

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P432

Case report: giant adrenal myelolipoma in CAH – should all patients be screened by ultrasound for adrenal masses?

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Introduction
Myelolipomas account for 5–15% of all resected adrenal masses and are considered as benign lesions consisting of fat and myeloid tissue. Their pathogenesis is mostly unknown, though altered mesenchymal stem cell function or a sustained respond to increased ACTH stimulation are discussed. Even though these findings are partly inconclusive, an increased incidence of myelolipoma in patients with congenital adrenal hyperplasia (CAH) has been reported, which may lead to increased ACTH levels if CAH is not treated adequately. Due to massive growth in a displacing manner with possible rupture and intra-abdominal bleeding, as well as difficulties to distinguish them from malignant lesions, surgical resection is often recommended. Thus, incidental findings may have therapeutic consequences and routine adrenal imaging in patients with congenital adrenal hyperplasia should be considered.
Case report
A 48-year-old male with congenital adrenal hyperplasia and salt-wasting syndrome due to 21-hydroxylase-deficiency presented frequently for medical surveillance in our outpatient clinic. With 0.05 mg fludrocortisone, a daily dose of 10 mg hydrocortisone complemented by 5 mg prednisolone in the evening, the patient showed no clinical symptoms and his laboratory results were within the reference range. During a routine visit the patient underwent abdominal screening by ultrasound. This examination revealed huge bilateral hyperechogenic adrenal masses (3.6 $\times$ 9.5 cm in the right, 10.4 $\times$ 10.4 cm in the left adrenal gland). We performed a contrast-enhanced sonography, that showed an early arterial peak enhancement (after 17 seconds) without any significant wash-out, which is consistent with bilateral adrenal myelolipomas. Additional MRI using opposed-phase sequence supported the suspected diagnosis. However soft tissue sarcoma was still a potential differential diagnosis. Due to size and possible malignancy at the MRI scan, bilateral adrenalectomy was performed and a mass of 1083 g at the left and 96 g at the right adrenal gland was extracted. Histopathological diagnosis was bilateral adrenal myelolipoma as anticipated by the previous findings.
Conclusion
We conclude that due to the increased frequency of adrenal masses and potentially needed therapeutic interventions, patients with CAH should receive imaging of the adrenal glands. Because myelolipomas can be identified by ultrasound (US) with high sensitivity and specificity, US should be considered as the imaging modality of choice. If malignancy is suspected due to ultrasound criteria, contrast-enhanced-ultrasound or CT/MRI should be considered. Further epidemiological studies are needed to define the incidence of adrenal masses in patients with CAH and to examine the pathogenesis of this disease.

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P433

Molecular events in a large series of advanced stage III-IV adrenocortical cancer: looking for new therapeutic options

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Adrenocortical cancer (ACC) is a rare cancer with poor prognosis and scant treatment options.
Purpose
To look for new therapeutic approaches issued from the screening for common genetic variants in a large series of advanced ACC.
Experimental design
Whole exome sequencing have been performed in 10 advanced (stage III and IV) ACC samples to identify the recurrent variants. The presence and the frequency of most interesting variants on this series together with the results of the literature were confirmed using target gene sequencing (Ion Torrent) in a validation cohortof 68 advanced ACC samples..
Results
Among the genes explored the most commonly altered gene was *TP53* (35.5%) followed by *CTNNB1* (22.1%); *APC* (19.1%); *ZNRF3* (11.8%); *RB1* (5.9%) and *DAXX* (5.9%); *MED12* (2.9%); *MEN1* (1.5%). Twenty percent of the evaluated samples presented a genetic variants in both Wnt and cell cycle pathways, while 33.8% did not have any genetic variants in the explored genes of these pathways.
Conclusion
Based on DNA alteration analyses performed in the largest series of advanced ACC, Wnt and cell cycle pathway alterations represent critical targets for future therapeutic development.

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P434

A severe ACTH-dependent Cushing syndrome associated to a possible concomitant primary adrenal-dependent hypercortisolism: a challenging case

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Background
Cushing syndrome (CS) represents a challenging disease. The major difficulty is to distinguish between the two main etiologies of ACTH-dependent hypercortisolism. However, in rare cases, the concomitant presence of both an ACTH-dependent and a primary adrenal disease should be considered.
Case report
We evaluated a 67-year-old woman for a severe ACTH-dependent CS (midnight serum cortisol 332 ng/ml; urinary free cortisol [UFC] 3000 mcg/day; cortisol after low-dose dexamethasone suppression test: 387 ng/ml, ACTH between 32 and 51 pg/ml), with metabolic syndrome and hypokalemia. Her past medical history was remarkable for right nephrectomy for renal clear cell carcinoma. During the oncological follow-up, a 45 mm mediastinic mass, suggestive for thymoma, and bilateral adrenal masses (right 40 mm; left 15 mm) were detected. Laboratory tests showed lack of cortisol response to high-dose dexamethasone suppression test (179 ng/ml) and lack of cortisol and ACTH response to CRH stimulation. Even if dynamic tests and clinical features were suggestive for an ectopic ACTH secretion, ACTH levels were detectable, but not as high as expected for an ectopic disease. Therefore, we considered mandatory to exclude a pituitary etiology of hypercortisolism: MRI showed a small lesion suggestive for pituitary microadenoma, but inferior petrosal sinus sampling ruled out an ACTH gradient between petrosal sinus and peripheral vein, suggesting an ectopic ACTH secretion. The patient underwent a 68Ga-PET-CT, which showed an increased uptake corresponding to the known thymoma. To justify the 'detectable', but not 'high' ACTH levels, we hypothesized the coexistence of an ectopic ACTH secretion (thymoma) and an autonomous hyperfunctioning bilateral adrenal hyperplasia, which could cause a partial inhibition of ACTH secretion. The patient underwent thymectomy. Histology showed a neuroendocrine tumor, with foci of atypical carcinoid, and focal reactivity for ACTH at immunohistochemistry. In support to our hypothesis of a double etiology of CS, the degree of hypercortisolism considerably improved and the patient did not experience hypocortisolism, as expected after successful surgery for ACTH-secreting tumor. In fact, in this case, the partial autonomous adrenal activity (subclinical CS) probably compensated the expected hypocortisolism related to the fall of ACTH levels. Three months after surgery, the patient stopped anti-diabetic and anti-hypertensive therapy, while laboratory evaluation showed a normalization of UFC.
Conclusion
This case shows how the challenging diagnostic work-up of CS can be complicated further by the coexistence of more than one etiology and highlights the importance of applying a stepwise and methodical approach to its diagnosis.

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P435

One-hour glucose level of the oral glucose tolerance test: the new valuable indicator of insulin resistance in patients with adrenal incidentalomas

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One-hour (1 h) glucose level of the oral glucose tolerance test (OGTT) was proven to be a better predictor of insulin resistance (IR) in nondiabetic population than the two-hour (2 h) postload glucose level. Specifically, the 8.6 mmol/l cut-off was shown to be an early marker of impaired glucose tolerance (IGT). Previous studies have shown that nondiabetic patients with adrenal incidentalomas (AI) have higher IR than healthy control (HC). However, despite the subtle cortisol secretion, there was no significant difference in the 2 h OGTT glucose level between patients with AI and autonomous cortisol secretion and nonfunctional AI (NAI). The aim of this study was to examine the value of 1h OGTT glucose level as an indicator of IR in AI patients. 105 nondiabetic subjects were drawn from a series of patients with AI. The AI subjects - 33 NAI and 72 with (possible) autonomous cortisol secretion (P)ACS) were age-, sex- and body mass index (BMI)-matched with 34 HC. We have evaluated OGTT, homeostasis model assessment (HOMA-IR) and index of whole-body insulin sensitivity (ISI-composite). AI patients had significantly higher 1h glucose level than HC (8.2 ± 2.5 vs 7.1 ± 2.2 mmol/l, $P=0.021$) and patients with (P)ACS had significantly higher 1 h glucose level than NAI (8.5 ± 2.6 vs 7.3 ± 1.98 mmol/l, $P=0.002$). There was no difference in 2h glucose level between AI and HC nor between NAI and (PACS). Also, there was no difference in number of patients with IGT between patients with NAI (26/7) and (P)ACS (50/22). In patients with (P)ACS there was a significant, positive correlation between the 1 h glucose level and cortisol after 1mg dexamethasone suppression test (1 mg DST) ($r=.278$, $P=0.018$) whereas there was no correlation between the 2 h glucose level and 1mg DST cortisol. Furthermore, we have divided patients with NAI and (P)ACS in: A– 1 h glucose >8.6 mmol/l and B – 1 h glucose <8.6 mmol/l. In both NAI and (P)ACS, A group had significantly lower ISI-composite than B (NAI: $P=0.03$, (P)ACS: $P=0.03$), and significantly higher HOMA-IR (NAI: $P=0.05$, (P)ACS: $P=0.038$). In patients with AI, 1h OGTT glucose level is a valuable indicator of IR. Moreover, in patients with (P)ACS, 1h OGTT glucose level seems to be a better indicator of the subtle cortisol secretion than the 2h OGTT glucose level.

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P436

Measuring steroids hormones by liquid chromatography–tandem mass spectrometry in 21-hydroxylase deficiency (21OHD) reveal large interindividual differences in hormone levels amongst patient with the same genetic mutation

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Background
We have previously shown that LC-MS/MS analyses of steroid hormones are superior to immunoassays monitoring 21OHD, due to better specificity and the possibility to multiplexing several steroid hormones in the same assay. This may lead to better understanding of the individual steroid hormone profile in patients with CAH. Here we present four patients cases with the same genotype in the *CYP21A2* gene, and evaluate their steroid profile by LC-MS/MS analyses.
Method
Four female patients from a cohort of 104 Norwegian patients diagnosed with CAH between 1972 and 1999 were selected. Mutations in the *CYP21A2* gene were identified by direct DNA sequencing and deletions were determined by real time PCR. *CYP21A*2 mutations were divided into two groups according to their enzyme activity; group Null (no enzyme activity), two patients, group B (2–10% enzyme activity), two patients. Serum concentrations of testosterone, androstenedione, 17 - hydroxyprogesterone, 21-deoxycortisol, 11-deoxycortisol, deoxycorticosterone (DOC), corticosterone, cortisone and cortisol were determined by an in-house LC-MS/MS method developed at the Hormone Laboratory in Oslo.
Results
The results are presented in table 1 and shows large interindividual differences in steroid profiles amongst patients with the same genotype/phenotype.

Table 1 Patient cases and LC-MS/MS hormone profile [nmol/l]; (H) above reference, (L) below reference

Mutation group and geno-type*	Pheno-type	Age	17-OHP	21DF	11DF	DOC
			<2.4	<0.7	<3.2	<0.41
Null	SW	31	3.4 (H)	9 (H)	0	0.18
Null	SW	36	811 (H)	268 (H)	0.19	0.51(H)
B	SV	63	0.6	9 (H)	0	0.08
B	SV	50	196 (H)	50 (H)	1.8	0.21

Table 1 Continued

B	F	E	T	A	Medication
1.3–36	120–600	13–92	<1.9	1.4–5.2	Ref.
0 (L)	0 (L)	0.4 (L)	0.41	1.8	Dexamethasone 0.5 mg evening + fludrocortisone 0.1 mg morning
21	16 (L)	3.5 (L)	3.7 (H)	29 (H)	Prednisolone 5 mg + fludrocortisone 0.05 mg morning
0.1 (L)	0 (L)	0.2 (L)	0.51	0.36	Dexamethasone 0.5 mg evening
2.6	162	49	3.8 (H)	27 (H)	no

*First row: reference values. Genotype Null = no enzyme activity, B= severe enzyme failure, SW= salt wasting, SV= simple virilizing,, F (female), 17OHP (17- hydroxyprogesterone), 21DF (21-deoxycortisol), 11DF (11-deoxycortisol), DOC (Deoxycorticosterone), B (corticosterone), F (cortisol), E (cortisone), T (testosterone), A (androstenedione)

Conclusion
Using LC-MS/MS steroid homone multiplexing in patients with 21OHD reveal large interadindividual steroid profiles within the same genotype. On may speculate that these differences may have clinical implications and may lead to better individualize treatment.

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P437

Hypoadrenalism in Advanced HIV

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Background
Large populations of HIV and tuberculosis occur in South Africa and, amongst these patients, Addison's disease is probably underdiagnosed. Preliminary data in 60 HIV-positive patients with a CD4 count less than 100 cells/mm^3 showed that the overall prevalence of hypoadrenalism was 6.7%, with 1 patient having primary hypoadrenalism and 3 patients having central hypoadrenalism. This report describes the prevalence of hypoadrenalism and its associations in a larger cohort.
Methods
Consecutive HIV-positive patients with a CD4 count less than 100 cells/mm^3 and concurrent opportunistic infection, who were admitted to a medical ward, were assessed with simultaneous early morning plasma cortisol and ACTH, analysed by immunoassay (Roche Cobas 6000 platform). Where the basal cortisol was less than 500 nmol/l, a 250 µg *Synacthen* test was performed. Patients were excluded if they had received steroids in the three months prior to enrolment. Anti-tuberculous and antifungal therapy were not considered exclusion criteria for enrolment.
Results
A total of 222 patients (112 males and 110 females) were evaluated. The median age and interquartile range at presentation was 36.0 (31.0–41.0) years. The median duration of feeling unwell prior to admission was 14.0 (14.0–30.0) days. A *Synacthen* test was performed in ($n=87$, 39%) of the cohort with ($n=14$: 6%), demonstrating a 30-minute peak cortisol of less than 500 nmol/l or ($n=8$; 4%) if a cut-point of 430 nmol/l was used. 4 additional patients were diagnosed by basal cortisol alone; median cortisol 308.0 (267.5–330.8) nmol/l and elevated ACTH. The proportion with central hypoadrenalism was ($n=12$; 4%), compared with primary hypoadrenalism ($n=6$; 2.7%) and the risk factors for developing these two states included pulmonary tuberculosis (OR 2.20; 95% CI 0.49; 20.39) and weight loss (OR 3.96; 95% CI 0.97;13.76). The number of patients with relative adrenal insufficiency i.e. a cortisol increment, less than 200 nmol/l ($n=38$) was 17.1%. The median maximal stimulated cortisol response following a *Synacthen* test was 678.0 (548.0–790.0) nmol/l.
Conclusions
As the proportions of hypoadrenalism are 8.1% and relative adrenal insufficiency (17.1%), the clinical significance needs to be determined.

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A case of late recognition of the malignant cause of chronic pancreatitis

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Pancreatic neuroendocrine tumors constitute a disease with steadily increasing prevalence worldwide in part owing to the increased detection of early stage disease. Here we present the case of a 49 year old male patient, who was admitted with clinical, laboratory and CT features of acute pancreatitis. A clear cause for the pancreatitis could not be detected. Excessive alcohol intake was reliably denied, and the patient did not take any drugs. Gallbladder and bile ducts were intact without stones, serum calcium and triglycerides were normal, there was no positive family history, and hepatobiliary infection was excluded. Pancreatitis due to microlithiasis was suspected. Two weeks after the initial admission the patient was discharged with recommendation for cholecystectomy and imaging in 3 months due to three small intrahepatic lesions. In the new CT scan, the lesions had marginally increased in size. Remarkable in the laboratory exams was a mild, persistent hyperlipasemia. Tumor markers (AFP, CA 19-9) were slightly elevated. We performed an MRT-guided biopsy of one hepatic lesion. The histopathological result was negative. Due to the missing cause of pancreatitis, we proceeded to a second biopsy of the lesions, which this time histopathologically confirmed the infiltration by a neuroendocrine carcinoma with high proliferation rate. A systematic chemotherapy with cisplatin and etoposid was initiated. This case underlines that pancreatic neuroendocrine carcinoma, particularly in its early stage, may mimic, despite high malignancy, a pancreatitis with non-specific symptoms, causing delay in the initiation of therapy. Serum tumor markers can be helpful, especially if a clear cause or typical clinical, laboratory or imaging features are missing. The individualized decision for pathological validation with high sensitivity and specificity corroborates the final diagnosis, weighing the potential complications of the procedure against the diagnostic benefits.

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Imaging studies of a parathyroid carcinoma case

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Parathyroid carcinoma is a rare neuroendocrine tumor, responsible for less than 1% of all cases of primary hyperparathyroidism. The sole curative treatment is complete surgical removal and thus, an accurate preoperative diagnosis is necessary. Due to the rarity of this disease, there is no staging guidelines. Imaging of parathyroid glands is usually obtained with ultrasonography, computed tomography, scintigraphy and positron emission tomography. These imaging modalities have been used and described for parathyroid adenomas. However, there is only limited data on their use in parathyroid carcinoma. On a 51-year-old-woman presenting with severe hypercalcaemia suspicious of parathyroid carcinoma, we performed different imaging studies and we compared the results with histology. 99mTc-sestamibi scintigraphy showed a lesion in the left inferior parathyroid gland and a pathological left thyroid nodule. 11C-methionine PET/CT and 18F-choline PET/CT detected additional lesion in the right inferior parathyroid gland and one left submaxillary lymphnode. The lesions showed a higher uptake of 18F-choline than of 11C-methionine. 18FDG Pet/CT missed both lesions in the inferior parathyroid glands and showed a slight hypermetabolism in the left submaxillary lymphnode. After surgery, histology confirmed the presence of a multifocal parathyroid carcinoma, as shown by 11C-methionine PET/CT and 18F-choline PET/CT. In this case, 18FDG Pet/CT was not useful. In conclusion, 11C-methionine PET/CT and 18F-choline PET/CT should be considered for parathyroid carcinoma staging.

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Neuroendocrine neoplasms (NEN) arising in uncommon sites: epidemiological and clinical features

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Background and aim
Neuroendocrine neoplasms (NEN) show increasing incidence and varying biology, but epidemiological and clinical data for other than gastroenteropancreatic (GEP) and thoracic NEN are scattered. Furthermore the best therapeutic approach in NEN arising in uncommon sites is still debated. Aim of this study is to assess the epidemiological and clinical features of NEN arising in uncommon sites in a monocentric series of a referral center.
Materials and methods
Epidemiological and clinical data of 182 patients with histologically confirmed NEN, referred at the Federico II NET Center of Naples, from 2002 to 2018, with newly diagnosed, sporadic and histologically confirmed NEN were retrospectively reviewed. NEN arising in uncommon sites were selected, while GEP and thoracic NEN, as well as pheocromocitoma, paraganglioma and medullary thyroid cancer were excluded.
Results
NEN arising in uncommon sites were diagnosed in 11 patients (6%), 6 males, 5 females, mean age 66 years (range 48–86). Median age at diagnosis was 64 years (range 48–85). Uncommon primary sites were: skin 4 (37%), rhinopharynx 2 (18%), bladder 1 (9%), breast 1 (9%), prostate 1 (9%), ovary 1 (9%), vagina 1 (9%). Clinical presentation is not specific and diagnosis was confirmed by anatomopathological examination. Mean Ki67 index, available in 8 patients, was 64% (range 5–80). Primary tumor was surgically resected in all patients, locally advanced in 5 (45%) and distant metastases occurred in 3 patients (27%), with primary located in bladder, rhinopharynx and prostate. Five (45%) patients underwent radiotherapy, 3 (27%) received therapy with somatostatin analogs (SSA), 1 (9%) platinum-based chemotherapy, 1 (9%) both SSA and platinum chemotherapy, 1 (9%) temozolomide. Median progression free survival (PFS) was 34 months $\pm$13.2 (CI 95% 8–60). Median overall survival (OS) was 36 months (CI 95% 5–66). Seven (64%) patients were died at the time of the last follow-up, 5 of them due to disease related causes.
Conclusions
NEN arising in uncommon sites occur in older ages and often show an aggressive biological behavior, with high ki67 index. Surgery is the most common therapeutic approach, followed by radiotherapy. Low PFS and OS highlight the need of adequate therapeutic approach and identification of risk and prognostic factors.

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P441

Microwave ablation of the adrenal gland for treatment of functioning adrenocortical tumours: porcine *in vivo* study

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Objective
To evaluate MTA as a precision ablation methodology for adrenocortical tissue, simultaneously evaluating effects on adjacent non-targeted tissue.
Methodology
A directional MTA applicator was used *in vivo* on adrenals of 8 male pigs: (i) sham ($n=2$); (ii) 45 watts for 60 seconds ($n=3$); (iii) 70 watts for 60 seconds ($n=3$). Blood was drawn intraprocedurally and at 48h for measurement of metanephrines, cortisol, ACTH and aldosterone (LCMS). Animal sacrifice/tissue harvest occurred at 48 h. Ablation-zone volume was assessed by basic histology (H&E). Tissue function was assessed by expression of CYP17 and CYP11B1 (IHC). Tissue damage was assessed by expression of damage associated molecular patterns (DAMPs) HSP70 and HMGB1 (IHC).
Results
A specific ablation zone ($0.67 \pm 0.37\ cm^3$) was achieved, morphologicaly demonstrating coagulative necrosis, absence of DAMPS, and absence of steroidogenic enzyme expression. Non-targeted adrenocortical tissue was preserved functionally and structurally as confirmed by the expression of DAMPs and steroidogenic enzymes within the cells, and delineated by an immune cell infiltrate. Medullary damage occured in all ablated adrenals, consistent with cellular necrosis in the tissue, raised intra-procedural metanephrines, and transient intra-procedural hypertension.
Conclusion
For the first time, MTA is shown as a safe, effective method to precisely ablate adrenal cortex of volumes equivalent to FAT, while preserving adjacent non-targeted cortex. Intraprocedural alpha blockade is necessary to pre-treat possible intra-procedural medullary catecholamine surge. This presents exciting short-term translational potential for the therapy of FAT
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Simplified model for diagnosis of secondary adrenal insufficiency using non-fasting cortisol and clinical parameters

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Objective
Although rapid adrenocorticotrophic hormone (ACTH) stimulation test is a standard test for primary and secondary adrenal insufficiency (AI), it is considered a costly and time-consuming method due to sampling three times in an hour. We aimed to develop a simpler diagnostic model of secondary AI using non-fasting basal cortisol and clinical parameters related to AI such as history of exogenous steroid use or hyponatremia.

Methods
Total 430 patients who had 250 ug ACTH stimulation testing as part of their diagnostic work-up were retrospectively analyzed. A peak cortisol levels <18 μ/dl after ACTH stimulation indicate abnormal adrenal function.
Results
Among participants who undergo ACTH stimulation test, 144 patients (33.4%) showed inadequate increase of cortisol and were diagnosed as AI. The receiver operating characteristic curve analysis showed an overall area under the curve (AUC) for basal cortisol of 0.853 and for 30 minute cortisol of 0.953. When we combined basal cortisol with clinical parameters related to AI, the AUC increased from 0.853 to 0.922, which was comparable to that of 30 minute cortisol ($P=0.0782$). In our study, participants with basal cortisol levels ≥ 14.8 μ/dl had normal adrenal function, whereas <3.6 μ/dl had abnormal adrenal function. Among several simplified diagnostic models, basal cortisol level <3.6 μ/dl and history of exogenous steroid use had the highest accuracy (85.5%, $P<0.001$) for predicting secondary AI.
Conclusion
Basal cortisol level <3.6 μ/dl with history of exogenous steroid use had high diagnostic accuracy, diminishing the need for formal ACTH testing. We suggest that this result can be helpful for clinicians for diagnosing secondary AI in terms of time and cost effectiveness.

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P443

Type 1 gastric neuroendocrine tumor study in Hospital Clínico San Carlos (HCSC), Madrid

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Introduction
Type 1 Gastric neuroendocrine tumors account for 70 to 80 percent of all gastric neuroendocrine tumors (G-NETs) and they are found more commonly in older adults, particularly women. They are associated with autoimmune metaplastic atrophic gastritis (AMAG) with or without pernicious anemia. They are usually smaller than 1 cm and often multiple. Our goal is to describe different characteristics of type 1 G-NETs and to study possible prognostic factors related to the progression-free survival (PFS).
Material and methods
Descriptive, observational, retrospective and inferential study of 31 patients diagnosed with Type 1 G-NET and neuroendocrine cell micronodular hyperplasia, diagnosed and followed in the Endocrinology department of HCSC during the last 15 years. We define Progression-Free Survival (PFS) as the proportion of patients who remain without progression of the disease after a defined period of time. SPSS 23.0 was used for statistical analysis.
Results
The mean age at diagnosis was 57.97 (SD 13.19). 61% of the patients were female. 31.3% presented micronodular hyperplasia. 60.4% were grade 1 type 1 G-NET. 75.6% presented a single lesion. Median size was 0.4 cm (IQR 0.3–0.6). 41.9% of the lesions were located in the body of the stomach and 32.3% additionally in the fundus. Ki67 was $\leq 2\%$ in 95.3% of the cases. Only 10.4% were treated with somatostatin analogues. Median serum chromogranin A was 7.35 nmol/l (IQR 4.56–10.0). As for survival analysis, 32.3% presented tumor progression or relapse. Median PFS was 5 years (CI 95% 1.805–8.195). Relapse was found to happen earlier in males (81% within the first year) than in females (41%) (Log Rank 1.485, Breslow 2.944). Median PFS was 5.00 years (CI 95% 1.611–8.389) in patients younger than 60, compared to 3.00 years (CI 95% 0.614–5.386) in those older than 60.
Conclusions
Our sample describes the general characteristics of population with Type 1 G-NET in terms of sex, age, location, size and others. Our study seems to demonstrate that these tumors have a higher chance of relapse in the short and medium term. Regarding survival analysis, we observed males and patients older than 60 present a shorter PFS, which might reflect the need for periodic gastroscopic check-ups more frequently in those groups of patients. Further prospective studies with a larger number of cases are needed in order to identify prognostic factors in the relapse of G-NETs in these patients.

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P444

The Arg244His missense mutation in SDHB-1 leads to altered metabolism in Caenorhabditis elegans: a new disease model

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The succinate dehydrogenase (SDH) enzyme complex consisting of four subunits (SDHA, SDHB, SDHC and SDHD) has a dual function in the process of mitochondrial energy generation. It converts succinate to fumarate as part of the TCA cycle and also transfers electrons to ubiquinone as part of the electron transport chain. Mutation in any subunit of the enzyme complex increases the risk for the development of neuroendocrine tumors including paraganglioma (PGL) and pheochromocytoma (PHEO). As the SDH enzyme complex is closely linked to the supply of precursors and the regulation of metabolic processes, the study of the molecular background of SDH deficiency in relation to carcinogenesis, cancer survival and metastasis, must be supplemented by characterizing metabolism, which could open new ways to develop more effective therapeutic methods. While human SDHA, SDHC and SDHD mutations mainly cause benign tumors, those in SDHB are strongly associated with malignant PHEO/PGL. The Arg230His missense mutation in the human SDHB gene causes a familial form of malignant PHEO, representing a serious therapeutical challenge. Therefore we aimed to develop an in vivo model for functional characterization of this mutation using a highly conserved *C. elegans* ortholog. The human Arg230His mutation corresponds to the Arg244His SDHB-1 mutation in the worm.
For our experiments, we used the *sdhb-1(gk165)* deletional derivative and two transgenic lines carrying the Arg244His mutation and genomic wild-type SDHB-1, which were crossed in *sdhb-1(gk165)* null mutant background. We found that the Arg244His mutation of the SDHB-1 enzyme significantly delays development, shortens lifespan and changes the metabolic profile of the animals. Characterization of the latter was performed as follows: TCA cycle metabolites were detected by LC-MS, whereas oxygen consumption was measured by Seahorse technique. Interestingly in both the deletional and Arg244His point mutants, succinate level was elevated, suggesting that neither mutant possesses SDH activity. These data are in line with our bioinformatic analysis which suggests that the Arg244His substitution exerts a significant effect on the structure of SDHB-1 and might result in an inactive complex. Interestingly, the metabolic profile of Arg244His mutants was also strongly altered compared to the null mutant, which raises the prospect of a rewired metabolism reminiscent of tumor cells undergoing metabolic reprogramming. Transcriptomic profiles of deletional and point mutants compared to wild-type worms further confirmed these biochemical alterations. Our new model mimics the SDH impairment and it may serve a novel tool in deciphering new insight of SDH-associated human diseases.

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P445

11C-Metomidate PET/CT Identifies Unilateral Primary Aldosteronism in a Multi-ethnic Cohort

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Introduction
Patients with unilateral primary aldosteronism (PA) can be cured with adrenalectomy, and adrenal vein sampling (AVS) remains the gold-standard test.

However, AVS is invasive, technically-challenging and criteria for determining lateralization differ between centres. 11C-Metomidate PET/CT (MTO) imaging offers a promising non-invasive alternative for identifying unilateral PA.
Methods
All patients with confirmed primary aldosteronism who were keen for a surgical cure underwent both AVS and MTO. AVS was done under continuous ACTH-stimulation and successful cannulation was demonstrated if adrenal vein cortisol was greater than peripheral vein cortisol by >5. All test results including CT, AVS and MTO were reviewed by a multi-disciplinary panel to determine unilateral PA. The accuracies of MTO and AVS to identify unilateral PA were compared to the final conclusion of the multi-disciplinary panel.
Results
12 patients, mean age 48.9±9.3 yr, 6 females (50.0%) were enrolled in the study, with 8 patients Chinese (66.7%), 3 Malay (25.0%), and 1 of other ethnicity (8.3%). 9 patients were deemed to have unilateral PA by the panel, with AVS identifying 8 (sensitivity 88.9%) and MTO identifying 7 (sensitivity 77.8%). All 12 patients had successful AVS (bilateral cannulation), with 8 patients having lateralization ratio >4, consistent with unilateral PA. MTO identified 7 patients with unilateral PA, and the mean SUV_{max} of the tumor was 37.1±8.7, while the mean SUV_{max} of the contralateral normal gland was 22.7±5.8. In these patients, the mean SUV_{max} ratio of tumor: contralateral adrenal was 1.69±0.39. Three patients had bilateral PA on both AVS and MTO, and the mean SUV_{max} of the adrenals was 21.8±5.5. Two patients had lateralization on AVS, but on MTO, the tumor SUV_{max} (26.3±18.3) was lower than the normal contralateral gland (38.4±30.6). One patient with lateralization on MTO (Lateralization SUV_{max} ratio of 1.48) did not lateralize with AVS.
Conclusion
11C-Metomidate PET/CT has potential to accurately identify patients with unilateral PA, and this may obviate the need for invasive adrenal vein sampling. While most patients have congruent findings on both AVS and MTO, these tests may identify different subtypes of unilateral PA. Further genotyping of these tumors will be important to understand further the underlying pathophysiology and the utility of these localization tests.

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P446

Prevalence of non-carcinoid syndrome (non-CS) diarrhoea in patients with neuroendocrine tumours (NETs): a systematic literature review (SLR)

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Background
Approximately 20% of NET patients develop CS, characterised by diarrhoea and flushing. However, CS is not the only cause of diarrhoea among NET patients. Non-CS causes should be considered to allow for appropriate management. We investigated the reported occurrence of diarrhoea from various non-CS causes in patients with gastroenteropancreatic NETs (GEP-NETs), to explore the need for differential diagnosis (DDx) of NET diarrhoea.
Methods
MEDLINE/Embase/Cochrane Library were searched in September 2018 with terms for NETs, CS and diarrhoea. Congress abstract books/bibliographies/ClinicalTrials.gov were hand-searched. Two independent reviewers screened articles at title/abstract and full text stage. Articles reporting evidence on potential causes of diarrhoea in GEP-NET patients were included.
Results
19 articles reported on non-CS causes of diarrhoea. 14 reported on pancreatic enzyme insufficiency (PEI) in NET patients, predominantly on/after treatment with somatostatin analogs (SSAs); 17.3%–84% of patients experienced steatorrhoea, and where reported, 14.3%–46.1% of NET patients received pancreatic enzyme replacement therapy. Faecal fat measurement confirmed PEI in 11.6% of patients on SSAs, and faecal elastase test was used to explore PEI in 3 further studies. Variation in reported proportions could result from heterogeneity in study design and patient population. Small intestinal bacterial overgrowth (SIBO) diagnosed by hydrogen and methane breath test was reported in 23.6%–62% of NET patients; bile acid malabsorption (BAM) in 80% by SeHCAT scan. Single cases of colitis (20%) and *Campylobacter coli* infection (7.1%) were reported in 2 studies of patients with CS diarrhoea. While conditions such as PEI were reported, most cases were not confirmed with clinical tests, or it was not clear if they were truly causing diarrhoea instead of, or in addition to, CS. Additional studies suggested other potential causes of diarrhoea without quantitative data, including short bowel syndrome, chemotherapy-associated diarrhoea, dumping syndrome, laxative abuse and lymphangiectasia.
Conclusions
Quantitative evidence on prevalence of diarrhoea of different aetiologies in NET patients is lacking. PEI was most commonly reported, suggesting that it is important to consider in DDx of NET diarrhoea. Limited data on BAM, SIBO and infection, and lack of data on other potential causes of diarrhoea, could result from little awareness among clinicians or lack of investigation into these causes; management of diarrhoea in NET patients should involve experienced clinicians e.g. gastroenterologists and surgeons. Further research is required to determine the prevalence of each cause, to inform and highlight the importance of DDx of diarrhoea in NET patients.

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P447

Down-regulation of the Ataxia Telangiectasia Mutated Gene (ATM) is associated with increased metastatic potential and decreased overal survival in patients diagnosed with gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

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Introduction
Neuroendocrine tumors (NETs) are rare tumours that develop in cells of the neuroendocrine system. They comprise a heterogeneous group of neoplasms that range from the benign and multi-focal to the highly malignant and metastatic. Here we conduct itegrated genome and immunohistochemistry analysis (IHC) of the Ataxia Telangiectasia Mutated Gene (ATM) as well as analysis of overal survival in patients diagnosed with NETs.
Material and Methods
The study accrued 65 patients with NETs over a period of 2 years, from 2015 to 2017. During the study period, 36 patients were diagnosed with early and advanced neuroendocrine tumors of the lung (L-NET) and 29 neuroendocrine tumors of the gastroenteropancreatic system (GEP-NET). Tumor-DNA were isolated from fresh-frozen tumor tissue. The IHC-Analysis as well as Real-Time-PCR was performed for ATM-Gene. Survival analysis of the subjects was performed using Kaplan-Meier and Cox regression methods.
Results
We have not found any realations between genomic profile of the ATM-gene and overal survival (OS) in patients diagnosed with L-NET. The down-regulation of the ATM-gene was strongly positively correlated with metastatic GEP-NETs ($P<0.001$) compared to non-metastatic GEP-NETs ($P<0.08$). All patients diagnosed with GEP-NETs and with ATM-negativity by IHC, showed decreased OS compared to those with ATM-positivity.
Conclusion
Our study identified that ATM-gene down-regulation was strongly associated with metastatic potential of GEP-NETs. In view of the role played by ATM-gene-expression on the behavior of GEP-NETs and progression of the disease, the ATM-gene negativity could be considered as a possible prognostic stratification tool.

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P448

GEP-NET tumors as the first geno-phenotypic association in MEN1 syndrome – the possibilities for a European MEN1 network

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Objective
Phenotypic variability and lack of genotype-phenotype correlations still represent a major challenge in the surveillance of patients carrying germline MEN1

(Multiple Endocrine Neoplasia type 1) mutations. MEN1 associated gastro-enteropancreatic neuroendocrine tumors (GEP-NETs) are highly penetrant and show an indolent course. However, they are still the leading cause of death in MEN1 syndrome. Some single-center and national studies reported higher prevalence of GEP-NETs among patients with mutations predicted to affect the function of menin protein significantly (nonsense and frameshift mutations). In the present study we aimed to collect findings from MEN1 databases to identify genotype-phenotype correlations and compare them to our results on the Hungarian MEN1 cohort.

Design and methods

Clinical and genetic data of the Hungarian MEN1 index patients referred to our national referral center between 2001 and 2017 were collected and reviewed retrospectively. Patients carrying a frameshift, nonsense, splice site mutation or large deletion were considered as high-impact mutation carriers while missense or inframe mutation carriers were classified as low-impact mutation carriers. We collected data from those national databases, where the information published was sufficient enough for the current metaanalysis. Our data were compared to the Italian ($N=362$) and German ($N=258$) MEN1 cohorts, in particular considering GEP-NETs. Correlations between genotypes and clinical manifestations were calculated with χ^2 and Fisher's exact test.

Results

The combined MEN1 database consisted of 620 patients. Patients carrying high-impact mutations predicted to affect the function of menin protein significantly, presented GEP-NETs significantly more frequently compared to those carrying low-impact mutations (260 vs. 76; $P=0.008$). Collecting patients carrying MEN1 mutations from the European national databases would result in a number of cases more than 2.700, and a number of GEP-NETs as high as 1.250. Unfortunately, the data quality available in these studies has not allowed us to draw further conclusions.

Conclusion

This study further confirmed findings of previous studies, revealing that GEP-NET associates with high impact MEN1 mutations, thus it may have prognostic consequences. Creating a European database of MEN1 patients could be a useful tool to find further genotype-phenotype associations and to help practitioners in everyday clinical practice.

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Prevalence of neuroendocrine tumors in a subgroup of young patients: single center experience

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Neuroendocrine tumors encompass a heterogeneous group of tumors arising from the diffuse neuroendocrine system. The incidence of NETs rises with age, with the peak after 65 years. However, all NETs observed in adults may be diagnosed in children too. There are a very few studies addressing NETs in young patients. This study summarizes clinical, histopatological and genetic characteristics of young patients with NETs. This is a retrospective study describing clinical, histopathological and genetic characteristics in patients below 31 years of age, with NETs of various localizations, treated in one center from 2004–2018. Among 914 consecutive patients with NETs of different primary sites, 65(7.1%) patients 30 years of age or younger (age range 9 – 30, mean 23.5 years) were diagnosed (female 58.5%, male 41.5%). The number of diagnosed patients increased with age (age groups 0–10 years: 1, 11–20: 16, 21–30: 48 patients). The majority of them had pancreatic (pNETs, 30.8%), followed by appendiceal (24.6%) and bronchial NETs (brNETs, 23.1%). There was no difference in frequency of pNETs and brNETs in comparison to older patients ($P>$ 0.05). Conversely, appendiceal NETs were significantly more frequent in young (24.6% vs. 2.6%, $P<0.01$) and were associated with appendicitis (14, 93.3%). The most frequent pNETs were NET-G2 (50%), followed by NET-G1 (23.3%) and NET-G3 tumors (20%). There was no difference in Ki-67 index between young and older patients with pNETs ($P>0.05$). However, metastatic disease at the time of diagnosis was more frequent in older patients (65.6% vs. 35.3%, $P<0.01$). The most frequent brNET was atypical carcinoid (46.7%), followed by typical carcinoid (40%) and small cell NEC (SCNEC, 13.3%). Ki-67 was significantly lower in younger patients (9.8% vs. 29.1%, $P<0.01$), although metastatic disease was equally present in both younger and older patients ($P>0.05$). Among all, metastatic disease was noted in 56.9% patients. Genetic cause was found in 12.3% patients having either pancreatic or brNETs. *MEN1* gene mutations were found in 6 patients, one patient with pNET had VHL syndrome, one NF1. Except two patients with brNETs, all patients had associated tumors and positive family history. All *MEN1* negative patients with multiple ($n=2$) or associated tumors ($n=2$) were screened for *CDKN1b* mutations, and were negative. The prevalence of different type of NETs in young patients is comparable with older patients, except for the appendiceal NETs. Metastatic disease is equally present as in older patients. Despite early tumorigenesis, genetic cause is known in a small portion of patients.

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P450

Prognostic role of angiogenesis-associated factors Tie2 and Angiopoietin 2 in patients with neuroendocrine neoplasms: The NETTARE Unit experience

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Introduction

The role of Angiopoietin (Ang)/Tie2 kinase pathway in neuroendocrine neoplasms (NENs) has recently received increasing attention, but its clinical role remains unclear. Tie2-receptor inactivation favours chronic inflammation. The balance between its agonist and antagonist regulates its signalling. Aim of this study was to measure serum soluble Tie2 (sTie2) and Ang-2 in patients followed at the NETTARE Unit (NeuroEndocrine TAsk foRcE of 'Sapienza' University).

Methods

A prospective observational study was carried out from June 2017 to December 2018 recruiting 43 consecutive patients with proven NENs (25 well-differentiated and 18 poorly-differentiated NENs) and 32 non-neoplastic controls (Ctrl) recruited among patients with thyroid disorders, matched for age, sex, BMI, smoking and comorbidities (diabetes mellitus, cardiovascular and inflammatory disorders). Serum levels of sTie2 and Ang-2 were determined by ELISA. Groups were compared using Mann-Whitney test.

Results

The mean age of the 43 NENs patients was 66.14 ± 13.4 years (58.1% males) and tumour sites were: gastroenteropancreatic (GEP) NENs (53.5%), lung (39.5%), others (6.9%). Among GEP-NENs, most patients had a well-differentiated NENs (56.5% G1, 26.1% G2, 17.4% G3) and among lung NENs the majority were small and large cells carcinomas (72.2%). Locally advanced or metastatic disease (TNM stage III or IV) represented 66.6% of the sample. A positive correlation was found between Ang-2 and sTie2 levels in NENs patients ($P=0.033$), adjusted for age and sex. sTie2 (ng/ml) and Ang-2 (ng/ml) levels were significantly higher in NENs than controls (sTie2: NENs 53.67 ± 34.72; Ctrl: 33.04 ± 17.24, $P=0.021$; Ang-2: NENs 3.41 ± 2.12; Ctrl: 1.45 ± 1.39, $P<0.001$). Regarding grading, both sTie2 and Ang-2 were found higher in poorly differentiated NENs *vs* control ($P=0.011$ and $P<0.001$, respectively), while Ang-2 levels were also found higher in well-differentiated NENs *vs* control ($P=0.007$) and in poorly-differentiated *vs* well-differentiated NENs ($P=0.009$). Patients with locally advanced and metastatic disease exhibited higher Ang-2 levels than those with localized disease (stage III-IV 3.99 ± 2.13; stage I-II 2.29 ± 1.75, $P=0.019$). Compared to controls, Ang-2 levels were found higher in GEP-NENs ($P=0.003$), while both Ang-2 and sTie2 levels were found higher in lung NENs ($P<0.001$ and $P=0.017$, respectively).

Conclusions

The present study documents, prospectively, an association between NEN aggressiveness (staging and grading) and Ang/Tie2 inactivation. In both GEP and lung NENs, sTie2 and Ang-2 levels could play a role as novel additional markers for the diagnosis and prognosis of NENs.

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P451

Attributes valued by patients, health-care practitioners (HCPs) and caregivers using pre-filled delivery systems: a systematic literature review

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Background
The development of a new syringe for lanreotide Autogel, in conjunction with patients, caregivers and HCPs, identified and integrated several upgrades to the previous design that could improve patient care.
Aims
To better understand which attributes are pertinent to users, and how user preferences can be optimally assessed, we conducted a systematic literature review of relevant studies of pre-filled devices.
Methods
PubMed was searched in November 2018 for terms (human attributes) AND (injectable OR syringe), and widened with a hand-search through references of review articles to detect more reported attributes that are of importance to users. Eligible publications reported users' preferences and/or degree of importance of certain attributes of pre-filled devices. Articles should only include one of the following chronic diseases: acromegaly, neuroendocrine tumour (NET), multiple sclerosis (MS), and rheumatoid arthritis (RA). Studies in paediatric population were excluded. Attributes that were considered important to users when selecting an injectable device, were extracted from the publications.
Results
Of 185 publications found in PubMed seven were selected along with seven others from the hand-search: one each in HCPs (77 nurses), patients with acromegaly ($n=25$), patients with acromegaly and their partners (41 patients, 18 partners); five in patients with MS ($n=35$–422); four in caregivers, HCPs and patients with RA (23–640 patients, 10–33 caregivers, 10–90 HCPs); and two review articles discussing lanreotide in NET and acromegaly. Main user-selected attributes included: pre-filled systems, ease and comfort of use, control over the device, needle size and invisibility (shielded prior to injection and retracted into the device post injection), plunger design and sturdiness, confidence that full dose has been delivered, and potential for self-injection.
Conclusion
Few publications discussed patient, HCP or caregiver preference using pre-filled delivery systems. Further studies evaluating the preference when using chronic treatments such as somatostatin analogues, may identify additional attributes relevant for future developments.

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P452

Identification of a molecular signature of hypercortisolism by whole blood methylome analysis

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The prolonged exposure to an excess of circulating cortisol (Cushing's syndrome) causes various complications. An accurate and early diagnosis is critical for effective surgical management and optimal prognosis. However, the current diagnostic approach based on hormonal assays can be complex and requires multiple tests. The identification of novel, specific and easily measurable biomarkers of hypercortisolism may help to improve the diagnosis and to evaluate the complications. As already shown in several diseases/disorders, stress-associated epigenetic markers can be measured at whole blood level by analyzing the leukocyte DNA methylation profile.
Objective
To analyze the whole blood methylome in patients with Cushing's syndrome before and after hypercortisolism cure to identify specific features related to DNA methylation.
Methods
Methylome analysis was performed on leucocyte DNA from paired blood samples of 32 patients with confirmed hypercortisolism. Samples were obtained before ('pre') and several months after ('post') the cure. Methylome data were generated by the Infinium®MethylationEPICBeadChip assay (Illumina) and pre-processed by the *minfi* package (version 1.24.0) developed for the R software (version 3.4.4), in order to obtain the methylation data for the entire set of CpGs ($n=\sim850000$). To eliminate aberrant values, the *minfi* 'cpgCollapse' function was used to group physically adjacent CpG loci into clusters ($n=\sim400000$), estimating a single methylation value per cluster. Data analysis was performed on R by both unsupervised and supervised approaches.
Results
Unsupervised clustering of samples, based on the most variable features, showed a distribution of the 32 samples in pairs, each corresponding to an individual. Twenty-four out of the 32 patients showed a signature of hypercortisolism, corresponding to a group of features differentially methylated in the pre-compared to the post-cure samples. A supervised comparison performed on a training sub-cohort ($n=12$ patients, 24 samples) identified the most discriminating features of hypercortisolism, further used to classify each sample: 10/11 classified as 'pre' were indeed pre-cure samples, 9/9 classified as 'post' were indeed post-cure samples, 4/24 samples were classified as undetermined. These same features tested on a validation sub-cohort ($n=20$ patients, 40 samples) allowed to properly classify 13/13 pre-cure samples and 13/13 post-cure samples, with 14/40 samples classified as undetermined.
Conclusions
Whole blood methylome analysis allows to detect a specific epigenetic signature of hypercortisolism, with a high rate of discrimination in patients with Cushing's syndrome. This approach promises to be powerful to explore the genomic regions involved and to identify specific biomarkers of hypercortisolism-related complications.

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P453

Risk factors for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs): a case-control study from NETTARE Unit

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Introduction
GEP-NENs represent a heterogeneous group of neoplasms with increasing incidence in the last years. Pathogenesis and risk factors of sporadic GEP-NENs are not clear and still debated. The aim of this study is to evaluate the main risk factors for sporadic GEP-NENs in patients followed by the NETTARE Unit (NeuroEndocrine TAsk force of of 'Sapienza' University of Rome).
Methods
We performed a case-control study including 32 consecutive sporadic GEP-NENs and 109 age- and sex-matched controls, affected by benign thyroid or adrenal non-functioning nodules. We collected data on demographic aspects, clinical features and potential risk factors (family history of cancer, smoking, alcohol, body mass index, age of menopause, use and duration of contraceptive, hormonal replacement therapy, personal history of cancer, diabetes mellitus, inflammatory bowel disease, celiac disease, autoimmune atrophic gastritis and pancreatitis). The two groups were compared using χ^2 test for comparison of proportions for categorical variables, Student's *t*-test for normally distributed continuous variables and Mann-Witney test for non-normally distributed continuous variables.
Results
Among the 32 GEP-NENs patients mean age was 58.5 ± 11.8 years, with F:M ratio of 1.3 (18 females and 14 males). The most frequent tumor site was pancreas (65.6%), followed by ileum (28.1%). Most patients had a well-differentiated NEN, 78.1% G1 neuroendocrine tumors (NET), 15.6% G2 (NET), while 6.2% had a neuroendocrine carcinoma (NEC). Only the 28.1% had locally advanced or metastatic disease at diagnosis (TNM stage III or IV). A family history of cancer was more frequent in GEP-NENs group than in the control one (90.6% *vs* 55.0%; $P<0.001$). Particularly, the percentage of GEP-NENs patients with a family history of non-endocrine GEP cancer was significantly higher than controls (34.4% *vs* 13.8%, $P=0.008$). Lung (21.9%), colon-rectum (21.9%) and breast (12.5%) were the most common non-endocrine cancer sites in the family history

of GEP-NENs patients. No other risk factors were found significantly different between the two groups.
Conclusions
This case-control study suggests that a family history of cancer, particularly of non-endocrine GEP tumor, is associated with GEP-NENs in the offspring. If confirmed in larger cohorts, this finding could have a significant impact on the early screening and prevention strategies for GEP-NEN.

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P454

Selective arterial calcium stimulation test in two cases with occult insulinoma

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Introduction
80–90% of insulinomas are smaller than 2 cm, equally located in the head, body and tail of pancreas. Computer tomography (CT) is 75%, magnetic resonance imaging (MRI) is 55–90%, endoscopic ultrasonography (EUS) is 85–95% and selective arterial calcium stimulation test (SACST) is 95–100% sensitive in the diagnosis of insulinomas. Here, we presented two cases of insulinoma which could not be located by conventional methods and evaluated with SACST.
Case 1
A 29-year-old male who described hypoglycemic symptoms especially after exercise in the last 4 months was admitted to the hospital for a prolonged fasting test. At the 8th hour of the test, laboratory results were as follows; blood glucose 36mg/dl, insülin 21 uIU/dl, c-peptide 4 ng/dl, proinsulin 22 pmol/l and cortisol 18 ug/dl. Blood ketone and anti-insulin antibody were negative. No pathology was observed in the abdominal CT and EUS. Abdominal MRI revealed a 10 mm diameter nodular lesion in the posterior medial of the stomach which was suspicious for insulinoma. It was seen only in T2A sequence in the venous phase in contrast-enhanced examination. Galium-68 Dotatate scintigraphy showed no involvement in the pancreas. SACST was performed. A ten-fold increase in insulin levels was observed in the splenic artery and distal pancreatectomy was performed.
Case 2
A 41-year-old woman who had episodes of hypoglycemia for 3–4 months was referred with a pre-diagnosis of insulinoma. The patient underwent a prolonged fasting test. At the time of hypoglycemia (blood glucose 45 mg/dl), serum insülin was 7.8 uIU/dl, c-peptide was 2.2 ng/dl, proinsulin was 8 pmol/l and, serum ketone and anti-insulin antibody were negative. There was no contrast enhancement in the pancreas in the abdominal MRI, but a suspicious hyperintense area of 10 mm diameter was seen in T2A sequence. There was no pathology in abdominal CT and EUS. In SACST, a five-fold increase in insulin levels was detected in the mesenteric artery which was suggestive for an insulinoma lesion in the head of pancreas. Surgical excision was recommended but the patient refused.
Conclusion
Although the biochemical diagnosis of insulinomas are usually not complicated, the localization might be problematic. Because of the low sensitivity of non-invasive methods in tumors smaller than 2 cm, invasive methods can be used for the localization like in our cases.

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P455

Can pancreatic tumor in von Hippel-Lindau syndrome be a prognostic factor?– a case study

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Introduction
Von Hippel-Lindau (VHL) disease is an autosomal dominant disorder characterized by formation of tumors and cysts in various organs. Renal cancer and central nervous system angiomas (whose frequencies in VHL disease are estimated for 70% and 76% respectively) are considered main prognostic factors, with renal cancer being the most common cause of death. Neuroendocrine tumors of the pancreas occur in only 10 to 20% of VHL patients and are benign in the majority of cases. Surveillance in VHL does not comprise screening for pancreatic tumors.
Aim
The aim of the study was to present a patient with VHL disease. Despite the fact, that the patient was affected by renal cancer, retinal and central nervous system haemangioblastomas, it was pancreatic tumor that eventually led to her death.
Case study
E.W., aged 44, with VHL disease confirmed genetically (mutation: 525C> A,Y175X), was admitted to the Endocrinology Clinic in Lublin, Poland because of pancreatic tumor detected in computer tomography scanning. At that moment the patient presented already with haemangioblastomas of retina and was after treatment for renal cancer and brain neuroblastomas (clinically: blindness of right eye, amblyopia of the left eye, hemi-paresis, balance disorders, slowed down and shunted speech, left nephrectomy due to clarocellulare kidney cancer). The computer tomography revealed a richly vascularized neoplasm mass with calcifications and fluid component in pancreas' head. Somatostatin receptor scintigraphy confirmed overexpression of receptors in that area suggesting its neuroendocrine character. No evident hormone activity of the tumor was stated. Neither tissue sample collection (despite the fact that the patient undergone esophageal ultrasonography) nor the surgery were performed because of high risk of perioperative hemorrhage. Thus, the pancreatic tumor was classified as unresectable. Control image studies revealed progression of the tumor (48×57 mm in the first CT scanning in 2011 vs 61×76 mm in the last CT scanning in 2018). The growing pancreatic tumor lead eventually to high occlusion of gastrointestinal tract. Again, at this moment, the patient was disqualified from surgery again. On account of malnutrition and cachexia, parental feeding was impleneted. However, the patient died.
Conclusion
Neuroendocrine tumors of pancreas, though usually of low mitogen activity, and not very common in VHL disease, should be regarded as a prognostic factor in the disease. Thus, screening for them should be an obligatory element of surveillance in VHL.

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P456

An investigation into the role of parathyroid hormone in the regulation of aldosterone secretion in hypertensive cardiovascular patients

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Hypertension or elevated blood pressure (BP) is quantitatively the most important risk factor for development of cardiovascular diseases (CVDs), whereas aldosterone contributes significantly in the development and severity of hypertension. Interestingly, parathyroid hormone (PTH) stimulates aldosterone synthesis by regulating renin-angiotensin-aldosterone system (RAAS). Conversely, RAAS controls PTH secretion, as angiotensin receptor is expressed by human parathyroid tissues and upon activation directly stimulates PTH secretion. In the present study, an interplay between plasma concentrations of aldosterone and PTH was investigated. Hundred hypertensive CVD patients between the age of 21 and 60 years with and without diabetes were included in the investigation. Hundred age and gender matched healthy subjects served as controls. Plasma concentrations of aldosterone were measured using RIA system. Our results showed that 84 patients had low PTH levels, whereas 16 patients exhibited normal concentrations of PTH. Of the 84 patients with low PTH concentration, 48 had normal aldosterone, 29 had low aldosterone and 7 patients had high aldosterone concentrations whether treated with RAASi, non-RAASi, combination of both or remained untreated. All of the 16 patients having normal PTH concentrations also had normal aldosterone concentrations irrespective of any or no treatment. A positive correlation between aldosterone and PTH concentrations was observed in all groups. Similarly, there was a positive correlation between aldosterone concentrations and BP, and PTH and BP in all groups except for patients having

high aldosterone and low PTH concentrations. The majority of hypertensive CVD patients fell in the age group of 51–60 years, were males, married, smokers, diabetics, belonged to middle class socioeconomic status, had a disease duration of 1 to 10 years, had exercise free life style, normal BMI and a positive family history of CVD. In conclusion, the present study demonstrates lower concentrations of PTH and normal concentrations of aldosterone in majority of hypertensive cardiovascular patients.

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P457

Plasma levels and regulation by the hypothalamic–pituitary–adrenal axis of Androst-5-ene-3β,7α/β,17β-triols in human

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Dehydroepiandrosterone is the most abundant steroid hormone circulating in the human body, we focused on its 7-hydroxylated derivatives. Many observations in rodents have demonstrated the anti-inflammatory and immune modulating activity of 7β-hydroxy-androst-5-enes, and on the basis of these experiments androst-5-ene-3β,7β,17β-triol is considered as a potential agent in the treatment of autoimmune diseases. In contrast to the fairly abundant information on the levels and effects of androst-5-ene-triols in experimental animals and of their the pharmacological perspective, little is known about androst-5-ene-3β,7α/β,17β-triols circulating in human blood, their regulation by hypothalamo-pituitary-adrenal axis, or their daily concentration variability. All data measured by GC/MS from our laboratory of androst-5-ene-3β,7β,17β-triol (β-AET) and androst-5-ene-3β,7α,17β-triol (α-AET) were analysed firstly basal levels from healthy men and women, concentrations during the daytime and also the physiological response to ACTH and hypoglycemia. Finally, the results from various groups of patients (schizophrenia, depression and anxiety, IgA nephropathy, tinnitus, epilepsy, multiple sclerosis, male and female smokers, women at delivery and with postpartum depression, women with Alzheimeŕs disease) compared to healthy control were compared. The local ethical committee approved the study. The range for α-AET was 0.009–0.180 nmol/l in females and 0.090–0.364 nmol/l in males; and 0.009–0.149 nmol/l for β-AET in females and 0.025–0.435 nmol/l in males. The levels in the healthy people were slightly lower for females than for males; the difference was not significant. The daily profiles showed the decrease from the morning hours to 10 pm, with small temporal increases associated with food consumption. After ACTH stimulation, the 7α-epimer concentration increased within 90 min by nearly 100% in men and about 30% in women. Whereas for the 7β-epimer no significant increase was found. Neither of the triols showed any significant stimulation by ITT. The ratios of the 7α-epimer to 7β-epimer concentrations were mostly near 1.0, slightly exceeding 2.0 only in women and in men with psychiatric diagnoses of schizophrenia or depression. We summarize some data on androst-5-ene-3β,7α/β,17β-triol concentrations under various conditions, which could help understanding impact of these hormones in human physiology and also in the development of several diseases. This study was supported by the project MHCZ–DRO (Institute of Endocrinology – EU, 00023761).

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P458

A case of non metastatic pheochromocytoma in a patient with multiple sclerosis

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Pheochromocytoma is a rare neuroendocrine tumor; many cases are sporadic but 1/3 are familial or syndromic and associated with many susceptibility genes including germline mutations of the gene encoding succinate dehydrogenase (SDH) subunits. We describe the case of a 70-years-old woman with arterial hypertension poorly controlled by therapy in a patient with secondary progressive multiple sclerosis started at 25 years of age, associated with euthyroid autoimmune thyroiditis, hepatic angiomas, cholelithiasis and right adrenal inhomogeneous incidentaloma detected at abdomen CT, cm 4×3. Functional adrenal analysis detected elevated urinary normetanephrine; screening for MEN was negative. The patient underwent laparoscopic right adrenalectomy: histology confirmed the suspicion of pheochromocytoma with PASS score =4. Complete genetic testing for known loci associated to pheochromocytoma was performed. In detail, VHL, SDHA, SDHB, SDHC, SDHD, SDHAF2, RET, TMEM127, MAX genes were analysed in order to detect point mutation or large rearrangement, respectively by Sanger sequencing and MLPA (Multiplex ligation-dependent probe amplification). Moreover, FH, SLC25A11 and MDH2 genes were investigated. Molecular analysis only identified a synonymous substitution in exon 12 of SDHA gene, c.1554A>G p.(Ser518=). The identified sequence variant affects a non-conserved nucleotide and does not alter the protein sequence. In silico splicing analysis does not predict consistent changes at the acceptor site 3 basepairs upstream, and this prediction was confirmed by the use of a minigene assay. The immunohistochemistry highlighted a positive staining for SDHA and the expression of the SDHA protein sustained the non-pathogenicity of the identified variant. Even if the SDHA c.1554A>G was not present in GnomAD exomes and genomes (v2.0.1), it appeared to be a 'private' variation, as no additional evidence of pathogenicity has been identified. Therefore, it has been classified as likely benign. After about three years the patient was normotensive, urinary metanephrines were in the normal range and multiple sclerosis was clinically stable.

In conclusion

- we reported a rare case of pheochromocytoma in a patient affected by multiple sclerosis;
- even if the PASS score suggested a potential biologically aggressive behaviour, after three years of follow up there are no evidences of metastasis or relapses;
- the extensive genetic analysis identified no pathogenic mutations, only a 'private' variation in SDHA gene without functional evidence of pathogenicity, classifying the pheochromocytoma as sporadic.

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P459

Bilateral gynecomastia revealing a secreting adrenal adrenoma on a 5-year-old boy

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Introduction

Gynecomastia is a benign proliferation of the human mammary gland that results from an imbalance between androgens and estrogens. It can be physiological at different stages of life (birth, adolescence, senescence) or secondary to drugs or diseases leading to androgen decline or estrogen elevation. We report a case of an important gynecomasty in a 5 year old boy.

Case report

A boy 5-year-old with no medical history consulted for a gynecomastia evolving since 2 years. On examination, he presented a statural advance and a voluminous bilateral gynecomastia stage B4 of Tanner. The external genitalia were normal and prepubar. The bone age was 7 years. Testicular ultrasound was normal. Abdominal ultrasound, supplemented by a CT scan, revealed a calcified adrenal mass of 2×3 cm. The investigations showed an estradiol level of 20 pg/ml; HCG, blood and urinary cortisol, T4, TSH and 17OHProgesterone were normal. The child had ablation of the adrenal tumor without incident. Histopathological examination revealed an adrenal adenoma. Three months later; we noticed a significant decrease in gynecomastia with a decrease in the value of blood estradiol.

Conclusion

Our observation is particular by the caricatural clinical presentation and the nature of the tumor since adrenal adenomas are exceptionally secreting.

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P460

Steroid hormones and cancer immunity - insights into adrenocortical carcinoma

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Context
Adrenocortical carcinoma (ACC) are endocrine malignant neoplasms associated with severe aggressiveness. By applying of 'multiple omics' approach, we recently categorized ACC patients based on their steroidogenic activity and expression of immune activation marker, which is along with prognosis; an 'immune' phenotype with good and a 'steroid' phenotype with bad outcome.
Hypothesis
Our central hypothesis focuses on the steroid phenotype since it is associated with a glucocorticoid-induced T-cell anergy that ca be rescued by inhibitors of the adrenal steroidogenesis and by reactivating the immune system. Initially, we investigate tumor-infiltrating immune cells and try to identify tumor-specific mutant antigens (TSMA).
Methods
We performed immunofluorescence analysis targeting tumor-infiltrating $CD4^+$ and $CD8^+$T-cells, regulatory T-cells, B-cells and macrophages/dendritic cells in 58 primary ACC. Additionally, we quantified the expression of the immune checkpoint markers programmed-death 1 (PD1) and its ligand PD-L1 using IHC. Furthermore, ACC-associated somatic mutations were analyzed *in silico*. The binding affinity (BA) to MHC receptors of mutant peptide and wild type was predicted using netMHCpan.
Results
Most ACCs show infiltrates by T-cells (80%, 37 ± 65 cells/HPF), both cytotoxic (72%, 24 ± 53) and helper cells (57%, 19 ± 16 cells/HPF), Tregs (48%, 4 ± 4) and Mϕ/DC (73%, 6 ± 4) and an intra-tumoral expression of PD1 (36%, 15 ± 30) and PD-L1 (83%, 34 ± 82), while B-cells were absent. Interestingly, the $CD4^+$ ACC-infiltrating immune cells are associated with overall survival (HR for death: 0.34, 95%CI 0.12–0.95, $P = 0.005$). The *in silico* analyses revealed more than 30 potentially relevant TSMA (e.g. RPL22, CTNNB1, ATRX) and in some of them very strong altered BA was detected (RPL22: in HLA A*03:02: 30.3 nM mut. vs 2556.4 nM in wt).
Conclusion
First, tumors of ACC patients are characteristically infiltrated by $CD3^+$ $CD4^+$T-helper-cells that positively influence patients' overall survival suggesting prognostic relevance. Second, mutated peptides change their BA to HLAs presenting tumor specific neoantigens that might be recognized by the immune system and be targetable via immunotherapeutic approaches. Prospectively, these generated data will be further investigated and verified *in vitro.*

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P461

Multiple endocrine neoplasia: A case report of a pancreatic neuroendocrine tumor in a long evolving MEN1 patient

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a rare, autosomal dominant inherited syndrome caused by mutations in the MEN1 tumor suppressor gene and is characterized by the occurrence of parathyroid, pancreatic islet and anterior pituitary tumors. We present the case of a female patient known to have pituitary and parathyroid tumors in a MEN1 syndrome evolving for more than 20 years before associating pancreatic neuroendocrine tumor.
Case report
At the age of 18, our patient was diagnosed with a prolactinoma, which debuted with secondary amenorrhea, galactorrhea and symptoms of mass effect. After initiation of dopamine agonists, she had more than 50% shrinkage of tumor mass and remission of galactorrhea, but persistent high levels of prolactin. Because she refused both surgery and radiotherapy, she was maintained on a regimen of high dose of dopamine agonist. During further workup, she was diagnosed with primary hyperparathyroidism at the age of 33 and at the time of diagnosis our patient had undergone removal of only on gland that seemed to be affected at parathyroid scintiscan. Pathology confirmed an adenoma of the right lower parathyroid. Genetic screening confirmed germline menin mutation. During regular follow up, at the age of 45, she was diagnosed with a large pancreatic mass (2.73/2.61/3.16) cm and biopsy revealed a well differentiated neuroendocrine pancreatic tumor. In MEN I patients the most common found pNET are gastrinomas, usually developed in the duodenum and, although family history was positive for gastrinoma in her mother, maternal grandfather and brother, our patient developed a nonfunctioning neuroendocrine tumor. This case demonstrates the extremely varied phenotypic clinical patterns, even within the same family. The patient eventually underwent cephalic pancreaticoduodenectomy and pathology confirmed a neuroendocrine tumor classified as intermediate grade (KI67 10%, NEN G2). So matostatin receptor immunohistochemistry revealed a moderately positive score $> 66\%$ of tumor cells and the patient was initiated treatment with somatostatin receptor analogue. Although the role of surgery for non-functioning pancreatic tumors remains controversial, malignant pancreatic neuroendocrine tumors are a major cause of death in MEN1 patients and most consensus recommend surgery for tumors that are more than 1–2 cm in size and/or show significant growth over 6–12 months.
Conclusion
We present the case of a patient that exhibits the classic history of MEN I syndrome, including prolactinoma, parathyroid adenoma and nonfunctional neuroendocrine pancreatic tumor. This case illustrates the considerable phenotypic variability of tumor type manifestations even in the same family.

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P462

A clinical case of adrenal incidentaloma: inconsistency of a prediction to reality

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Introduction
The incidence of adrenal incidentalomas is 5% among patients undergoing radiological imaging. Differential diagnosis is extremely important, as it determines the tactics of both therapeutic treatment and surgical intervention. Currently, algorithms for the differential diagnosis of adrenal masses have been developed and are widely used. Nevertheless, the compliance with strictly regulated diagnostic protocols does not always allow to make an accurate diagnosis.
Clinical case
A 39-year-old man addressed the clinic with the left adrenal incidentaloma. From the history, it was established that from the age of 35 he had been suffering from arterial hypertension with periodic crises up to 200/100 mm Hg. At 36 he was diagnosed with impaired fasting glucose and therefore started taking Metformin. At 37 chronic glomerulonephritis was detected. In 2018 (at the age of 39) a planned ultrasound of the kidneys revealed a formation in the projection of the upper pole of the left kidney. Contrast CT scan: large left adrenal formation ($41 \times 42 \times 56$ mm) with fuzzy edges, +33 HU, absolute washout-30%. The patient was referred to an endocrinologist. Objectively: BMI–29 kg/m^2, BP-160/90 mmHg., heart rate-80 bpm, a single < 1 cm-wide purple striae revealed in the right axillary region. 1 mg overnight dexamethasone suppression test was performed: suppression of serum cortisol did not occur: 4.03 μg/dl (< 1.8). The level of basal ACTH and the 24-hour urinary fractionated metanephrine (twice) were within normal limits. Based on the results of laboratory examination (twice, normal 24-hour urinary fractionated metanephrine), and the presence of a high-density adrenal mass with delayed contrast, pheochromocytoma was ruled out and glucocorticoid-producing adrenocortical carcinoma was suspected. Laparoscopic left adrenalectomy was performed. According to the results of the histological examination, the removed material corresponded to pheochromocytoma. Due to the apparent discrepancies of the obtained laboratory and instrumental data and morphological findings, the biopsy material was sent to an expert level institution for reassessment, where pheochromocytoma/paraganglioma was confirmed: chromogranin A – strong positive, inhibin, melanA – negative, Ki67 $< 1\%$. Final diagnosis: left adrenal glucocorticoid-secreting pheochromocytoma. After surgery hemodynamic parameters stabilized, blood glucose level returned to normal.
Conclusion
This case demonstrates that the observance of strictly regulated algorithms of differential diagnosis may not allow making the correct diagnosis. At the preoperative stage, all data had indicated in favor of adrenocortical carcinoma but the immunohistochemical study performed after the operation verified

pheochromocytoma. Thus, it is necessary to continue research aimed at improving the diagnostic algorithm.

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P463

InfeCtious disease in patients with Adrenal endocRinOpathies: the ICARO prospective observational study

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Introduction
Cushing's Syndrome (CS) is associated with an increased frequency and severity of infections. Mild hypercortisolism (MI) from adrenal incidentalomas has been associated with various complications, but data on infections are scarce. Retrospective data on patients with adrenal insufficiency (AI) showed an increased mortality attributed to infections. The approach used was very heterogeneous for all these studies. The aim of the study is to prospectively evaluate the rate, duration and severity of infectious disease in patients with various degrees of glucocorticoid excess and defect, through a unique validated self-reported questionnaire.
Methods
From January to December 2018, 634 participants completed a modified version of the German National Cohort Questionnaire, containing 46 items on the frequency of respiratory, gastrointestinal tract, bladder, kidney and skin infections over the past 12 months. Group of interest were subjects with CS, MI or AI on conventional replacement therapy. Control group consisted of patients not affect by overt endocrinopathies. Exclusion criteria were severe comorbidities, complications of endocrinopathies (i.e. uncontrolled diabetes) and malignancies. A cumulative odds ordinal logistic regression with proportional odds was run to determine the effect of adrenal disorders, age and gonadal status on infections.
Results
347 participants met the inclusion criteria for the group of interest: 137 patients had adrenal endocrinopathies (31 CS, 85 AI and 21 MI), the remaining 210 were classified as controls. Compared to healthy subjects, the odds of increased number of Urinary Tract Infections (UTIs) in 12 months was 7.8 in CS (95%CI, 3.3 to 18.6; $P<0.001$), 2.9 in MH (1.0 to 8.3; $P=0.046$) and 2.4 in AI (1.2 to 4.8; $P=0.017$). Age ($P=0.149$) and gonadal status ($P=0.551$) did not modify the associations with increased UTIs. Furthermore, CS and MI patients took antibiotics to treat UTIs more often than controls (respectively $P=0.006$ and $P=0.007$). The odds of increased number of pneumonia was 2.8 in CS (1.1 to 6.8; $P=0.024$). AI patients felt more vulnerable about infections than controls (20% vs 9.8%; $P=0.012$) and they were more frequently admitted to hospital compared to controls (23.6% vs 12%; $P=0.038$).
Conclusions
Our findings indicate a higher prevalence of self-reported infections, especially of the urinary tracts, among patients with imbalances in glucocorticoid levels, not only in overt CS, but also in MI and AI. The results underline the need for further studies on the relationship between glucocorticoids and the immune system.

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P464

EGFR and IGF1R affect Sunitinib activity: novel targets for Broncho-Pulmonary Neuroendocrine Neoplasm treatment

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Background
Available medical treatments for Broncho-Pulmonary Neuroendocrine Neoplasm (BP-NENs) derived from clinical trials are not specific for the management of this malignancy. Sunitinib, a multi-receptor tyrosine-kinases (RTKs) inhibitor, mainly described as VEGFR inhibitor, has shown its efficacy in Pancreatic NENs but there are not available data about its action in BP-NENs. Our aim was to understand the effects of RTKs inhibition promoted by Sunitinib in order to evaluate new putative targets useful in malignancy treatment. Furthermore we investigated the effects of Erlotinib, an EGFR inhibitor, and Linsitinib, an IGF1R inhibitor, in order to understand their possible effects in BP-NENs.
Methods
BP-NENs cell lines and primary culture were treated with the indicated compound/growth factors. After treatment cell viability, apoptotic activation and RTK phosphorylation were evaluated.
Results
Our results showed that after treatment with Sunitinib and/or IGF1, EGF and VEGF, the antiproliferative effect of Sunitinib was counteracted by EGF and IGF1 but not by VEGF. Therefore, we evaluated with alpha-screen technology the phosphorylated EGFR and IGF1R levels in primary cultures treated with Sunitinib and/or EGF and IGF1 and found a decrease in p-IGF1R after treatment with Sunitinib and an increase after co-treatment with IGF1. We assessed cell viability and caspase activation on BP-NEN cell lines after treatment with Linsitinib and/or Erlotinib. Results demonstrate that these two agents have a stronger antiproliferative effect compared to Sunitinib.
Conclusion
Our results indicate that EGF and IGF1 impair Sunitinib activity on BP-NEN. IGF1R and EGF1R could represent putative molecular targets in BP-NENs treatment.

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P465

Measurement of metanephrine in adrenal venous sampling may help subtyping primary aldosteronism

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Objective
Adrenal venous sampling (AVS) is the gold standard method to assess lateralization of aldosterone secretion in patients with primary aldosteronism (PA). The selectivity index ($SI_{cortisol}$, the adrenal to peripheral vein ratio of cortisol concentrations) determines correct catheter positioning during AVS. The lateralization index ($LI_{cortisol}$, the aldosterone to cortisol ratios between adrenal veins) distinguishes unilateral aldosterone producing adenoma (APA) from bilateral adrenal hyperplasia (BAH). The use of cortisol is not always reliable and the ratio of adrenal to peripheral vein free metanephrine concentrations has been alternatively suggested for SI determination. The aim of our study was to assess the performance of $SI_{metanephrine}$ and to determine the $LI_{metanephrine}$ threshold in AVS.
Design and method
This retrospective study conducted at the HEGP ESH excellence center included 245 patients who had 1) AVS with simultaneous adrenal and peripheral vein samplings without cosyntropin stimulation between 07/2013 and 05/2017, 2) adrenal and peripheral vein samples stored at $-80\,^{\circ}C$ to measure retrospectively free metanephrine. Receiver operating characteristic (ROC) curves were used to assess the performance of $SI_{metanephrine}$ and $LI_{metanephrine}$.

Results
Based on $SI_{cortisol}$ and $LI_{cortisol}$, 198/245 patients had successful AVS ($SI_{cortisol}$ above 2) among whom 108 had APA ($LI_{cortisol}$ above 4) and 90 BAH ($LI_{cortisol}$ below 4). 48/245 patients had failed AVS. Among the 245 AVS, 434 adrenal samples had $SI_{cortisol} \geq 2$. A $SI_{metanephrine}$ of 16 was the optimal threshold for successful AVS. This cutoff confirms the selectivity of 22 AVS among the 48 considered as non-selective with $SI_{cortisol}$. 65 patients underwent unilateral adrenalectomy with a 6-month follow up confirming PA biochemical cure (PASO criteria). ROC curve analysis of $LI_{metanephrine}$ plotted APA ($n=65$) *versus* BAH ($n=52$) (AUC $=0.954$). There was a large overlap of $LI_{metanephrine}$ between APA and BAH. A threshold of $LI < 2.5$ confirmed BAH (100% specificity) while a threshold $LI > 10$ confirmed APA (100% specificity). A $LI_{metanephrine}$ threshold of 5 had 80% sensitivity and 95% specificity to distinguish between APA from BAH.
Conclusion
We confirmed that $SI_{metanephrine}$ is superior to $SI_{cortisol}$ in assessing the selectivity of AVS. A threshold of 16 for $SI_{metanephrine}$ decreased the rate of AVS falsely considered as failed. In contrast, $LI_{metanephrine}$ did not have enough sensitivity/-specificity to distinguish between APA and BAH. The lack of a gold standard to confirm BAH may participate in this finding. A prospective study would be needed.

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P466

A case of metastatic pheochromocytoma diagnosed at a young age with hypertensive attack

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Introduction
Although the radiographic and histological features are the same as benign pheochromocytomas, malignant and metastatic pheochromocytoma is differentiated by invasion of the surrounding tissues and organ metastasis. Here, we present a young patient with a diagnosis of metastatic pheochromocytoma presenting with hypertension attacks, headache and flushing.
Case presentation
A 22-year-old woman with a history of hypertension who had been suffering from headache new-onset flushing and hypertensive attacks in holter blood plessure for 6 years and is presented. MRI scan of abdomen revealed a solid mass of $70 \times 62 \times 64$ mm in right supra renal space which suppressed the right kidney and metastatic lymphadenomegaly suppressing the inferior vena cava at the portocaval area. Laboratory: ACTH 40.2 pg/ml, serum cortisol 20.8 μg/dL, 1-mg dexamethasone-suppression test: cortisol 0.5 μg/dL, calcitonin 4.29 pg/ml, aldosterone 339 pg/ml, renin 7.04 ng/ml per h. 24-hr-urinary cortisol and metanephrine level were normal but 24-hr-urinary normetanephrin level was elevated (40 nmol/24 hr (N: 38–208), 283 μg/24 hr (N: 276–341) and 11345/24 hr (N:88–444)). Neck ultrasound was normal. Right surrenalectomy and periportal lymph node dissection were performed. Histopathological examination of the surgical specimens was consistent with pheochromocytoma with lymph node metastasis. Genetic testing for hereditary pheochromocytoma revealed heterozygous c.890G > A /p.Arg297 His change in the 5th exon in the RET gene. *In the first month after surgery* 24-hr urinary cortisol, metanephrine and normetanephrine levels were found to be normal.
Discussion
Pheochromocytoma is more frequent present in 4th to 5th decades of life and is the cause of hypertension in 0.2% to 0.6% of patients. 10% of these are malignant as proven by the presence of metastases. Our case was diagnosed during the investigation of hypertension attacks at a young age. Genetic screening should not be forgotten in patients who were diagnosed as unilateral pheochromocytoma at a young age.
Keywords: Hypertension, metastatic pheochromocytoma
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Calcium and Bone 2

P467

Discovery of a novel NOTCH2 mutation causing Hajdu Cheney Syndrome in a kindred with remarkable phenotypic diversity

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Introduction
Hajdu Cheney Syndrome (HCS) is a rare genetic autosomal dominant disorder affecting multiple organ systems, characterized by distinctive facial features, acroosteolysis and severe osteoporosis. In a limited number of cases, the disease appears in association with polycystic kidney disease (PKD) or Crohn's disease (CD). Splenomegaly has also been reported. Heterozygous gain-of-function mutations in *NOTCH2* gene have been confirmed to be the cause of HCS. Treatment with bisphosphonates or denosumab is reported to result in bone mineral density (BMD) increase.
Objective
We report a novel mutation in exon 34 of *NOTCH2* gene, in a Greek pedigree, with diverse phenotype among members.
Description of the pedigree
The mother is a 48-year-old woman, with typical facial characteristics of HCS and a history of a T12 vertebral fracture, after parturition of her first male child, at 21 years of age, who presents with acroosteolysis and low BMD, but no further clinical fractures despite two subsequent pregnancies and the lack of antiosteoporotic treatment. The first male offspring is a 29-year-old male with severe osteoporosis and multiple morphological vertebral fractures. At age 25, he received a two-year treatment with teriparatide, with no improvement in BMD, but no incident fractures. Her second offspring passed away at the age of 10 months due to cystic fibrosis. The third offspring is a 21-year-old female with HCS clinical characteristics and vertebral fractures since 10 years of age. She received disodium pamidronate (during childhood) for 2 years. At 17 years of age, she developed severe CD, with functional hypothalamic hypogonadism and recurrent multiple vertebral fractures. She is on hormone replacement therapy and has received two courses of yearly zoledronic acid, with stabilization of BMD and no further incident fractures. None of the subjects had splenomegaly or renal defects on ultrasound examination.
Genetic testing
Heterozygous c.6758G > A (NM_008163.1) nonsense mutation, leading to a Trp2253Ter protein. This mutation has been classified (SCV000620308), however, this is the first report in association with HCS.
Conclusions
1) Bone involvement can present with diverse severity in different members of the same pedigree, ranging from low BMD to multiple fragility fractures.
2) Antiresorptive therapy may be more rational than osteoanabolic therapy, since increased osteoclastogenesis is the primary pathophysiological mechanism; however, it remains to be definitely shown.
3) Apart from the characteristic bone manifestations, pulmonary disease and CD were diagnosed in different members of the family, indicating the significant role of NOTCH2 signaling pathway in different tissues.

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Discovery of a novel CASR mutation causing Familial Hypocalciuric Hypercalcemia in a Greek family

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Introduction
Familial hypocalciuric hypercalcemia (FHH) causes lifelong hypercalcemia, which, in general, is not associated with significant morbidity. FHH1, the most common type of the disease, is inherited in an autosomal dominant pattern and caused by inactivating mutations in the Calcium Sensing Receptor (*CaSR*) gene,

located in chromosome 3. Inactivation of *CaSR* in parathyroid cells results in a shift of calcium set point to higher values with consequent hypercalcemia. Mutations in *GNA11 and AP2S1* have been associated to the less frequent FHH2 and 3 disease types. FHH should be recognized and differentiated from primary hyperparathyroidism, in the workup of hypercalcemia, since FHH is not curable by surgery.

Objective

We describe a novel *CaSR* mutation in a female subject with FHH type 1.

Case

A 37-year-old female with no specific symptoms was referred for hypercalcemia, with normal PTH levels and low urinary calcium excretion confirmed at several occasions (table). Physical examination was unremarkable. Upon recommendation, other members of her family were tested for hypercalcemia. Her father, two paternal aunts and one of her two siblings also presented with asymptomatic hypercalcemia. It was reported that the paternal grandmother had been diagnosed with primary hyperparathyroidism and had been submitted to parathyroid surgery, years before.

	Serum Calcium (mg/dl)	Serum Phosphorus (mg/dl)	Serum Magnesium (mg/dl)	Serum Albumin (g/dl)	Serum creatinine (mg/dl)	25OH D ng/ml	PTH pg/dl	24h Urine Calcium (mg/24h)	Urine Ca/creat ratio
Jun 2018	11.6	2.7	1.9	4.57	0.5	24.25	52.3	43.7	0.04
Jan 2018	11.1	2.5		4.4			48	89	0.08

Genetic testing

Sequencing results showed that patient carried a heterozygous novel mutation c.1657G > T in exon 6 of the *CaSR* gene. The novel mutation is a G to T transition at nucleotide 553 resulting in a Gly553Trp (Glycine to Tryptophan) missense mutation. The pathogenicity of the novel mutation was classified with several online tools as SIFT, PolyPhen and Align-GVGD. In silico analysis classified the mutation as 'likely-pathogenic'. The G556W mutation could markedly change the structure of protein.

Conclusions

We report a novel missense mutation of *CaSR* gene, in association with FHH in a pedigree. Asymptomatic hypercalcemia seems to be the only manifestation, so far, associated with this specific mutation. The diagnosis of FHH, could prevent patients from an unnecessary parathyroidectomy.

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A case of apparently sporadic primary hyperparathyroidism carrying a germline mutation of CDC73 gene

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We report the case of a 35 yrs- old man, who was referred to our Department in 2012, for symptomatic nephrolithiasis and low bone mass. Biochemical evaluation showed moderate hypercalcemia [albumin-corrected calcium 13.1 mg/dl (8.6–10.2) and markedly elevated PTH levels [1391 pg/ml (13–65)] consistent with the diagnosis of primary hyperparathyroidism (PHPT). Neck ultrasound revealed three enlarged parathyroid glands. The patient underwent right superior and inferior and left superior parathyroidectomy (PTx). Histology showed hyperplasia in two glands and atypical adenoma in the other. After surgery, a persistence of PHPT was evident with serum calcium of 11,4 mg/dl and PTH 724 pg/ml. Neck ultrasound revealed an hypoechoic lesion localized under the left lobe of the thyroid, that showed an uptake at ^{99m}Tc-MIBI scintigraphy. No other endocrine lesions were present. The patient underwent left inferior PTx. Histology revealed an atypical adenoma. Post surgical hypoparathyroidism was diagnosed and the patient started calcium and calcitriol treatment. The patient continued to have symptomatic nephrolithiasis with a reduction of kidney function. Taking into account the young age, histology and multigland parathyroid involvement, genetic analysis of the *MEN1* and *CDC73* gene was carried out. Genetic analysis revealed a germline mutation of the *CDC73* gene, leading to the substitution of a guanine to a adenine in splicing donor site 3. The genetic screening was negative in the parents and siblings indicating that the mutation was *de novo*. *CDC73* mutations are responsible for hyperparatyroidism-Jaw tumor syndrome (HPT-JT), a rare autosomic dominant disease characterized by multigland parathyroid involvement, increased prevalence of parathyroid carcinoma and atypical adenoma, benign ossifying fibromas of the jaw, benign and malignant renal lesions and uterine tumors. The patient did not have kidney lesions and ossifying fibroma of the jaw. During the follow up there was evidence of permanent postsurgical hypoparathyroidism with good control of serum calcium, phosphate and magnesium, but not of 24-h urinary calcium on treatment with calcium and calcitriol. Thus, the patient started thiazides diuretics leading to a reduction of 24-h urinary calcium and improvement of nephrolithiasis. In conclusion, we described a case of an apparently sporadic PHPT who carries a germline mutation of the *CDC73* gene. It is of great importance to recognize this syndrome to confirm the diagnosis, screen the associated lesions, make a familial screening and plan the adequate surgery. Moreover, our patient need a careful treatment on standard therapy and monitoring of postsurgical hypoparathyroidism.

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P470

Successful management of tertiary hyperparathyroidism associated with hypophosphataemic rickets in an adult

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Introduction

Chronic hyposphosphataemia is caused by increased concentrations of fibroblast-growth factor 23 (FGF23), mostly attributed to inactivating mutations of the phosphate-regulating endopeptidase homolog, X-linked (PHEX) gene. Secondary or tertiary hyperparathyroidism (THP) constitutes a rare complication of the disease, partly attributed to chronic supplementation of phosphate salts.

Case presentation

A 31-year old woman was admitted to our department on occasion of hypercalcaemia and hypophosphataemia. Until admission, she was being treated with oral alphacalcidol (0.5 μg/day) and phosphate (5 g/day). Her paediatric history included severe gait disturbances, clubfoot, osteotomies of the tibia and tooth reconstructions, a cluster of signs and symptoms compatible with the diagnosis of rickets. Biochemical and hormonal assessment on admission showed mild hypercalcaemia [corrected serum total calcium concentrations: 10.9 mg/dl (normal range: 8.4–10.4 mg/dl)] and hypophosphataemia [serum phosphate concentrations: 1.8 mg/dl (normal range: 1.9–2.5)], with high parathyroid hormone (PTH) [721 pg/ml (normal range 10–65)] and low 25-hydroxy-vitamin D levels [15 ng/ml (sufficiency defined as > 30 ng/ml)]. Renal function was normal [estimated glomerular filtration rate (eGFR): 114.9 ml/min/1.73 m^2], as were the 24-h urinary calcium concentrations [114 mg/24-h (normal range: 50–300)]. The maximum tubular resorption of phosphorus factored for glomerular filtration rate (TmP/GFR) was estimated at 0.96 mmol/l (female range: 0.96–1.44) indicative of hypophosphataemia due to renal loss of phosphate. Bone mineral density was normal, whereas bilateral nephrocalcinosis was observed on renal ultrasonography. Neck ultrasound showed enlargement of the right (inferior and superior) and the left superior parathyroid glands. A sestamibi scintigraphy scan was indicative of a hyperfunctioning right inferior parathyroid gland and, therefore, the diagnosis of THP was set. Afterwards, a gradual increase in alphacalcidol dose (1.5 μg/day) and cinacalcet (60 mg/day) was added to the patient's regimen. Two months later, she underwent an uneventful parathyroidectomy, including removal of three enlarged parathyroid glands. Histological diagnosis was consistent of multiple parathyroid adenomas. Post-operative PTH and calcium concentrations were within normal range and so far remain normal, during a follow-up of 18 months.

Conclusions

THP may rarely develop during the course of chronic hypophosphataemia and should be taken into consideration, when hypercalcaemia develops. Early recognition and successful management with either parathyroidectomy or cinacalcet are recommended. Nonetheless, optimal dosage of alphacalcidol and phosphate salts, minimizing treatment-related adverse effects, is the mainstay of treatment in these patients.

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P471

Parathyroid hormone (PTH) levels are not associated with cancer in patients with primary hyperparathyroidism

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Introduction
The development of malignancies in patients with Primary Hyperparathyroidism (PHP) occurs in the context of Multiple Endocrine Neoplasia (MEN) Syndrome. The association of PTH levels with cancer in patients with sporadic PHP has not been clarified. The aim of this study was to investigate whether PTH levels are related to the presence of thyroid cancer (TH) or other types of cancer in patients with PHP.
Methods
We included patients with biochemical diagnosis of PHP based on PTH, Calcium, Albumin, Phosphorus, Creatinine and 25 (OH) Vitamin D3 levels, who had undergone parathyroidectomy. Exclusion criteria were secondary, tertiary hyperparathyroidism and parathyroid hyperplasia in histology.
Results
84 (69 females) patients with mean age 63.13 years were included in the study. The mean PTH levels were 133.6 pg/ml (47–398). 19 patients developed any type of cancer, and 5 of them developed TC. The mean PTH levels were 132.8 pg/ml in patients who did not develop TC, while in patients with TC the mean PTH levels was 145.8 pg/ml ($P=0.675$). Furthermore, among patients with any type of cancer, PTH levels were higher (146.18 pg/ml) compared to patients who did not develop cancer, whose PTH levels were 129.92 pg/ml ($P=0.35$).
Conclusion
PTH levels, although higher in patients with any type of cancer and PHP, show no statistically significant correlation. Larger prospective studies are needed to explore a possible association between these entities.

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Osteoporosis induced after sleeve gastrectomy in a patient affected of mild asymptomatic primary hyperparathyroidism

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Introduction
Osteoporosis is a major health problem in our countries. Primary hyperparathyroidism and obesity surgery increase this risk of adverse events such as fractures. We report the case of a patient with mild asymptomatic hyperparathyroidism with low serum mild hypercalcemia non-osteoporotic who developed osteoporosis after obesity surgery improved by parathyroidectomy.
Case
This is a female 55-year-old patient with past history appendectomy, stripping, hyperparathyroidism (November 2013), hypertension, type 2 diabetes (HbA1c 6.1%), helicobacter pylori infection, depressive syndrome, and menopause. His treatment includes candesartan, metformin, lecardipine, sitagliptin. In his preoperative assessment of obesity surgery we note: weight 131 kg, 1.62 meter, BMI 49.9 kg/m^2, BP 176/109 mmHg. In laboratory 8/12/2014 Calcium 2.7 mM, calciuria 368 mg/l, PTH 100.7 pg/ml ($N<72$), low vitamin D at 25 ng/ml and normal creatininemia. In 2013, she had been evaluated for her hyperparathyroidism, the osteodensitometry (november) evidenced the absence of osteoporosis. Surveillance had been proposed. She had a sleeve gastrectomy on November 3, 2014, and a treatment with multivitamin including vitamin D, 1 gram of calcium postoperatively but also esomeprazole 40 mg/d I addition to other treatment. Blood calcium was still slightly increased after surgery. In July 2017, there was the appearance of osteoporosis on the spine (L1-L4), and osteopenia on the femur. It was decided the parathyroidectomy of right P3 on January 4, 2018, calcium and PTH were normalized and on January 5, 2019 we noted the disappearance of osteoporosis (same machine). Her weight was 91 kgs (BMI 34.7 kg/m^2). This observation seems to demonstrate that the presence of a mild non-symptomatic primary hyperpararthyroidism can be significantly worsen after sleeve gastrectomy and may be improved after parathyroidectomy.
Conclusions
Patients with non-symptomatic hyperparathyroidism before obesity surgery should be monitored by bone densitometry after.

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P473

High prevalence of severe vitamin D deficiency in Egyptian females

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Introduction
Despite Egypt being a sunny country (latitude 22–32°N) and enjoying a high year-round UV exposure (highest UV index in Cairo 12 in July and lowest 3 in December), it harbors a high prevalence of vitamin D deficiency especially in females (Botros et al, Endocrinol Nutr, 2015;62(7):314–321).
Aim of work
We aimed to study a larger representative sample of Egyptian males and females, to identify the extent of the phenomenon and characterize the population affected.
Methods
25-(OH) vitamin D was measured in samples from 5046 patients, of whom 3954 were females. The samples were collected throughout 2017 from 55 sampling locations across Egypt. All the samples were centrally analyzed in Royal Lab, a nation-wide Reference Laboratory in Cairo (ISO 15189 accredited since 2013), using Chemiluminescence immunoassay.
Results
1357 of the females (34.3%) and 164 of the males (10.9%) had severe vitamin D deficiency (<10 ng/ml) [Table 1]. Only 869 (17.2%) of all the subjects studied had Vitamin D >30 ng/ml. Females had significantly lower Vitamin D then Males (17.7 ± 15.9 vs 24.5 ± 23.2 ng/ml, $P<0.001$). Age of the subjects was inversely proportionate to vitamin D level ($P<0.05$).

Table 1

25 OH Vitamin D (ng/ml)	Gender Male (%)	Female (%)	Total (%)
Severe deficiency (<10)	164 (15.1)	1357 (34.3)	1521 (30.1)
Moderate def. (10–20)	420 (38.4)	1447 (36.6)	1867 (36.9)
Insufficient (20–30)	245 (22.4)	544 (13.7)	789 (15.6)
Normal (>30)	263 (24.1)	606 (15.3)	869 (17.2)
Total	1092	3954	5046

Conclusion
Vitamin D deficiency in Egypt has reached epidemic proportions. Females are the most affected members of Society. Urbanization and Social factors are thought to cause that phenomenon. Growing awareness is reflected by more subjects asking to be tested for Vitamin D sufficiency.

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P474

Hypophosphatemia in osteoporotic patients referred to a single third level centre: prevalence, clinical features and diagnostic challenges

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Chronic hypophosphatemia (HP) can be observed among patients (pts) evaluated and treated for osteoporosis, but its prevalence and management are poorly defined. In this study we analyze prevalence, clinical features and diagnostic workup for chronic HP among pts attending a third-level osteoporosis office. Chronic HP was defined as serum phosphate levels persistently <2.7 mg/dl over a period ≥ 6 months. Tubular reabsorption of phosphate (TRP) was measured and, in presence

of renal wasting, serum FGF23 was required (DIASORIN; normal values 23.2–95.4 pg/ml). When non-suppressed FGF23 levels were detected, a diagnosis of Tumour Induced Osteomalacia (TIO) was considered. Positive family history for bone diseases, hyperparathyroidism, vitamin D deficiency, and interfering drugs were excluded. Among 2055 pts followed from January 2017 to December 2018, nineteen were diagnosed with chronic HP due to renal wasting (0.92%). Circulating FGF23 measurement helped distinguish FGF23-independent renal wasting (2 pts, both diagnosed with Fanconi's syndrome; FGF23 levels: 5 pg/ml and 18.5 pg/ml, respectively), from FGF23-dependent forms ($n=17$; median FGF23 level: 52 pg/ml, range 35–103). Among the latter cases, one patient had a clinical diagnosis of hypophosphatemic rickets, though any mutation of the *PHEX* gene could be detected. The remaining 16 pts (12 females) had no osteomalacia or muscle symptoms, while 7 out of 16 (44%) had a history of fragility fractures. On anti-osteoporotic treatment (bisphosphonates or denosumab), these pts showed poor bone mineral density (BMD) improvement and serum alkaline phosphatase levels remained above the first tertile of normal range in half of them. ^{68}Ga-DOTATOC-PET was carried out in 8 pts; it identified suspicious lesions associated with increased uptake only in 4 of them (50%). Pts with positive PET had the lowest phosphate levels (median 2.25, range 1.6–2.5 mg/dl), the highest FGF23 levels (median 70.5, range 48–84 pg/ml), the lowest BMD values and the worst responses to anti-osteoporotic treatments. Following imaging and histologic studies, one meningioma and one paraganglioma were identified; two other patients with thyroid and left inguinal uptakes, respectively, are waiting to complete diagnostic workup. In conclusion, prevalence of chronic HP is nearly 1% among osteoporotic pts, but clinical management is challenging. Mild asymptomatic HP can be associated with normal or only slightly elevated FGF23 levels and negative ^{68}Ga-PET. Nonetheless, chronic HP can affect bone metabolism and efficacy of anti-osteoporotic treatments.

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P475

McCune-Albright syndrome: report of two cases

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Introduction
McCune-Albright syndrome (MAS) is a rare non-inheritable genetic disease. It is attributed to an early embryonic postzygotic somatic activating mutation of GNAS, leading to a mosaic that causes polyostotic fibrous dysplasia, café au lait macules and polyendocrinopathy.
Aim
To present two cases of this rare syndrome.
Case report
A 38-year-old male patient presented with a bone lesion of the forehead and acromegalic features. Acromegalism and hyperprolactinemia were confirmed (IGF-1 586 ng/ml, GH 1.7 ng/ml post OGTT, PRL 54.26 ng/ml). Pituitary MRI showed enlargement of the pituitary gland and a macroadenoma of 12.6 mm. Facial skull CT demonstrated fibrous dysplasia of the frontal and sphenoid bone. No compromise of the optic nerves or the external auditory canals was detected. Bone scan revealed fibrous dysplasia of the sacrum as well. Bone turnover markers were elevated (P1NP 143 ng/dl, β-CTX 0.767 ng/ml). Diagnosis of MAS was established. Partial biochemical control was accomplished with cabergoline and pegvisomant. Treatment was successfully switched to lanreotide autogel (IGF-1 285 ng/ml, GH1,1 ng/ml, PRL18.05 ng/ml). Bone turnover markers were restored with zolendronic acid infusion. Partial surgical removal of the craniofacial lesion restored facial deformity and confirmed histologically the diagnosis of fibrous dysplasia. A 77 year-old female patient previously diagnosed with MAS: café au lait macules of the right thigh, polyostotic fibrous dysplasia of the calvaria, left humerous, hiliac and femoral bone, hyperthyroidism due to toxic polyglangular goiter and bilateral adrenal adenomas, presented with bone pain. Bone turnover markers were elevated (ALP 172IU/L, P1NP 106.9 ng/ml) despite yearly infusions of zolendronic acid. Serum phosphorous was normal. Bisphosphonate treatment with 6-month intervals was decided. Serum TSH was suppressed under 5 mg of methimazole per day. Euthyrodism was restored with titration to 7.5 mg/day. Serum ACTH was low normal (8.7 pg/ml) and cortisol failed to suppress after ODST (F 100 nmol/l post dexa), indicating autonomous cortisol production, although no clinical findings of Cushing's syndrome were present.
Conclusions
The phenotypic spectrum of MAS is wide, depending on the time during embryogenesis that the somatic mutation occurs, thus requiring thorough endocrine work up and individualization of the therapeutic approach. Management within the frame of a multidisciplinary team is often mandatory.

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P476

Pineal chordoid meningioma in patient with familial hypocalciuric hypercalcemia, a combination of two rare conditions: Report of a clinical case

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Introduction
Familial hypocalciuric hypercalcemia (FHH) is a rare condition (1–2% of causes for hypercalcemia) and may be confused with primary hyperparathyroidism. Diagnosis of FHH must be suspected in patients with a family history of chronic hypercalcemia, no symptoms and low urinary excretion. This disease is due to mutations in the calcium-sensing receptor (CASR) gene. Meningiomas are common intracranial tumors (15–20% of primary neoplasms of the central nervous system). By contrast, chordoid meningioma is a rare subtype, usually large and located in the supratentorial region.
Case report
21-year-old male, who underwent an endocrine examination due to mild chronic hypercalcemia. This condition was supposedly known ever since the patient was 7 years old. Physical examination revealed marfanoid habitus and postural asymmetry (compatible with a previously diagnosed scoliosis). After tests results (mild hypercalcemia and hypocalciuria) confirmed the originally suspected diagnosis (FHH), genetic testing showed the presence in heterozygosis of change c.76G>T (p.Ala26Ser) in the CASR gene; a mutation that is not recorded in regular databases. Two years after this diagnosis, the patient returned for consultation due to generalized cephalea over a period of several weeks and bitemporal hemianopsia. Imaging (nuclear magnetic resonance) revealed a $12\times12\times15$ mm solid lesion in the pineal region, significantly enhanced by IV contrast. A left paramedian suboccipital incision was performed on the patient. The results from the subsequent histological analysis and immunohistochemistry tests were compatible with the diagnosis: Grade II chordoid meningioma.
Discussion
FHH and chordoid meningioma are both very rare diseases and very different in nature. While FHH is hereditary, generally asymptomatic and presents low clinical relevance, chordoid meningioma is a sporadic tumor, usually large upon diagnosis and presenting obvious symptoms. Given the combination of both conditions, the described patient is an interesting case for in-depth analysis.

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P477

Hypercalcemic crisis of unknown origin: A case report

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Introduction
Hypercalcemia is one of the most common endocrine disorders. Most outpatients's cases are due to primary hyperparathyroidism and run with chronic and low-moderate hypercalcemia. We report a case of acute and severe hipercalcemia of unknown origin. Diagnostic procedure is discussed.

Case report
A 53-year-old man was admitted to the Intensive Care Unit due to progressive deterioration of consciousness in the last 48 hours, associating respiratory failure that required orotracheal intubation. Medical history, collected to his relatives, revealed that the patient was heavy smoker and, had suffered from lumbar pain resistant to analgesia, for the last 2 months. Admission laboratory routine highlighted impaired renal function, a marked neutrophil leukocytosis and acute phase reactants elevation. A cranial and thoraco-abdominal CT scan was performed, which showed a right basal pulmonary condensation without masses or pathological enhancements as well as a crushing L4-fracture. A 12 mm neck nodule was observed under the right thyroid lobe suggesting a possible parathyroid adenoma. An extremely high serum calcium levels (19.3 mg/dl) was detected afterwards. Before the analytical and radiological findings, Endocrinology Unit was consulted for study and treatment of probable parathyroid crisis. Expanded study of phospho-calcium metabolism showed, in addition to hypercalcemia, lower-normal i-PTH levels (15.1 pg/ml, N: 15 – 68.3 pg/ml), decreased levels of 25-OH vitamin D (7.8 ng/ml, $N>$ 30 ng/ml), hypercalciuria (792 mg/24 h) and hypophosphaturia (0.38 g/24 h). These findings led to determine PTHrp levels which were high (5.7 pmol/l, normal $<$ 2.0 pmol/l). A cervical ultrasound identified the cervical nodule as adenopathy. After dialysis and zoledronate, hypercalcemia was reversed. Among studies searching for hidden neoplasia, only a bone marrow biopsy revealed infiltration by squamous cell carcinoma without being able to demonstrate the primary tumor by any other test.
Conclusions
Hypercalcemia is a common analytical finding and requires an adequate etiological characterization for an adequate diagnostic and an adequate therapeutic planning. We highlight the unusual observation of a severe and acute hypercalcemia development as the primary presentation of a neoplasm whose primary location could not be evident.

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P478

Trabecular bone score - a more sensible indicator in predicting negative change than bone mass density?

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Background
Glucocorticoid-induced osteoporosis is common in chronic diseases as inflammatory bowel disease. Although BMD (bone mass density) is used for the estimation of the quantity of the bone, on the contrary, TBS (trabecular bone score) is a new parameter, a gray-level textural assessment of bone microarchitecture, providing estimation of quality of bone. Several studies showed increased level of TBS during teriparatide treatment in glucocorticoid induced osteoporosis.
Case report
We report the case of a 23-year-old female, diagnosed with Crohn disease in 2014, initially managed with ileal resection and subtotal colectomy. In august 2018, she was performed DXA (dual energy-X ray absorptiometry) that revealed BMD spine $=0.883$ g/cm^2, Z score $=-2.4$ DS, TBS $=1293$. The X-ray of the spine showed L2 compression. At that moment she had stable disease on treatment- Crohn disease activity disease CDAI $=130$ on prednisolone 24 mg/day, anti TNF, Imuran. Bone markers were crosslaps $=0.09$ ng/ml and osteocalcin $=9.1$ ng/ml, with normal endocrine assessment. After 6 months of treatment, she increased methyl prednisolone, receiving 48 mg/day, lost 6 kilos and stopped anti TNF treatment, and her CDAI was 220 (mildly to moderate disease); she was on teriparatide for 6 months and Vitamin D 2000 UI/day. Although DXA scan revealed increased BMD spine $=0.948$ g/cm^2 ($+6.5\%$), Z score $=-2$ DS, TBS decreased $=1,269$ (-2.4%). Crosslaps were 0.14 ng/ml and osteocalcin 8.3 ng/ml.
Conclusion
Treatment with teriparatide can be efficient in Crohn disease, but in case of disease severity and high dose glucocorticoid treatment, TBS may represent a more sensitive and precocious marker of negative change in bone mass, as shown by bone markers.

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P479

Relationship between serum levels of 25-OH vitamin D and parameters of bone mineralization (BMD) and bone quality (TBS) in clinical practice

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Introduction
Vitamin D is a hormone essential for calcium absorption and bone mineralization, which is positively associated with bone mineral density. The aim of our study was to evaluate the relationship between 25-OH vitamin D values and parameters of bone mineralization (bone mineral density - BMD) and bone quality (trabecular bone score - TBS) in patients from day to day clinical practice.
Materials and methods
We evaluated 433 postmenopausal women (mean age 61.84 ± 13.62 years) consecutively referred for DXA evaluation in a tertiary endocrinology center. Lumbar BMD was measured using GE Lunar DXA equipment and trabecular bone score (TBS) was evaluated with TBS iNsight software version 3.1.
Results
17.1% of our patients had a lumbar BMD T Score <-2.5 SD, 48.8% had a T score between -2.49 and -1 SD and the rest of them had a normal BMD T score. Regarding vitamin D status, 160 (37%) patients had normal 25-OH vitamin D levels, 152 (35%) had levels between 20 and 30 ng/ml and the rest (28%) had vitamin D deficiency (less than 20 ng/ml). We found a significant negative correlation between serum 25-OH vitamin D levels and BMI ($r=-0.245$, $P<0.001$), lumbar BMD T score ($r=-0.250$, $P<0.001$) and trabecular bone score ($r=-0{,}109$, $P<0.05$). Surprisingly, patients with osteoporosis had higher levels of 25-OH vitamin D (30.95 ± 13.7 ng/ml) compared with osteopenic (27.01 ± 11.6 ng/ml) and normal BMD patients (23.65 ± 8.75 ng/ml). However, after controlling for age, BMD and BMI, 25-OH vitamin D levels positively correlated with TBS values ($r=0.105$, $P<0.05$).
Conclusions
In daily clinical practice, it is not uncommon to find higher vitamin D levels in osteoporotic patients, probably due to lower BMI and to the higher probability of taking vitamin D supplements. After controlling for age, BMI and BMD, 25-OH vitamin levels were correlated to TBS, a surrogate marker of bone quality.

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P480

Seasonal variation of osteoporotic hip fracture admitted in trauma centers in Bucharest

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Hip fracture remains the most important clinical manifestation of osteoporosis, with many studies demonstrating a relationship between seasons and the incidence and mortality after hip fracture.
Objective
We aimed to identify a seasonal variation (four seasons) in incidence of osteoporotic hip fracture admitted in trauma centers in Bucharest.
Materials and methods
We observed the seasonal variation of 1176 patients, mean age $78.19+/-11.35$ years old, with 68.96% over 75 years old, admitted in trauma centers in Bucharest from September 2017 to august 2018 with hip fracture.
Results
In the study population we observe a higher incidence in spring (March–May) with 28.48% (3.33 fracture/day) compared to lower incidence in autumn 21.52% (with 2.7 fractures/day). The highest incidence was registered in January and July and the lowest in February (4.1 fractures/day compared to 2.5). The incidence of fractures per day in the months with snow in Bucharest (January, February and March 2018) was higher than the months without snow regardless of the season, 3.55 compared to 3.1 fractures/day. There is significant difference in age distribution during the year, regardless the season or month ($P>0.005$).
Conclusion
We observe a slight decrease in incidence of hip fracture from spring to autumn, this can be related to a decrease in neuromuscular function in vitamin D-replete subjects, we need further studies to correlate this effect. We didn't observe a difference in age distribution with the four classical seasons. The incidence of fractures/day during the snowy months was higher compared to the rest of the year.

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P481

Calcitonin response to calcium infusion test in patients with primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (PHPT) is disorder of one or more parathyroid glands, characterized by inadequately increased PTH secretion, almost always followed by hypercalcemia. Calcitonin, secreted by parafollicular C-cells in thyroid gland, is hypocalcemic hormone which partly acts as physiological antagonist of PTH.
Aim
To evaluate calcitonin response in calcium infusion test in patients with primary hyperparathyroidism.
Method
Study consisted of 15 patients with confirmed PHPT (57.20±11.38yrs) and 15 healthy subjects-HC (57.20±11.41yrs) matched for age and gender. In all subjects, basal levels of total serum calcium (Ca), ionized calcium (Ca^{2+}), phosphate (P), PTH levels were measured. Calcium infusion test (CIT) was performed in all subjects when ionized calcium, calcitonin and PTH were measured in −30, 0, 1, 2, 3, 5, 8, 10 min after calcium infusion. Statistical analysis included Spearman correlation, Student T test.
Results
Basal levels of Ca, Ca^{2+}, PTH were statistically significantly higher in PHPT group compared to HC (Ca:2.83±0.25 vs 2.41±0.06 mmol/l, Ca^{2+}:1.44±0.14 vs 1.16±0.04 mmol/l, PTH (128.20±91.76 vs 41.77±12.83 ng/l). There was no statistical difference in calcitonin levels between groups (6.60±3.94 vs 6.76±2.97 ng/l). In CIT, maximum increase of Ca^{2+} was registered in 1.minute in both groups. After calcium infusion, average maximum calcitonin levels were 20.42±11.40 ng in PHPT group in the 1.minute with gradual decrease up to 10.81±7.80 ng/l in 10.minute. In HC group average maximal levels of calcitonin were 38.89±24.51 ng/l in 2.minute with gradual decrease up to 21.74±9.52 ng/l in 10.minute.
Conclusion
We showed decreased response of calcitonin in calcium infusion test in patients with PHPT compared to healthy subjects. This is in accordance with some earlier studies. In chronic hypercalcemia, responsiveness of C-cells is decreased on acute increase of serum calcium levels. In PHPT there is up regulation of calcitonin secretion set-point, depending on calcium levels.

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P482

Effect of hyperparathyroidism on coagulation: an analysis by modified rotation thromboelastogram (ROTEM)

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Introduction
Parathyroid hormone (PTH) is a peptide-based hormone that controls the level of ionized calcium in blood and extracellular fluids. Hemostasis is regulated by the balance between natural stimulants and inhibitors on platelet functions. Disruption of the balance between inhibitor and stimulants leads to thrombosis or bleeding. There are studies on the association of hyperparathyroidism with thrombotic disease. Thromboelastography is a method of evaluating the whole process of coagulation from the beginning of the clot formation to fibrinolysis. By measuring the viscoelasticity of blood clots by thromboelastography, we can provide information on the effect of various factors such as plasma factors, platelets and leukocytes in the whole stage of coagulation and fibrinolytic processes.
Material and methods:
Patients who were scheduled for operation due to hyperparathyroidism were included in the study. Thromboelastographic evaluation was performed in the hyperparathyroidic preoperative period and postoperative periods. 30 patients were planned to be included in our study who do not have hematologic, liver and kidney disease and without antiplatelet and anticoagulant use. We wanted to share the data of the first 7 patients as a preliminary evaluation, since the study was not completed and patient recruitment continued.
Results
The preoperative and post-operative thromboelastography results of the patients did not Show a statistical difference ($P>0.005$) (Table 1). There was not a correlation between calcium values and thromboelastogram results.
Conclusion
Since the data we have covers a limited number of patients, we anticipate that we will reach more detailed information upon completion of our study. In the light of the results we obtained in the preliminary evaluation, we believe that the data we will provide as a result of the study will provide motivation for further studies.

Table 1

	Mean ± Std. Dev.		
	Before	After	P*
ICT	190±32,5	256,71±52,19	0.09
ICFT	101,43±34,55	97,71±46,78	1.00
IMCF	60,86±4,67	64,71±10,03	0.25
ECT	82,14±4,98	69,57±40,34	0.61
ECFT	108,86±41,59	130,43±55,98	0.24
eMCF	63,43±5	67,57±7,59	0.18
Ca	11,40±0,52	9,00±0,33	0.018
Plt	235428,57±81985,48	265000,00±90432,295	0.138
PTH	472,15±57,10	42,30±1,83	0.018

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P483

Parathyroid hormone excess due to denosumab application and concomitant parathyroid adenoma with an atypical scintigraphic pattern- a case report

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Introduction
Primary hyperparathyroidism comprises one of the major causes of hypercalcaemia and is mostly due to solitary parathyroid adenoma. Denosumab is a novel antiresorptive agent for osteoporosis treatment and has been associated with a compensatory increase in PTH levels during the first months after injection, a fact that may interfere in the diagnostic procedures when dealing with concomitant small parathyroid adenomas without standard scintigraphic pattern.
Case report
A 60-year old female patient with postmenopausal osteoporosis presented for evaluation due to PTH-excess (354.4 pg/ml) and serum calcium at the upper reference range (9.8 mg/dl). The patient had been under 3-year denosumab treatment and had received the last injection 2 months ago. The neck ultrasound revealed a hypoechoic lesion below the right thyroid lobe, the adjunctive ^{99m}Tc-sestamibi scintigraphy turned however non-suggestive for parathyroid adenoma. A novel PTH estimation at 4 months showed considerable PTH decline (86.3 pg/ml) with synchronous 25 OH-D3 insufficiency and persistent normocalcaemia. Therefore, a conservative follow-up was initially decided, presuming that denosumab was responsible for the initial PTH excess in combination with 25OH-D3 insufficiency. The biochemical reassessment at 6 months and after denosumab withdrawal revealed only marginal hyperparathyroidism (72.5 pg/ml). However, mild hypercalcaemia manifested during the following 3 months with relapse of hyperparathyroidism despite accomplishment of 25OH-D3 sufficiency. A second ^{99m}Tc-sestamibi scintigraphy was performed, showing intense tracer retention at the inferior pole of the right thyroid lobe at the early phase and a normal washout at the late phase, therefore raising suspicion of a small parathyroid adenoma either rich in p-glycoprotein or poor in oxyphylic cells. A possible hyperfunctioning thyroid lesion at this anatomic position was excluded by ^{99m}Tc-pertechnate-thyroid scintigraphy. 1 month later and because of persistent hyperparathyroidism and hypercalcaemia with new-onset hypercalciuria a third ^{99m}Tc-sestamibi scintigraphy was conducted for validation. The test suggested presence of a right inferior parathyroid adenoma, thus correlating with the neck ultrasound. The patient underwent right inferior parathyroidectomy. PTH and calcium levels normalized directly intraoperatively. The histopathological analysis confirmed the diagnosis of a small parathyroid adenoma, consisted exclusively of chief cells.

Conclusion
Denosumab may cause PTH elevation, sustainable months after its application. This phenomenon may cause misinterpretation of the laboratory tests and delay definitive diagnosis of primary hyperparathyroidism due to small parathyroid adenomas without standard scintigraphic pattern. Therefore, a careful patient follow-up is required, as well as a possible imaging reassessment in order to detect the underlying cause of PTH excess.

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P484

Bone mineral density and 10-year probability of fractures in type 2 diabetic patients with different vitamin D status

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Objective(s)
Last data showed advantages of TBS assessment of bone quality over BMD in patients with type 2 diabetes (T2D). We perform DXA in patients with T2D and calculated 10-year probability of fracture using FRAX® tool.
Material and methods
A total of 252 (172 females) T2D patients aged 36 to 86 y.o (mean 61.0 ± 8.8) were examined. BMD was performed in 124 patients (110 females) using DXA (Lunar Prodigy, USA). BMD adjusted for TBS was calculated for 33 patients (10 male). Serum 25(OH)D (immunoassay) and iPTH (ELISA) levels assessed in 70 patients, HbA1c was determined by standard method.
Results
The study results showed that normal BMI had 20 (7.9%) patients, while 232 (92.1%) were overweight/obese. Mean HbA1c was 8.8 ± 1.7%, diabetes duration was 1–30 years (13.1 ± 6.4). More than 50% diabetic subjects were treated by insulin or in combination with antihyperglycemic drugs. Serum 25(OH)D level was between 7.5 and 44.5 ng/ml (22.7 ± 9.4). Normal vitamin D status had 22.9%, 77.1% were insufficient/deficient. Negative correlation was found between 25(OH)D and iPTH ($r = -0.37$, $P = 0.002$). We did not find association between 25(OH)D and glycemic control (HbA1c). Twenty four (9.5%) patients had fractures in their medical history, 31.5% patients had low BMD. BMD in patients with or without fractures was the same. 10-year probability of fractures calculation showed major osteoporotic fracture risk was from 0.4 to 24.0% (6.9 ± 3.8) and hip fracture risk – from 0 to 15.0% (0.9 ± 1.5). Fracture risk was associated with age ($r = 0.40$, $P = 0.0001$) and BMI ($r = -0.20$, $P = 0.001$), and didn't associate with diabetes duration and type of medications, HbA1c, 25(OH)D or iPTH levels. TBS was from 1.02 to 1.53 (mean 1.28 ± 0.1). Twenty two (66.7%) patients, including 5 men, had BMD lower than 1.35 g/cm^2. DXA results showed decreased BMD only in 10 diabetic patients, while using TBS data 22 of diabetic patients had impaired bone quality. FRAX score showed that 10-year probability of hip fracture or major osteoporotic fracture risks did not clinically differ (0.8% & 0.6%; 8.5% & 7.4%) when we used or did not use TBS.
Conclusion(s)
Study results showed that patients with T2D had obesity, low serum 25(OH)D level and normal BMD in most cases. BMD in patients with or without fractures did not differ. Using BMD adjusted for TBS identified decreased bone quality in sixty seven percent of T2D patients.

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P485

Life threatening 'hypocalcaemia' secondary to proton pump inhibitor induced 'functional hypoparathyroidism'

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Introduction
Common causes of generalised seizures are epilepsy, meningitis, head injury and hypoglycaemia. But this is an unusual presentation of generalised seizures secondary to hypocalcaemia due to prolonged use of PPI's. PPI's are amongst the most commonly prescribed drugs due to their effective medicinal profile. They are generally well tolerated, however, are now increasingly reported to be associated with adverse effects. There has been some discrepancy about whether or not it causes electrolyte imbalance, but the goal of this presentation is to identify that prolonged use of PPI's particularly in elderly patients, is associated with hypomagnesemia which in turn can induce hypocalcaemia by impairing the secretion and action of Parathyroid hormone.
Case details
Our case is a 73 year old gentleman, who presented to Emergency department with generalised seizure which was refractory to treatment. He was intubated and sedated. Venous blood gas showed very low level of calcium. Electrolyte profile confirmed low magnesium (0.23 mmol), low calcium (1.61 mmol), low potassium (2.6 mmol) and high phosphate of (1.7 mmol). He was given intravenous calcium, potassium and magnesium and the electrolytes were quickly reversed. He had low/normal PTH which was clearly inappropriate for the severe hypocalcaemia. He was extubated and moved to endocrine ward. Replacements were continued over next three days to maintain the electrolyte profile. Brain imaging and LP was normal. However he continued to become Hypocalcaemic. It was identified that he was taking Omeprazole for a long time and none of the other medications he was taking are known to cause hypocalcaemia. Omeprazole was immediately stopped and serial calcium and magnesium levels became stable. He was discharged on magnesium and calcium supplements along with Alfacalcidol to augment the calcium absorption. A repeat set of bloods was done one month later and all electrolytes, Vitamin D and PTH levels were normal.
Conclusion
The goal of this presentation is to correlate the use of PPI, severely low magnesium levels, subsequent profound hypocalcaemia, patient age, personal idiosyncrasy and the effect of stopping the culprit drug and quick reversal of electrolyte imbalance. Where most of the reported cases were found to have mild-moderate electrolyte changes with myalgia and paresthesias, our case was unique in the presentation being life threatening with generalised seizures and refractory to treatment initially. But effective replacement of electrolytes and timely identification of the cause saved the patients life and we avoided any long term adversities for the patient.

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P486

Dynamic thiol/disulfide homeostasis and oxidant status in patients with hypoparathyroidism

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Purpose
In this study, we aimed at determining the dynamic thiol/disulfide homeostasis and oxidant balance, and investigating the relation of these parameters to the severity of the disease and the serum calcium levels.
Material and method
55 patients with iatrogenic hypoparathyroidism follow-ups, and 40 healthy volunteers were included in the study. The blood dynamic thiol/sulfide balance, Total Antioxidant Status (TAS), Total Oxidant Status (TOS), Paraoxonase Enzyme Activity (PON) levels were measured in serum samples.
Findings
In our study, it was found that the disulfide, disulfide/native thiol, disulfide/total thiol levels were higher in the hypoparathyroidism group. A negative correlation was found between 25 hydroxy vitamin D (25 – OH vitamin D) and disulfide, disulfide/native thiol and disulfide/total thiol, and a positive correlation was found between native thiol and total thiol ratio; and the corrected calcium levels and PON levels were negatively correlated.
Discussion
Consequently, a change in favor of disulfide was found in the dynamic thiol disulfide homeostasis in the hypoparathyroidism group in our study.

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P487

Hypercalcaemia: hypervitaminosis D or not ?

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Abstract
The most commonly used techniques to measure vitamin D are automated immunoassays, which are known to be affected by interferences, especially from immunoglobulins present in the patient's serum. We present a case of a patient with IgA myeloma in whom interference with the vitamin D assay was identified. An 76-year-old male, known to have: ischemic heart disease, atrial fibrillation, COPD, type 2 Diabetes Mellitus and hypertension was referred to the Endocrinology team with symptoms that included low back pain, weight loss of 8 kilograms over one month and hypercalcaemia [adjusted calcium 2.78]. He was found to have a high concentration of 25-OH vitamin D [$>$389 nmol/l] without any signs of vitamin D toxicity. He was not taking vitamin D supplements or any other multivitamin preparation and had minimal sun exposure. The initial and subsequent samples run by the ARCHITECT 25-OH vitamin D assay (chemiluminescent microparticle immunoassay technology, Abbott Laboratories, Abbott Park, IL) showed a high concentration of 25-OH vitamin D of $>$389 nmol/l and $>$389 nmol/l, respectively. Further fresh samples taken for 25-OH vitamin D2 and 25-OH Vitamin D3 were analysed by tandem-mass spectrometry (MS/MS) showed results of $<$ 5 nmol/l and 17 nmol/l, respectively. Our patient had high concentrations of circulating IgA paraproteins [35.3 g/l] and heavy bone marrow infiltration. Paraproteins may interfere in the assay. In conclusion, we report a case of a patient with IgA myeloma with high concentrations of 25-OH vitamin D detected by the Abbott ARCHITECT, but not by a reference method (MS/MS). The most likely cause of the discordant results is interference in the immunoassay by the paraprotein. This is the only confirmed case of a high vitamin D due to myeloma paraprotein interference in our Health Board. Since this incident the review limits have changed and any result $>$200 nmol/l is now reviewed.

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P488

Primary hyperparathyroidism with ectopic mediastinal adenoma complicated with brown tumors

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Abstract
Brown tumors also known as osteitis fibrosa are a very rare complications of primary hyperparathyroism that occur in less than 2% of patients suffering from any form of hyperparathyroidism. Parathormone increases osteoclastic activity in the bones causing cystic bony changes, it's a reparative cellular process. Common sites of brown tumor are the ribs, clavicle, long bones and pelvic girdle. Our case is 55 years old tunisian men who was admitted to orthopedic department for bilateral knee pain evolving since 2 years. On laboratory analysis a primary hyperparathroidism was discovered, the analysis showed a malignant hypercalcemia (Ca = 3.3 mmol/l), hyperparathyroidism (PTH = 848 pg/ml), hypophosphatemia (P = 0.75 mmol/l). Cervical echography didn't show any parathroid adenoma. The cervico-thoracic scan showed a retrosternal adenoma compatible with un ectopic parathyroid adenoma. Bone scintigraphy showed multiple bone lesions of sternum, costs, left humerus and right femur evoking brown tumors. Our patient had an adenomectomy and the histopathological examination showed a 3 cm benign parathyroid hyperplasia. Our patient had a post surgical symptomatic hypocalcemia (ca = 1.87 mmol/l), he received a calcium intraveinous supplementation then a standard vitamin D analogues and calcium treatment.

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P489

Pregnancy, pancreatitis and hypoglycemia: Difficult management options in a case with MEN-1

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Abstract
A 32-year-old lady presented to us at 6 months of gestation with parathyroid hormone (PTH) -dependent hypercalcemia mediated pancreatitis and endogenous insulin dependent hypoglycemia, owing to parathyroid adenoma and possibly insulinoma, respectively. The parathyroid adenoma was localized on the MRI of the neck; however, no imaging for the insulinoma could be done due to the gravid state. Due to the simultaneous occurrence of tumors in two endocrine glands, namely, parathyroid gland and pancreatic islet cells, a diagnosis of MEN-1 (Multiple Endocrine Neoplasia) was considered. MEN-1 syndrome is very rarely seen in pregnancy. Owing to this rarity, no guidelines exist on management of MEN-1 during pregnancy. Our index patient was effectively managed with cinacalcet, alcohol ablation of parathyroid adenoma for hypercalcemia and with short and long acting octreotide for hypoglycemia during the antenatal period. She had a full-term LSCS delivery, with no maternal or neonatal complications, except for transient neonatal hypoglycemia. MEN-1 with pregnancy thus poses a diagnostic and therapeutic challenge and our case highlights the role of multimodal medical therapy for successful management.

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P490

Hyperparathyroidism – jaw tumor syndrome – differential diagnostic traps

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Introduction
Hyperparathyroidism-Jaw Tumor (HPT-JT) syndrome is a rare genetic disorder bearing a germline and a somatic CDC73 mutation. The features of HPT-JT are clinically difficult to ascertain because the parathyroid disease, ossifying fibroma in the jaw and other abnormalities, often occurs asynchronously and may be diagnosed and treated separately. The association of jaw ossifying fibroma with primary hyperparathyroidism (PHPT) is typical of HPT-JT.
Case report
V.D., a patient of 18 years old, childbearing confinement after birth, is hospitalized for a newly installed tumor located in the higher buccal vestibule, relatively well-defined, elastic, painless, with the deformation of the right genian region; it was observed five months ago, with volume increases during pregnancy. Morphological features correspond to a central granuloma giant cells. The blood tests reveal calcium and parathormone over the upper limit. The patient was operated in two times for a right parathyroid adenoma at the posterior thyroid pole and respectively for a left inferior parathyroid adenoma. A genetic examination was performed, but the HRPT2 gene could not be dosed. The phospho-calcic profile improved postoperatively, with diminished jaw tumor size and consistency. The diagnosis between brown tumor and jaw tumor syndrome is difficult to achieve; no anatomopathological elements were suggesting parathyroid cancer and also the CDC 73 gene may be absent in some patients. Young patient's age at diagnosis, recurrent parathyroid and jaw lesions should rise the possibility of HPT-JT syndrome. In January 2019, the patient is getting pregnant again; she is hospitalized in our clinic for an aggressive increase in the jaw tumor, at 12 weeks of pregnancy. There are no data in the literature about the increased risk of hyperparathyroidism or jaw tumor relapse during pregnancy, and therapeutic abortion is not recommended. The existence of estrogen or progesterone receptors at the maxillary tumor level was infirmed. Clinically and biologically there are no inflammation markers or inflammation signs, and phosphor-calcic balance is reasonable. Subsequently, in one week a dental abscess was diagnosed and treated at the jaw tumor level.
Conclusions
Clinical evolution, pathological history of hyperparathyroidism may be trapped in the differential diagnosis, and require increased attention, additional investigations to make the right medical decision.
Keywords: primary hyperparathyroidism, maxillar tumor, parathyroid adenoma
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P491

Rickets in a patient with melnick needles syndrome

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Introduction
Melnick Needles Syndrome corresponds to a rare skeletal dysplasia of genetic etiology, with dominant inheritance pattern attached to the X chromosome. Mutations related to the gene of filamina A, which is responsible for the synthesis of collagen, are responsible for the clinical and phenotypic manifestations of the disease, with predominantly female involvement. Rickets are caused by inadequate mineralization of the bone, which precedes the closure of the epiphyseal plaque. Of varied etiologies, clinical signs and symptoms refer to

hypocalcemia and/or hypophosphatemia, and their respective complications, requiring individualized treatment. This case report exposes a patient attending Melnick Needles syndrome and rickets.
Methods
Patient 14 years old, referred by pediatrics at age 13 due to symptomatic hypocalcemia, with paresthesias, and radiological exams with signs of osteopenia and low bone mineral density. History of respiratory distress at birth and marked delays in neuropsychomotor development. Karyotype 46, XX. Non-consanguineous parents, and no relevant pathologies. It presents a marked short stature (height inferior to P3), small face with hypoplasia of the middle part, proptosis, ocular hypertelorism, micrognathia, brachydactyly, genu varum, and other characteristic syndromic findings, allowing the diagnosis of Melnick Needles Syndrome by the geneticist at 8 years of age. age. She was followed in pediatrics because of the short stature, but she was not a candidate for GH therapy. Menarche at age 12, following with usual menstrual cycles. At initial physical examination, the signs of Chvostek and Trousseau were negative.
Results
Initial exams revealed hypocalcemia, hypophosphatemia and elevation of parathyroid hormone and serum alkaline phosphatase. It presents radiographs of long bones with severe bone demineralization, enlargement of metaphyses and small fractures with solution of continuity in the medial region of the femurs. In prospective research, reduced values of 25-hydroxyvitamin D and high levels of 1,25-dihydroxyvitamin D were identified. Treatment was implemented with cholecalciferol 7,000 UI/week, calcitriol 0.25 mcg 4 times a day, and phosphorus.
Conclusions
This is a picture compatible with rickets in a patient with Melnick Needles Syndrome. This association was not previously described, not allowing the establishment of a causal relationship between diseases.
Keywords: Melnick Needles Syndrome; rickets.

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P492

Hyperparathyroidism in patients with X-linked hypophosphatemia

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Background
X-linked hypophosphatemia (XLH) is a rachitic disorder characterized by renal tubular phosphate wasting resulting from increased circulating activity of the fibroblast growth factor FGF23. Secondary and tertiary hyperparathyroidism have been reported in XLH patients in small retrospective studies, however this complication has never been systematically evaluated in a large cohort.
Aim of the study
To compare parathyroid function of adult XLH patients with healthy subjects and to describe the prevalence and clinical presentation of hyperparathyroidism.
Methods
We conducted a prospective observational case-control study (CNIL 2171036 v 0) in a single tertiary referral center. Each XLH patients was compared to two healthy volunteers matched for sex, age and plasma 25-OH vitamin D concentrations. Healthy volunteers were selected among participants of the 'VARIETE' trial (NCT01831648). Univariable linear regression analysis was performed to define parameters influencing PTH concentrations in this population. Data are expressed as median and interquartile range (IQR).
Results
68 patients (51 women and 17 men) were recruited and matched with 136 healthy volunteers. Phosphatemia was significantly lower in XLH patients than in healthy controls (0.57 mmol/l, IQR 0.50-0.64 *vs* 1.11 mmol/l, IQR 1.03–1.21, $P<0.0001$). Calcemia was similar in both groups. Patients had higher PTH levels compared to healthy controls (53.5 ng/l, IQR 36.7–72.7 *vs* 36 ng/l, IQR 27.7–44, $P<0.0001$). Seventeen out of the 68 (25%) patients had a PTH concentration above the upper limit of the normal range. FGF23 concentrations were higher in patients than in controls ($P<0.0001$), whereas $1,25(OH)_2D$ concentrations were comparable. In patients, linear regression analysis showed an unexpected positive relationship between PTH and serum calcium concentrations ($R^2=0.1238$, $P=0.0033$) and a negative relationship between PTH and serum phosphate concentrations ($R^2=0.0575$, $P=0.0489$). Eight of the 68 (12%) patients (40 years, IQR 30–53) presented with autonomous hypercalcemic hyperparathyroidism, associated with nephrocalcinosis in two patients and osteoporosis in two patients. All underwent surgery with cervical exploration; four presented with a single parathyroid adenoma and four with hyperplasia. After parathyroidectomy, serum calcium concentrations decreased (2.20 mmol/l, IQR 2.15–2.27 *vs* 2.55 mmol/l, IQR 2.50–2.60) and phosphate concentrations increased (0.54 mmol/l, IQR 0.46–0.64 *vs* 0.47 mmol/l, 0.42–0.51).
Conclusion
Secondary hyperparathyroidism with disrupted physiological regulation of parathyroid function is frequent in adult XLH patients. Young-onset hypercalcemic hyperparathyroidism, resulting from parathyroid adenomas or hyperplasia, worsens hypophosphatemia and leads to renal and skeletal complications.
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P493

Hypocalcemic cardiomyopathy: a reversible entity?

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Introduction
Hypocalcaemia is a rare and potentially reversible cause of cardiomyopathy. Restoration to normal serum calcium levels usually leads to rapid improvement of cardiac function.
Case report
A 42-year-old woman with a history of total thyroidectomy, due to large nodular goiter in 2016, and acute pos-operative hypoparathyroidism, assumed to be transient, with no supplementation since early 2017. In September 2018 she was admitted due to acute cardiac failure, bronchospasm and retrosternal discomfort. At presentation, she also referred circumoral paraesthesia's, generalized muscular weakness and muscle spasms since the previous week. Chest radiograph showed mild cardiomegaly with signs of pulmonary congestion; prolonged QT-interval and some ST segment depression in V4-V6 on ECG; akinesia in left ventricular septum and apex with moderate-to-severe global left ventricular dysfunction on transthoracic echocardiography. Laboratory tests revealed severe hypocalcaemia (serum ionized calcium of 0.77 mmol/l; reference 1.13–1.32) with hyperphosphatemia (1.89 mmol/l; reference 0.87–1.45) and an inappropriately 'normal' PTH (18.9 pg/ml; reference 15–65). Treatment was immediately initiated with intravenous calcium and active vitamin D supplementation with a quick and positive clinical response. Left ventricular function was fully recovered after restoration of normal plasma calcium levels. At last clinical reassessment, she was asymptomatic with corrected total serum calcium level of 2.39 mmol/l (reference 2.10–2.65) and phosphorus level of 1.31 mmol/ (reference 0.87–1.45), under supplementation with 3 g of elemental calcium and 1 mcg of calcitriol.
Conclusion
This case report highlights the importance of considering hypocalcaemia as a potentially reversible cause of severe cardiac dysfunction. Surgical hypoparathyroidism usually occurs within few days after surgery but it can remain subclinical during several years, being only recognized later during acute exacerbation events.
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P494

Multiglandular parathyroid disease in patients with primary hyperparathyroidism and inconclusive conventional imaging

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Abstract
The incidence of multiglandular parathyroid disease (MGD) varies in the range 7–33%. Negative preoperative imaging is a strong predictor of MGD in patients

with primary hyperparathyroidism (PHPT). We retrospectively evaluated a cohort of 13 patients with PHPT and inconclusive MIBI scintigraphy and/or neck ultrasound (mean age 64 years, total calcium 2.74 mmol/l and parathyroid hormone (PTH) 114 ng/l). All subjects subsequently underwent additional imaging with flurocholine PET/CT (FCH) prior to surgery. In 10 of 13 patients a single parathyroid adenoma or hyperplasia were found whereas 3 patients had MGD (23%). In one patient with negative MIBI and ultrasound FCH showed three active foci. Two enlarged parathyroid glands were found at surgery (one oxyphil hyperplasia and one chief cell adenoma). In two patients a single enlarged parathyroid gland was excised. Histopathology confirmed one chief cell adenoma and one hyperplastic gland. In both cases hypercalcemia, however, persisted. After FCH imaging both patients underwent a successful reoperation of the second enlarged gland (one hyperplasia and one chief cell adenoma). In conclusion, sporadic MGD was present in 3 of 13 patients with PHPT and inconclusive conventional imaging. Two subjects with MGD had to undergo the second neck surgery for persistent hypercalcemia. Interestingly, the excision of a single pathologically enlarged parathyroid gland did not change their calcium and PTH in comparison with preoperative levels. These two enlarged parathyroid glands were not probably hypersecreting and functional. The question how the additional enlarged parathyroid glands contribute to a clinical picture of PHPT in patients with sporadic MGD remains to be elucidated.

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P495

Acute pancreatitis, caused by parathyroid gland adenoma: A case report

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Abstract
Parathyroid gland adenoma is benign, PTH-secreting tumour, which leads to primary hyperparathyroidism. Congenital hyperparathyroidism may occur without any other symptoms, on it's own, but often is part of MEN1 or MEN2 syndromes. PTH activates osteoclasts, that resorbs calcium from bone and brings calcium to blood serum. Also PTH also induces calcium reabsorption from kidney tubules band and blocks excretion of phosphates. Long time PTH secreting adenoma shows no clinical signs, often adenoma is diagnosed only when complications are present. We describe the case of a patient who had parathyroid gland adenoma, that manifested like acute pancreatitis. 58 y/o female applied to the family doctor for weakness, abdominal pain, nausea, vomiting. After eveluation of primary blood tests, hypercalcemia, elevated PTH levels were present, more diagnostic tests were performed. Parathyroid gland adenonoma was found in left lobe and a left inferior parathyroidectomia was performed. After operation, patients calcium and PTH levels normalized. Investigating patients with gastrointestinal tract pathology, especially those, who have acute pancreatitis, without anamnesis of other, more common causes (eg. alcoholism, gallstones etc.) calcium test should be considered, becouse primary hyperparathyroidism may manifest as acute pancreatitis.

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P496

A new and effective treatment option for challenging chronic hypoparathyroidism cases: Alternate-day dosing regimen

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Objective
In chronic hypoparathyroidism, conventional therapy consists of oral calcium supplements and active vitamin D analogs but some patients cannot achieve treatment goals despite the high dose of oral calcium supplementation. Therefore, parathyroid gland transplantation and recombinant human PTH have been investigating as new therapeutic options. Calcium absorption from intestinal cells occurs by transcellular path and paracellular path. Transcellular absorption occurs through transient receptor potential vanilloid type6 (TRPV6) receptors and is saturable due to oral calcium intake. Paracellular absorption is non-saturable but very slow and limited. Alternate-day oral calcium intake may upregulate TRPV6 receptors. The objective of this study was to investigate the effectiveness of alternate-day oral calcium intake in patients with challenging chronic hypoparathyroidism.
Methods
In this retrospective study, we evaluated 66 patients with chronic hypoparathyroidism admitted to our hospital within the last 2 years. 14 patients (who received $\geq$2000 mg/day daily calcium carbonate or who admitted to the emergency department at least once in the last 3 months for hypocalcemia) were switched to the alternate-day dosing regimen (ADR) (patients used oral calcium carbonate every other day), and data of these patients were analyzed retrospectively.
Results
All of the patients were female. Median age was 41.5 (19–63) years and median duration of disease was 70 (6–228) months. Two patients were using teriparatide. Before ADR; oral calcium intake was 3750 (2000–8000) mg/day, oral calcitriol intake was 0.88 (0.5–3)mcg/day, serum calcium level was 7.71 (7.1–8.7) mg/dL, serum phosphate level was 5.35 (3–6.5) mg/dL and 24-hour urine calcium level was 165 (22.5–331) mg/day. After ADR; oral calcium intake was 1500 (1000–2500) mg/day, oral calcitriol intake was 0.88 (0.5–2) mcg/day, serum calcium level was 8.25 (7.7–9.3) mg/dL, serum phosphate level was 5 (4–5.9) mg/dL, and 24-hour urine calcium level was 210.5 (21–564) mg/day. After ADR, oral calcium intake was decreased and serum calcium level was increased significantly ($P=0.001$ and $P=0.001$ respectively). Two patients did not need teriparatide after ADR and teriparatide treatment was stopped. Three patients were in parathyroid gland transplantation queue and all of them came out from the waitlist with their own request. The number of the emergency department visits in 3-month-period before ADR was 21 and it was decreased to 2, in 3-month-period after ADR ($P=0.02$).
Conclusion
Patients with challenging hypoparathyroidism can be controlled in a cheaper, more comfortable and more effective manner with ADR.

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P497

Reversible heart disease in iatrogenic hypoparathyroidism

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Introduction
Dilated cardiomyopathy (DCMP) is a serious and rare complication of unrecognized chronic hypocalcemia, whose etiologies are dominated by hypoparathyroidism. The peculiarity of this DCMP is due to the fact that it is reversible to different degrees after the correction of hypocalcemia. Its incidence is rare because of the early management of any hypocalcemia. The objective of our work is to highlight the interest of screening and treatment of postoperative hypoparathyroidism to avoid DCMP.
Observation
A 62-year-old patient having a history of thyroidectomy 5 years ago receiving 100ug per day of levothyroxine, history revealed dyspnea with tingling and tetany crisis. On examination, his blood pressure was 130/70 mmHg with negative Chvostek and Trousseau sign. The electrocardiogram showed a regular sinus rhythm, a complete left branch block and an extended QT interval. His transthoracic ultrasound showed dilated cardiomyopathy, global hypokinesia, and systolic dysfunction with a 20% ejection fraction. In the biological assessment we note: hypocalcemia at 50 mg/l, hyperphosphoremia at 109 mg/l, serum sodium concentration at 140 mmol/l, serum potassium at 3.9 mmol/l and TSH at 17 mIU/l. The patient was treated with intravenous calcium until the normalization of serum calcium with oral relay and active vitamin D supplementation. For his heart failure, he was put on ACE inhibitor in combination with a diuretic. The evolution was marked by an improvement of the cardiac function and o systolic fraction ejection increased to 55%.
Conclusion
Hypokinetic dilated cardiomyopathy is a rare but serious complication of hypocalcemia, which emphasizes the importance of routine phosphocalcic monitoring after thyroid surgery, and the prescription of vitamin and calcium substitution if needed. Its management is based on calcium and active vitamin D substitution, with close cardiological monitoring. Its evolution is marked by the more or less complete regression of heart failure.

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P498

Bilateral femoral fractures in a pacient with primary hyperparathyroidism: A case report

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Introduction
Primary hyperparathyroidism (PHPT) is a common endocrine disorder often diagnosed in asymptomatic individuals on routine biochemical screening, which, if left untreated, can have devastating consequences. The main target organs of PTH are the skeletal system and the kidneys. Asymptomatic hypercalcaemia in young adults is uncommon, and patients who remain asymptomatic should be monitored for the development of complications that justify surgery.
Case report
We present a case of a 44-year-old man with bilateral femoral fractures with no previous history of trauma, admitted to the orthopaedic department, requiring surgical management. Initial laboratory testing showed a calcium level of 12.69 mg/dl (adjusted calcium: 13.3 mg/dl), phosphorus level of 3.77 mg/dl, magnesium level of 1.02 mg/dl, elevated alkaline phosphatase of 577 UI/L, and an elevated PTH of 2541 pg/ml. A large right side paratracheal solid mass measuring 3.4 cm was identified on a chest CT scan, multiple pancreatic and kidney calcifications and kidney stones on an abdominal CT scan. An ultrasound scan of the neck showed a right inferior lobe parathyroid adenoma, which was further confirmed by a Sesta MIBI scan. 24-hour calcium excretion was 204 mg/day and he also developed renal failure as a result of nephrocalcinosis. Biochemical testing for Multiple Endocrine Neoplasia types 1, 2 were negative. Surgical management was performed and after removing the right inferior adenoma, the PTH marked a decrease from the initial value to 28.35 pg/ml, however, the patient developed hungry bones syndrome and needed prolonged intravenous calcium.
Conclusions
This case highlights the importance of early detection and management of hyperparathyroidism with the aim of preventing long-term complications. This young man, probably had hyperparathyroidism for a long-time undetected which has resulted in these severe complications. The orthopaedic and renal complications of hyperparathyroidism could have been avoided with early detection and treatment of the hyperparathyroidism.
Keywords: Pathologic fractures, nephrocalcinosis, parathyroid adenoma, Primary Hyperparathyroidism, serum calcium.

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P499

Uncommon cutaneous manifestation of primary hyperparathyroidism

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Introduction
Subcutaneous calcinosis are deposits of hydroxyapatite crystals in the skin. They are hard masses, poorly organized, located most often in the dermis or hypodermis. They are secondary to either local tissue alterations or the penetration of calcium salts into the skin, or to an abnormal phosphocalcic metabolism but which remains an exceptional complication in case of primary hyperparathyroidism. We report the case of a patient admitted to the endocrinology department for chronic hypercalcemia whose clinical and para-clinical exploration reveals primary hyperparathyroidism with subcutaneous calcinosis.
Observation
A 27-year-old female patient, was admitted in our department for etiological assessment of chronic hypercalcemia with a pathological fracture of the right femur and acute renal failure. Clinical examination found subcutaneous hard, painless, non-inflammatory nodules at the 2 elbows and at the lower gum. The elbow radiography showed radiopaque structures in favor of subcutaneous calcinosis. The etiological investigations of hypercalcemia was in favor of primary hyperparathyroidism. The evolution was marked by the decrease of the size then the disappearance of the lesions after normalization of the phosphocalcic balance after a symptomatic treatment.
Discussion
Subcutaneous calcinosis is rarely reported in primary hyperparathyroidism. Indeed, hyperphosphoremia is the main factor involved in the development of these subcutaneous calcinosis in the context of phosphocalcic disturbances, regardless of the level of hypercalcemia. Lesions tend to resolve spontaneously when calcium and phosphate levels normalize.
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P500

Body mass index is a biomarker of resistance to active vitamin D but not to calcium supplementation, in patients with hypoparathyroidism

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Background
Persistent Hypoparathyroidism (PH) is a condition characterized by inappropriately low concentrations of PTH that lead to hypocalcemia. The treatment cornerstones of PH are calcium and calcitriol supplementation; however, several patients do not achieve adequate control of the disease under this conventional therapy. Notably, no biomarker of risk of 'resistance' has yet been identified. Based on the fact that obesity alters the vitamin D-calcium homeostasis, inducing hypovitaminosis D and secondary hyperparathyroidism, and that body mass index (BMI) is inversely correlated with circulating levels of vitamin D (VD), we hypothesized that increased BMI could represent a biomarker of resistance to conventional therapy in PH.
Methods
To test our hypothesis we retrospectively evaluated the anthropometric characteristics assessed at PH diagnosis, in 84 consecutive patients (79 with post-surgical, 5 with autoimmune PH). All patients were followed for at least one year, and were under stable conventional treatment with active vitamin D analog and calcium from at least six months. In keeping with recent literature, patients were defined as resistant to calcitriol, if taking $\geq$1 µg calcitriol/day; and resistant to calcium, if taking $\geq$1500 mg calcium/day.
Results
We found that BMI was higher in VD resistant patients when compared to VD sensitive (28$\pm$5 vs 25$\pm$5 kg/m^2, $P<0.02$). In contrast, we found no difference in BMI between calcium resistant and calcium sensitive patients (28$\pm$6 vs 26$\pm$5 kg/m^2, P=NS). Furthermore, logistic regression analysis showed that BMI was independently associated with resistance to VD therapy (OR 1.13, 95% CI 1.02–1.26; $P=0.02$), in face of similar serum calcium levels obtained by therapy (8.7 vs 8.9 mg/dl, P=NS). Conversely, logistic regression analysis did not show any association between BMI and resistance to calcium therapy.
Discussion
This is the first study showing that increased BMI at diagnosis can predict the amount of active VD supplementation, but not the amount of calcium supplementation, in PH. The fact that obesity is associated with active VD resistance, but not with calcium resistance, on the one hand, supports previous evidences on a role of excess adipose tissue in the alteration of VD metabolism; and on the other hand, suggests that obesity does not impair calcium absorption and handling, and that patients on high calcium supplementation do not have lower BMI, as previously proposed. Hence, our work proposes BMI as a biomarker of resistance to active VD therapy in PH; and proposes weight loss as a therapeutic strategy to reduce resistance to active VD.
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P501

A man with maxillary swelling and tertiary hyperparathyroidism

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Introduction
Tertiary hyperparathyroidism can be developed in cases of persistent or non-curable secondary hyperparathyroidism or in any other case of long-standing hypocalcemia that leads to the autonomous function of at least one parathyroid gland. We present a case of a man with tertiary hyperparathyroidism and excessive maxilla swelling and extensive bone lesions.

Presentation
A 32 years old man, with chronic renal failure on dialysis for twelve years, referred to our department due to an elevated PTH and difficulty in mastication due to an excessive swelling of the maxilla gradually developed over a year. His tertiary hyperparathyroidism was known for five years, but he denied surgery and he was not compliant to cinacalcet treatment. On clinical examination he had an excessive maxilla swelling. Biochemical examination revealed: PTH = 4433 pg/ml, Ca = 10.7 mg/dl, P = 5.9 mg/dl, ALP = 631 U/L, 25(OH) D3 = 3 ng/ml, β-Crosslaps = 6148 pg/ml, TP1NP = > 10000 pg/ml. Plain bone X-rays showed: salt-and-pepper skull, bone erosions and absorption of distal phalanges and metacarpus of both hands, of the distal edge of the clavicle and of part of the periosteum of the humerus and radius. Generalized osteopenia and thickness of the periosteum of the humerus and femoral bone was also observed. CT head scan showed an abnormal texture, widening and periosteal absorption of both maxilla and mandible. Biopsy of the maxillary swelling showed findings compatible with brown tumour. The patient underwent near total parathyroidectomy and post surgery PTH levels were markedly decreased (PTH = 24.5 pg/ml).
Conclusion
Tertiary hyperparathyroidism may have a dramatic clinical outcome if it is left untreated. Brown tumours due to tertiary hyperparathyroidism are very rare and they demand careful investigation and great deal of suspicion for the diagnosis.

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P502

Evaluation of bone metabolism in women on aromatase-inhibitors before and after antiresorptive treatment

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Introduction
Adjuvant therapy with aromatase-inhibitors (AIs) increases bone loss and fracture risk. Concomitant antiresorptive treatment is currently recommended. The aim of this study was to evaluate the effects of AIs on bone metabolism and mineral density at 12 and 24 months.
Methods
Among 400 women on AIs who attended our Endocrinology Unit from 2014 to 2016, we retrospectively evaluated those who initially refused antiresorptive and took cholecalciferol supplements only. Laboratory parameters of bone metabolism were assessed before starting AIs, after 12 and 24 months. BMD was measured at baseline and after 24 months.
Results
A total of 54 women were selected. When starting AIs, age was 65 ± 9 years, menopausal age 50 ± 4 years, BMI 26.2 ± 4.1 kg/m^2. Sixteen had a normal BMD at DXA baseline measurement, 25 were osteopenic and 13 osteoporotic. Twelve months after starting AIs, 15 patients began bisphosphonates (BP), while the remaining 39 continued cholecalciferol supplements only, according to their choice. A BMD loss at both neck (−5.27%) and total hip (−4.24%) was observed in all patients on cholecalciferol supplements alone (P < 0,001), while spine BMD decrease (−3.14%) did not reach significance (P = 0.053). In the group starting BP at 12 months, 24-month BMD at both neck (−3.59%) and total hip (−3.27%) did not significantly change (P = 0.153 and P = 0.338), whereas spine BMD showed a significant decrease (−3.50%; P = 0.049). Considering the group taking cholecalciferol alone, univariate analysis was performed to evaluate if bone metabolism indexes after 12-month were predictive of BMD decline at 24 months for each DXA site. Percentage spine BMD loss was independently associated with CTX percent variation (P < 0.001) and BAP percent variation (P < 0.001). Percentage BMD loss at the femoral neck was independently associated with CTX percent variation (P < 0.021), PTH and 25OH vitamin D levels (P < 0.001 and P = 0.002, respectively). Percentage BMD loss at the total hip was independently associated with CTX percent variation (P = 0.006), PTH (P < 0.001) and 25OH vitamin levels (P = 0.002). On a multivariate analysis including spine, neck and total hip BMD along with bone metabolic parameters, only percent CTX change (P < 0.001) at 12 months was associated to spine BMD loss at 24 months (P = 0.002). Four new morphometric vertebral fractures were observed in the group on cholecalciferol supplements alone. No fractures were reported in the group starting BP 12 months after AIs.
Conclusions
Increase of bone turnover markers 12 months after starting AIs predicts BMD loss. Delayed antiresorptive treatment appears to be only partially effective in preserving BMD.

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P503

Discordance in biochemistry and ultrasonography: Nonsecretory parathyroid adenoma

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Aim
Although nonsecretory parathyroid carcinoma is relatively more frequent, nonsecretory parathyroid adenoma was also reported. It is thought to precede functioning parathyroid adenoma.
Case report
An iso-hypoechoic 6.5 × 9.5 × 16.1 mm thyroid nodule with irregular borders in the superior-posterior part of right thyroid lobe was observed in ultrasonography in a 44-year-old female euthyroid patient. Fine-needle aspiration (FNAB) biopsy resulted with non-diagnostic cytology (degeneration of follicular epithelial cells, colloidal material). A second FNAB was recommended but she admitted five years later. There was subclinical hypothyroidism with positive thyroid autoantibodies and normocalcemia in laboratory examination. The nodule in the superior-posterior part of right thyroid lobe was well circumscribed and hypoechoic with diameters of 5.4 × 13.2 × 18.1 mm. The ultrasonographical apperarence was found to be suspicous for an intrathyroidal parathyroid adenoma. Serum calcium was 8.99 mg/dL, albumin was 4.6 g/dL, parathyroid hormone was 70.22 pg/mL and 25-OH Vitamin D3 was: 6.52 ng/mL. Parathyroid hormone decreased to 37.94 pg/mL after replacement of vitamin D. The lesion was evaluated with FNAB and the cytological result was again nondiagnostic (small amount of colloidal material, a few epithelial cells). Parathyroid hormone washout was > 5000 pg/mL in fine-needle aspiration fluid. 24-hours urinary calcium excretion was 210 mg. In Tc99m-sestamibi SPECT/CT revealed persistent activity at superior-posterior part of upper pole of the right thyroid lobe. There was increased echogenity compatible with crystalloid in urinary system ultrasonography. Z score was within the expected range for age in bone mineral density. Surgical excision of the lesion was performed and a parathyroid adenoma was confirmed histopathologically.
Conclusion
Parathyroid hormone washout should be considered in a lesion with suspicion of intrathyroidal parathyroid adenoma even when primary hyperparathyroidism can not be shown biochemically. If surgery is not performed, patients should be followed for possible development of primary hyperparathyroidism.

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P504

Effect of zoledronic acid on trabecular bone score and other markers of bone health in heart transplanted patients

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Objective
Trabecular bone score (TBS) is associated with an increased risk of prevalent and incident fractures. It has a role of fracture assessment in secondary osteoporosis related to diabetes, acromegaly and hyperparathyroidism and in glucocorticoid-induced osteoporosis. However, it is understudied as a marker of bone health in heart transplanted patients. The aim of our pilot study was to evaluate the effects of zoledronic acid (ZA) on bone health including TBS in this population.
Materials and methods
We included 13 treatment naïve (TN) patients (9 men, 4 women) and 9 patients (8 men, 1 woman) who already received at least one application of ZA (TR). All patients received cholecalciferol, alfacalcidiol and calcium supplements. We measured TBS, bone mineral density (BMD), corrigated calcium (cCa), estimated glomerular filtration (eGF), c-terminal telopeptide (CTX), procollagen type I N propeptide (PINP), intact parathyroid hormone (iPTH).
Results
Groups were matched by age. Time from transplantation was 6.2 ± 5.4 months for TN and 76.1 ± 66.1 month for TR. In TR compared to TN, there were lower CTX 1151.9 ± 557.7 pmol/L; 2936.6 ± 1763.0 pmol/L; P < 0.009), lower Ca (2.11 ± 1.0 mmol/L; 2.24 ± 0.7 mmol/L; P < 0.002), and higher iPTH (83.6 ± 46.1 ng/L;

44.8±18.9 ng/L; $P<0.017$). There were no significant difference in TBS (1.285±0.08; 1.274±0.13), lumbar BMD (0.935±0.08 g/cm^2; 0.901±0.19 g/cm^2), neck BMD (0.681±0.09 g/cm^2; 0.731±0.14 g/cm^2), hip BMD (0.846±0.12 g/cm^2; 0.893±0.16 g/cm^2), T-score on lumbar (−1.4±0.7 SD; −1.6±1.8 SD), neck (−1.7±0.6 SD; −1.4±1.0 SD) and hip (−1.0±0.8 SD; −0.8±1.0 SD), PINP (39.39±13.53; 52.64±44.33), and eGF (76±14 mL/min/1.73 m^2; 70±18 mL/min/1.73 m^2), between TR and TN. No patients had fractures in the time of observation.

Conclusions

CTX was significantly lower in TR than in TN, whereas TBS and BMD were comparable between the groups. Lower CTX and lack of the differences in TBS and BMD despite the longer exposure to corticosteroid and immunosuppressive treatment in TR, imply a protective role of ZA on bone health after heart transplant. Ca was lower and iPTH was higher in patients treated with ZA, indicating that treatment with vitamin D and calcium should be more intensively tailored when patients receive ZA to prevent secondary hyperparathyroidism. The role of TBS in this population needs further investigation.

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P505

Impact of three doses of vitamin D on serum 25(OH)D parathyroid hormone in overweight and obese schoolchildren: A single blind randomized clinical trial

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Introduction

Trials on children and adolescents with excess weight are limited and lack parathyroid hormone (PTH) measures as a surrogate marker of vitaminD status in skeletal health. The present study addresses this key knowledge gap with the use of a dose-response randomized clinical trial (RCT) aimed at determining vitamin D requirement to increase 25(OH)D and suppress PTH concentrations in overweight and obese school children.

Methods

The current study was a single-blind RCT. A total of 378 children and adolescents, 6–13y of age, with age- and sex-specific body mass index (BMI) Z-score≥1 (WHO criteria) were recruited into the study. Participants were allocated to receive 600, 1000, and 2000 IU/d for 12 months. We measured dietary vitamin D, and serum 25(OH)D, PTH, calcium, phosphorus, and alkaline phosphatase at baseline, 6 and 12 months. In this intention-to-treat analysis, the intervention effect in dose level and overall time pattern, we fit a mixed effect model involving a random effect of participants within treatment groups and fixed effects of dose, time, and their interactions.

Results

Participants' mean(SD) age was 9.3(1.7) y; 52.3% were boys with BMI z scores of 2.55(0.73). The median (IQR) for 25(OH)D were 11.5(8.9), 11.7(10.5), 12.2(10.2) ng/mL at baseline and 23.1(8.0), 25.6(8.3), 28.6(10.4) ng/mL at the end of 12 months in 600, 1000, and 2000IU/d, respectively (P for group<0.0001; P for time<0.0001). Adjusting covariates did not change dose and time main effects ($P<0.0001$ and 0.021, respectively). Prevalence of vitamin D deficiency (<20 ng/mL) was 80.2, 77.5, and 75.5% in 600, 1000, and 2000 IU vitamin D daily at baseline, respectively, which returned to 34, 18.4, and 7.5% at the end of 12 months. The pattern of PTH response to 600 and 2000IU/d vitamin D was a slight increase at 6 months and a decrease at 12 months. The median (IQR) for PTH were 42.1(38.4), 38.8(29.9), 37.2(39.7) pg/mL at baseline and 44.9(20.5), 45.2(19.6), 43.9(20.8) at 12 months in 600, 1000, and 2000 IU vitamin D daily, respectively (P for group$=0.111$; P for time<0.0001). After adjusting covariates, time still had a significant main effect ($P=0.001$).

Conclusion

Children with excess weight benefited from daily supplementation of 1000 and 2000 IU/d compared with 600 IU/d in increasing 25(OH)D, but no evidence on suppression of PTH was found.

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P506

The relation between circulating levels of vitamin D and parathyroid hormone in children and adolescent with overweight or obesity: quest for a threshold

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Background and aim

The 25OHD concentration at which intact parathyroid hormone (iPTH) is maximally suppressed and below which PTH begins to rise (inflection point) has been used to define optimum 25OHD concentration. While it is not known if the lower 25OHD levels in obese children are associated with a PTH increase in the same manner as it is in normal weight children, we aimed to study the relation between circulating PTH and 25OHD levels and to search for a 25OHD threshold associated with a significant PTH increase.

Methods

This cross-sectional study was conducted on 198 boys and 178 girls aged ≥6 and ≤13 years with BMI ≥ 1SD (according to WHO criteria) recruited from primary schools of Tehran, the capital of Iran. Adjusted iPTH for BMI z-score, pubertal status, and dietary calcium intake were used. Restricted cubic splines showed a nonlinear relationship between iPTH and 25OHD concentration. Nonlinear regression was used to model the relationship between 25OHD and iPTH and identify a suppression point in 25OHD where iPTH reached a plateau and was maximally suppressed. Piecewise regression analysis models with a single knot for all possible values of 25OHD were fitted. The optimal threshold value was chosen based on adjusted R^2, the F statistic, model standard error, and the t value and associated P value for the threshold variable.

Result

The mean age(SD) of girls and boys was 9.3(SD) and 9.1(SD) years, respectively. Median 25OHD and iPTH were 13.8ng/mL and 38.9 pg/mL in boys and 9.9 ng/mL and 43.5 ng/mL in girls, respectively. The final equation in girls was: iPTH (pg/mL) $=43.91+59.41 \exp[(-0.188*25OHD]$. The point for near maximal suppression of iPTH by 25OHD for girls occurred at a 25OHD concentration of 20ng/mL (95% confidence interval: 28–48 ng/mL). No point of maximal suppression was found for boys. We also found a 25OHD threshold of 11 ng/mL for girls (f: 9.8) by linear piecewise regression modeling of adjusted iPTH. We noted a significant negative estimated slope above this threshold of 25OHD levels in girls ($\beta=-6.2$, 95% CI: −9.3 to −3.2). No significant inflection point for boys was observed.

Conclusion

In overweight/obese girls in this cohort, when the concentration of 25OHD was higher than 20 ng/mL, an iPTH mean plateau level was reached. When 25OHD concentrations approached 11 ng/mL, the slope in iPTH concentration accelerated.

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P507

Fahr syndrome revealing primary hypoparathyroidism: About two cases

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Introduction

Fahr's syndrome and primary hypoparathyroidism are two rare diseases. Fahr's syndrome is characterized by abnormal calcified deposits in basal ganglia and cerebral cortex and by the classic association with hypoparathyroidism. We report two cases of Fahr syndrome revealing an unknown primary hypoparathyroidism.

Observation 1

A 36 year-old man, with a history of schizophrenia and generalized tonic-clonic seizures since two years. He was admitted for severe hypocalcemia, which is symptomatic of tetany attacks, cramps and paresthesia with electrical abnormalities on the electrocardiogram. Cerebral scan showed calcifications in basal ganglia and cerebral cortex. The phosphocalcic assessment showed a hypocalcemia at 46 mg/L, a hyperphosphatemia at 89 mg/L and an intact parathyroid hormone level less than 0.1 µg/ml (8.7–79.6).

Observation 2
A 21 year old woman, with no particular pathological history, was admitted for severe hypocalcemia symptomatic of tetany attacks, signs of chronic hypocalcemia, complicated by the occurrence of a generalized tonic-clonic seizures. Cerebral MRI revealed calcifications in basal ganglia and cerebral cortex. The phosphocalcic assessment showed a hypocalcemia at 49 mg/L, a hyperphosphatemia at 87 mg/L and an intact parathyroid hormone level at 3 µg/ml (15–68). In both cases, the correction of hypocalcemia was initially made by administering calcium intravenously and then orally as well as taking alfacalciferol and neuroleptics. Which allowed a favorable evolution.
Conclusion/Discussion
Fahr's syndrome corresponds to mineral deposits in the blood vessel wall of the basal ganglia, it's a disease not well reported in the literature. These etiologies are dominated mainly by hypoparathyroidism. In the presence of neuropsychiatric manifestations associated with calcifications of the basal ganglia, it is imperative to look for phosphocalcic metabolic disorders, in order to detect hypoparathyroidism and thus adopt the most appropriate therapeutic measures.

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P508

Features of fractures in patients with types 2 diabetes mellitus

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In patients with type 2 diabetes mellitus (T2DM), the question of the magnitude of loss of BMD and the risk of fracture is discussed.
Objective
To study the relationship between the BMD deficiency in patients with type 2 diabetes with the risk of fracture of the distal radius.
Materials and methods
A comparative study of the loss of BMD in patients with fracture of the radial bone with type 2 diabetes mellitus and without diabetes mellitus was carried out. The study included 118 patients with type 2 diabetes mellitus and 175 patients not suffering from type 2 diabetes mellitus. The distribution by age in the groups was identical. The patients were sampled according to the city trauma clinic. The study included patients 50 years and older with a fracture of the distal forearm. All patients underwent X-ray densitometry on the DTX-200 device provided by Nicomed Takeda.
Results of the study
Depending on the magnitude of loss of BMD by T-test, patients were divided into 4 groups: 1 group, without loss of BMD; from 0 and above: 50.0% with T2DM; 19.4% without T2DM; 2 group - loss of BMD to - 1 SD: from 0 to −1.0: 15.3% with T2DM; 21.7% without T2DM; 3 group - loss of BMD from −1.0 to −2.5 SD: 19.0% with T2DM; 29.0% without T2DM; 4 group-loss exceeded −2.5 SD: 15.3% with T2DM; 29.7% without T2DM. As can be seen from the presented, in 65.3% of patients with T2DM low-energy fractures of the radial bone occur at normal or slightly decreased BMD values. While, in patients without diabetes mellitus, this loss is observed in 41.1%. Loss of BMD −2.5 SD and lower occurred in 15.3% of patients with type 2 diabetes mellitus and 29.7% without this pathology.
Conclusion
The obtained data give grounds to believe that in the case of type 2 diabetes in most patients, the leading factor in reducing bone strength and fracture risk is not a loss of BMD, but a violation of its quality due to a decrease in the intensity of remodeling and accumulation of the 'old' hypermineralized bone.

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P509

Association between 25 hydroxyvitamin D levels and insulin resistance in a cohort of obese subjects

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Objetive
Obesity is associated with lower serum vitamin D ($25(OH)D_3$) levels through several mechanisms. The aim of the study was to determine the prevalence of vitamin D deficiency and to examine the association between insulin resistance and $25(OH)D_3$ levels in a cohort of obese subjects.
Materials and methods
85 obese subjects were enrolled into the study from october to december 2018. Demographic, anthropometric and clinical parameters were assessed. Serum fasting levels of $25(OH)D_3$, insulin, glucose, uric acid and lipids (triglycerides, total, HDL and LDL cholesterol) were measured. Insulin resistance was assessed by using the homeostasis model assessment (HOMA2-IR, HOMA2-%S and HOMA2-%B). Vitamin D deficiency was defined by levels of $25OHD_3$ <10 ng/ml.
Results
85 obese subjects (58 women and 27 men), mean age 43.8 ± 14.5 years. BMI 43.6 ± 8.2 Kg/m^2, SBP 133.4 ± 18.7 mmHg, DBP 84.6 ± 11.1 mmHg, fasting glucose 100.8 ± 30.6 mg/dl, HbA1c 6.01 ± 1.05%, total cholesterol 18.4 ± 33.8 mg/dl, HDL-c 47.8 ± 10.4 mg/dl, LDL-c 111.5 ± 28.2 mg/dl, triglycerides 152.8 ± 84.8 mg/dl, $25OHD_3$ 17.5 ± 6.01 ngl/ml. Vitamin D deficiency was present in 5.88% of subjects. $25(OH)D_3$ levels were significantly and negatively correlated with HOMA2-% B ($P=0.07$) and serum insulin ($P=0.09$). $25(OH)D_3$ levels were also reported to be directly related to HOMA2-% S ($P=0.01$).
Conclusion
We found an association between vitamin D and hyperinsulinemia. These results suggest that serum vitamin D deficiency could be an insulin resistance marker.

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P510

Vitamin D repletion in chronic kidney disease patients with secondary hyperparathyroidism

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Secondary hyperparathyroidism (SHPT) as well as vitamin D deficiency are highly prevalent in patients with chronic kidney disease (CKD). Traditional therapy of SHPT includes administration of calcitriol, mainly in dialysis patients. Data about effects of native vitamin D repletion in such patients are still inconsistent. The aim was to assess effects of vitamin D repletion in CKD patients with SHPT and vitamin D deficiency. 88 patients, mean age 50.8 ± 14.6 years with CKD 3–5 stages, SHPT (PTH >65 pg/ml) and vitamin D deficiency (25OHD <20 ng/ml) were divided in 2 groups. 1st group (48 patients) received cholecalciferol 2000–3000 IU daily during 6 months, 2nd group (40 patients) do not receive vitamin D compounds. Initially and after 6 months of follow-up serum parathormone (PTH), 25OH-vitamin D (25OHD), creatinine, calcium and phosphorus were measured, estimated glomerular filtration rate (eGFR) was calculated by MDRD formula. In the cholecalciferol group after 6 months of observation mean 25OHD level significantly increase from 10.7 ± 6.1 to 23.0 ± 11.5 ng/ml, $P<0.0001$; PTH decrease from 207.7 ± 123.2 to 156.9 ± 103.0 pg/ml, $P=0.052$. 25OHD level >30 ng/ml was reached in 25% of patients, target PTH level in 16.7% of cases. In the control group after 6 months of observation PTH and 25OHD levels did not show significant changes. In both groups significant declining of kidney function were revealed (eGFR decreased in 1st group from 29.9 ± 18.5 to 24.1 ± 17.0 ml/min, in 2nd group from 25.8 ± 13.5 to 19.1 ± 13.4 ml/min), however calcium and phosphorus levels remained unchanged. Any other adverse effects related to vitamin D administration were not registered. We can assume that administration of cholecalciferol 2000–3000 IU daily in CKD patients with vitamin D deficiency and SHPT is safe. In the majority of cases this dosage is not efficient to obtain recommended optimal 25OHD level >30ng/ml and to treat or to control progression of SHPT. Further study is required to assess appropriate vitamin D repletion regimen in such patients and its capacity to control SHPT.

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P511

Gitelman's syndrome with concomitant primary hyperparathyroidism – case report

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Gitelman's syndrome, rare (lifetime prevalence 1:5000) autosomal recessive tubulopathy, is caused by SLC12A3 gene mutation (encoding part of sodium-chloride channel and magnesium channel). Typical finding is low level of potassium and magnesium due to increased output, secondary hyperaldosteronism and hypocalciuria. In this case, we present 28 years old woman with 1 year

nonspecific conditions similar to hyperventilation tetanic cramps: muscle fatigue, cluster headache, nausea and irregular vomitus. Before visit in our clinic neurological examination with brain MRI were performed with normal findings and therapy with some anxiolytics and antidepressants was prescribed with no effect. Physical examination was without abnormalities, laboratory examination revealed markedly hypokalemia 2.6 mmol/l, hypomagnesaemia 0.3 mmol/l, hypophosphatemia 0.6 mmol/l. We started intravenous substitution of potassium and examine urinary output – high excretion fraction of potassium and calcium and extreme high excretion fraction of magnesium (0.23 - urinary output 16 mmol Mg/day). After exclusion other causes we started treatment with spironolactone and Mg supplementation with good effect, in few weeks we changed spironolactone to amiloride due to breast pain. Hypercalcemia in correlation with hypercalciuria and low level of 25-OH D vitamine increased suspicion for concomitant primary hyperparathyroidism. Ultrasonography reveal 8mm nodulus in the locus of right lower parathyroid gland and 18-F choline PET/MRI confirm parathyroid adenoma. After surgery (histology – parathyroid adenoma) we started D vitamine treatment and hypercalcemia and hypercalciuria was disappeared. Patient remains on amiloride and magnesium treatment and low dose vitamine D with no symptoms and borderline hypokalemia and hypomagnesemia. Both parents and one brother was examined with normal blood and urinary levels of mentioned ions. Results of genetic testing were not yet available. After this diagnostic and therapeutic process we acquired six years old (age 14y) laboratory results from pediatric GP. That time was mild hypokalemia 3.5 mmol/l, hypomagnesaemia 0.6 mmol/l, hypercalcemia 2.7 mmol/l but unfortunately no further examination was initiated. We propose that long term chronic mild hypomagnesemia can increase PTH production in parathyroid gland (severe hypomagnesemia has opposite effect) and this could be reason for concomitant occurrence of two rare illness. Probability of independent lifetime prevalence of these diseases would be less than 1:1.000.000.

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P512

Primary hyperparathyroidism: diagnosis and management

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Introduction
Primary hyperparathyroidism is due to excessive and inappropriate production of parathyroid hormone. The treatment is essentially surgical. The objective of this work is to specify the clinical and paraclinical characteristics of this pathology and specify the methods of management.
Methods
A descriptive retrospective study conducted at the Department of Endocrinology Diabetology and Metabolic Diseases of the University Hospital of Casablanca for a period of 4 years (2014–2018) including all patients followed for primary hyperparathyroidism.
Results
Twenty-five patients were followed during this period for primary hyperparathyroidism. The average age was 56.7 years (34–76) with a clear female predominance (84%). 40% had hypertension, 20% diabetes. The clinical picture was variable, dominated by bone pain with pathological fractures in 53% followed by general signs. Serum calcium was elevated in 21 patients (84%) and parathyroid hormone in all patients. A cervical ultrasound was performed in all patients and objectified a picture in favor of a parathyroid adenoma in 40% of cases. MIBI scintigraphy, performed in 9 patients (36%) showed hyperfixation in 66% of cases including one case of ectopia. Tomodensitometry was performed in 10 patients and revealed an adenoma in 5 cases, one of which was ectopic. A single IRM was done that objectified an ectopic adenoma. 14 patients (56%) underwent surgery, the immediate operative follow-up marked by hypocalcemia. The pathological examination found a parathyroid adenoma in more than 95% of cases. The success rate of our surgical strategy was 100%. No cases of recurrence have been diagnosed.
Conclusion
Hyperparathyroidism is an increasingly common pathology affecting more women, the positive diagnosis is purely biological and the diagnosis of location is radiological and isotopic. Surgical treatment is the rule.

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P513

Clinical-biological presentation hyperparathyroidism primary function of vitamin D status

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Introduction
Primary hyperparathyroidism and vitamin D deficiency are two common conditions. Their coexistence also seems frequent and could aggravate clinical and biological manifestations of primary hyperparathyroidism. The aim of this work is to analyze the clinical and paraclinical parameters of this disease according to vitamin D status.
Methods
Retrospective study conducted at the Department of Endocrinology Diabetology and Metabolic Diseases of the University Hospital of Casablanca for a period of 4 years (2014–2018) including all patients followed up for primary hyperparathyroidism.
Results
Twenty-five patients were followed during this period for hyperparathyroidism. The average age was 56.7 years (34–76) with a clear predominance of women (84%), 77% of whom were menopausal. Vitamin D deficiency (25OHD <20 ng/ml) was present in 73% of patients. These patients had a higher PTH level with an average of 1169 pg/ml (157.3–3357) and a more frequently pathological bone densitometry.
Conclusion
In view of these results, the systematic determination of vitamin D during primary hyperparathyroidism should be done in order to better evaluate the severity of this disease and to consider possible vitamin supplementation.

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P514

Vitamin D insufficiency and hyperparathyroidism, general health and quality of life – a cross sectional study

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Introduction
Multiple adverse health outcomes are reported in response to low vitamin D and/or hyperparathyroidism.
Aim and methods
A cross-sectional study in a random sample of mainly non-vitamin D supplemented Danish women ($N=1580$) during winter-time. We investigated prevalence of vitamin D insufficiency, hyperparathyroidism, general health and quality of life (QoL) as assessed by a general health questionnaire and a validated hyperparathyroidism health-related quality of life questionnaire prior to blood sampling.
Results
Plasma PTH and 25(OH)D were inverse associated. In the total cohort, median 25(OH)D was 66 [50 to 83] nmol/l and PTH 5.2 [4.2 to 6.6] pmol/l. The prevalence of P-25(OH)D <50 and <25 nmol/l was 23.9% ($N=376$) and 2.8% ($N=44$), respectively. The prevalence of mild primary- (PHPT) and secondary hyperparathyroidism was 2.9% ($N=46$) and 6.9% ($N=109$) respectively. General health or QoL did not differ between women with normal biochemical findings and those with low 25(OH)D levels and/or SHPT. In 64% ($N=29$) of the 46 women with initial biochemical findings consistent with PHPT, the diagnosis was validated by consecutive measures of PTH and ionized-calcium. Among those, half ($N=14$) had a parathyroidectomy performed due to complications associated with the disease, including vertebral fractures (X-ray), low BMD (DXA) or renal calcifications (CT-scan). Women with PHPT complained more often of nocturia and had more often a history of kidney disease, whereas QoL did not differ from healthy women.
Discussion
Low 25(OH)D levels are prevalent during wintertime in Denmark, whereas elevated PTH levels occurs with a lower frequency. By itself, low 25(OH)D and/or high PTH levels are not associated with adverse health outcomes, as long as calcium are normal. However, even mild PHPT was associated with known complications to the disease.

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P515

Denosumab, alendronate and zoledronate failure to suppress bone resorption markers in a woman affected by severe osteoporosis and subclinical hypercortisolism due to an adrenal adenoma: A case report

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Context
ß-CTX are considered useful markers of response to denosumab and other anti-resorbtive treatments for osteoporosis. We report an unusual case of a completely absent effect of both denosumab and bisphosphonates on bone resorption markers.
Case description
In 2017 a 74-year-old woman sought medical attention at the Endocrinology Unit of Policlinico di Sant'Orsola for the evaluation of an adrenal adenoma associated with osteoporosis. Menopause age was 49. The 2-cm lipid-rich left adrenal adenoma had been incidentally discovered in 2008 and was morphologically stable. BMI was 30.0 kg/m^2. No signs of hypercortisolism were detected. A densitometry (DXA) scan performed in 2014 showed a femoral neck T-score of −2.3, total hip T-score of −1.1, spine T-score of −3.1. A 1-mg dexamethasone test detected subclinical hypercortisolism (1-mg post-desamethasone cortisol = 102 nmol/l). Renal function and 25-OH vitamin D levels were normal. High bone resorption markers were registered (ß-CTX = 1.097 ng/ml) while hyperparathyroidism was excluded. A DXA scan was repeated in May 2017 and a worsening of spine BMD (T-score: −3.9) was detected, whereas hip BMD was stable (neck T-score of −2.3, total T-score of −1.2). Three vertebral fractures were diagnosed on a morphometric X-ray of the spine. Denosumab 60 mg was started in May 2017. Six months later, bone resorption markers were elevated (ß-CTX = 1.533 ng/ml). Denosumab was continued and ß-CTX retested three months later, which again were confirmed inappropriately high (0.987 ng/ml). Six months after the 2ndadministration no change occurred (ß-CTX = 1.305 ng/ml). A Technetium-99 m Bone Scintigraphy was carried out in March 2018 to exclude primary or secondary bone disease, with no pathological findings, except for signs of osteoarthritis. Denosumab was then stopped and the patient switched to alendronate 70 mg weekly. Six months later, ß-CTX were still elevated (1.408 ng/ml), thus alendronate was stopped. Zoledronate 5 mg was administered intravenously. After one month, ß-CTX were unchanged (1.270 ng/ml). A DXA scan was repeated before the administration of zoledronate, in January 2019, and a bone mineral density (BMD) gain at the spine (T-score: −3.4) was observed, whereas hip BMD remained unaltered (neck T-score of −2.3, total T-score of −1.1). Other secondary causes of osteoporosis were excluded, including mastocytosis.
Conclusion
This is the first ever-described case of a failed response of bone resorption markers to denosumab. Despite high ß-CTX, spine BMD improved. Whether mild and long-standing hypercortisolism may explain a missed response of ß-CTX should be assessed by appropriate studies.

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P516

Immobilization induced hypercalcemia

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Introduction
Immobilization induced hypercalcemia, which was first described in 1941 by Albright, is an uncommon reason for hypercalcemia. It is associated with increased bone remodeling disorders and conditions associated with limited movement such as medullar lesions or vascular events. The exact mechanism of the disorder is unknown. Diagnosis requires an detailed evaluation to rule out other causes of hypercalcemia.
Case presentation
A 24 year old man was admitted to our hospital after a severe traumatic brain injury related to a car crush. Following the initial treatment of his injury, he remained in a chronic immobilization state and after seven months in intensive care unit he presented with hypercalcemia. On laboratory analyses; elevated ionized and total calcium levels with decreased PTHi levels were detected (table 1). Thyroid and adrenal gland functions were normal. He had no past medical history and he did not use any drugs which could cause hypercalcemia. For this reasons immobilization induced hypercalcemia were considered as the diagnosis. Initial therapy including fluid and diuretic therapy was administered. Although these therapy, there was no remarkable decrease on the levels of total calcium, and an infusion of 4 mg zoledronic acid was added to his treatment. Three weeks after zoledronic acid therapy, serum calcium levels increased and repeated administration of zoledronic acid was needed. Because mobilization of the patient is still not possible, intermittent zoledronic acid is needed currently.
Conclusion
Immobilization induces hypercalcemia is an uncommon disorder. This rare condition should be kept in mind in immobilized patients with hypercalcemia, especially in patients who are followed in intensive care units.

Table 1 The laboratory values of the patient.

Values	Results	Reference value
Total Calcium	13.4 mg/dl	8.6–10.2
Albumin	19 g/l	35–51
Corrected Calcium	15.08 mg/dl	8.6–10.2
Phosphorus	2.4 mg/dl	2.5–4.5
Creatinine	1.3 mg/dl	0.6–1.3
Parathyroid hormone	9.3 pg/ml	18.5–88
25-hidroxi vitamin D	17.7 ng/ml	>30

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P517

Denosumab in clinical practice: efficacy, complications and adherence

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Background
Denosumab is a monoclonal antibody against RANK ligand used for the treatment of osteoporosis. Although clinical trials demonstrate that denosumab is highly effective at reducing fragility fractures in postmenopausal osteoporosis, there have been few studies looking at real world outcomes. Our primary aim was to assess the efficacy of denosumab in practice.
Methods
We retrospectively formed a database of 257 patients seen in endocrinology outpatient clinics who have commenced denosumab for the treatment of osteoporosis between January 2011 and January 2018. Data were collected using standardised proforma including demographics, co-morbidities, bone mineral density (BMD), fractures, hospitalisations and biochemistry.
Results
There was a clear female preponderance (95% of patients), mean age at commencement was 75 years. 80% had post-menopausal osteoporosis, with a mean follow-up of 5 injections. Mean CTX at baseline was 0.37 ug/l, at 3 months the mean was 0.09 ug/l, with a mean 70% reduction in CTX. 91.2% had a CTX reduction >50% from baseline or below the lower limit of normal. Similar results were seen for P1NP with 80% of patients having a P1NP fall by >50% baseline or below the lower limit of normal. Mean baseline spine BMD was 0.826 g/cm^2, with a mean T-score of −2.9. Mean baseline hip BMD was 0.692 g/cm^2 (mean T-score −2.6). 38% patients had at least one repeat DXA. Spine BMD increased by a mean of 4.7%, 79% had stable or improved BMD 2–3 years after baseline. Similar results were seen for hip BMD, with a mean increase of 2.2 and 81% had stable or better hip BMD, 2–3 years after baseline scan. 18% had at least one episode of hypocalcaemia, 20% had at least one episode of vitamin D deficiency. 12.5% were hospitalised for infection, the majority (58.3%)chest related. 10.6% had a fracture related admission, the majority were femoral fractures (29%). The average time to fracture after commencing denosumab was 24 months. 23% patients reported complications, though the majority were episodes of hypocalcaemia or infection. <1% patients had osteonecrosis of the jaw and an incidence of 1.6% who had sub-trochanteric fractures. Denosumab was discontinued in 10% of patients, a further 5% of patients had denosumab inadvertently stopped or delayed.
Conclusion
Denosumab is highly effective at reducing biochemical bone turnover markers and improves BMD in the vast majority of patients, in the real-world setting. However, incidences of biochemical hypocalcaemia were high, as were discontinuation rates, with implications for future re-fracture rates.

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P518

Transition of denosumab to primary care is enhanced by use of a transfer pack

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Background
Denosumab, given 6 monthly as a subcutaneous injection, is well established as a treatment for osteoporosis. In the UK it is initiated in secondary care with most patients continuing with injections in primary care. Given concerns with hypocalcaemia and possible adverse effects on fracture risk due to abrupt cessation, robust monitoring in primary care is important. Our study compares two groups of patients on denosumab, one following a well-defined treatment pathway including a transfer information pack when transitioning to primary care, the other without. Our aim was to evaluate the success of this in improving adherence, reducing inadvertent cessation rates and re-referral.
Methods
We retrospectively formed a database of patients seen in outpatient clinics who had commenced denosumab for the treatment of osteoporosis between January 2011 and January 2018. We identified those who did (group 1, $n=257$) and did not (group 2, $n=57$) follow the treatment pathway, including a transfer information pack when transitioned to primary care. Data were collected using standardised proforma including demographics, co-morbidities, biochemistry, cessation rates and re-referral.
Results
Baseline demographics of each group were similar. There was a female preponderance in both (95% (group 1) 96% (group 2). Mean age at commencing treatment was 75 and 72 years respectively. Results are summarized below:

Category	Group 1 $n=257$ (%)	Group 2 $n=57$ (%)	*P*-values
Baseline CTX recorded	247 (96%)	3 (5%)	$P=<0.001$
Baseline DXA	257 (100%)	49 (86%)	$P=<0.001$
Repeat DXA	97 (38%)*	24 (42%)	$P=0.54$
Follow-up spine x-rays	69 (27%)	22 (39%)	$P=0.08$
Injection administration transferred to primary care	245 (95%)	30 (63%)	$P=<0.001$
Management of osteoporosis in primary care	217 (84%)	14 (25%)	$P=<0.001$
Biochemical monitoring (calcium/Vit D checked 8 weeks prior to injection)	128 (50.2%)	16 (32.6%)	$P=0.02$
Re-referral	17 (6%)	9 (16%)	$P=0.02$
Deliberate cessation	25 (10%)	11 (19%)	$P=0.04$
Inadvertent cessation	13 (5%)	16 (28%)	$P=<0.001$

NB some patients excluded in each category due to loss of follow up data. *49% of patients in group 1 were within their first two years of treatment.

Conclusion
Our study demonstrates the use of a transfer pathway improves the rates of transfer to primary care for both injection administration and follow-up whilst reducing re-referral significantly. Biochemical monitoring showed improvement in patients on the transfer pathway. Most importantly, a transfer pathway reduced the number of patients in whom denosumab was stopped either deliberately or inadvertently.

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P519

Fahr's syndrome secondary to hypoparathyroidism: about 11 cases

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Introduction
Fahr's syndrome (SF) is a rare anatomo-clinical entity, defined by non-arteriosclerotic striato-pallido-serrated calcifications localized in basal ganglia. It may be idiopathic or secondary to many etiologies dominated by phosphocalcic metabolic abnormalities, the main cause being primary or postoperative hypoparathyroidism.
Materials
This is a retrospective, descriptive study involving 11 patients with FAHR syndrome hospitalized at the Department of Endocrinology, Diabetology and Metabolic Diseases CHU IBN ROCHD, Casablanca from January 2010 to December 2018.
Results
The average age of our patients was 37 years (21–50), with sex ratio H/F: 4/7.The mean duration of evolution was 9 years, mean serum calcium at the time of diagnosis was 53.38 mg/l. The circumstances of discovery were epileptic seizures in ten cases (90.9%), extrapyramidal syndrome in one patient. Four patients had psychiatric disorders (36.3%) nine patients had bilateral cataract (81.8%). The brain scan showed bilateral and symmetrical basal ganglia calcifications in all patients. Hypoparathyroidism was secondary to thyroidectomy in two cases (18.1%) and idiopathic in nine cases (81.8%). The evolution was favorable with vitamin-calcium supplementation in all patients.
Conclusion
The SF, a rare entity whose clinical manifestations are not very specific, the association of hypoparthyroidism with epilepsy remains rare but deserves to be sought for the simplicity of the determination of the calcemia in order to detect a syndrome of Fahr and thus adopt the most appropriate therapeutic measures.

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P520

Vegan diet: a true danger in paediatrics

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Veganism is spreading in western societies, as a new 'healthy' and ecological diet. But in children, it can lead to malnutrition, with damaging consequences in a still-developing organism. We report the case of a thirteen-month-old boy born at term with appropriate measurements and no medical history. He was kept at home by his mother, and his father was a senior executive. He was brought to the Hospital because of hypotonia and loss of walking ability. He didn't babble, had difficulties to hold sited, presented with lanugo and ulnar metaphysis dilation. At examination he presented with growth and weight failure, but curves were not available since he lacked medical follow-up. His body measurements were 7.3 kg (*−3 DS*), 71 cm (*−2 DS*), IMC 14.5 kg/m^2 (*−2.2 DS*). He had no vaccination and had not received D vitamin complements. The parents reported that he was breastfed his first six months, then they introduced a vegan diet with home-made rice milk. Biological investigations revealed hypocalcaemia (*calcium 2.*21 mmol*/l*) with hypophosphatemia (*phosphorus 0.*6 mmol*/l*); elevated alkaline phosphatases (1066 U*/l (Normal Values (NV)<35)*); elevated PTH (*21.*2 pmol*/l (NV0.8–5.2)*); Vitamin D deficiency (*25OH-Cholecalciferol 17.8 nmol/l (NV75–250)*). He also has a low pre-albuminemia (*2.0 µmol/l (NV2.7–6.4)*), and deficiencies in vitamin A (*0.6 µmol/l (NV0.7–1.5 µmol/l)*), vitamine B6 (*6.8 nmol/l (NV20–134)*), vitamin C (*15.9 µmol/l (NV28–85)*), and iron deficiency anaemia (*Haemoglobin 9.*8 *g/dl, iron 7 µmol/l (NV11–24)*). Whole body X-rays showed bilateral diaphysis fractures on fibula and ulna, rickets features (diffuse osteopenia aspect, ribcage bumps, cupula deformation of metaphysis).
Management
The boy was placed in a care facility where he received supplementations (25OHvitD3 100.000UI/month, oral calcium 500mg/day, oral iron and vitamins) and progressive dietary diversification. Treatment permitted a marked increase in his psychomotor development and restoration of walking ability. His muscle tone improved and he restarted smiling and babbling. He gained weight and recovered a normal growth velocity. His abnormal lab-test got progressively normal. He went back home after three months and acceptation of this new diet by the parents.
Conclusion
We reported here severe rickets associated with several fractures and nutritional deficiencies responsible for developmental regression and growth retardation, in a child under vegan-diet. The long-term consequences of such prolonged and severe deficiencies are unclear and developmental retardation may persist in this child. It appears crucial for health professional to ask for diet inhabits and to detect possible deficiencies, even in wealthy families, in order to prevent the damaging consequences of restrictive diet on children's development.

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P521

A rare case of cushing disease and hypophosphatasia

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Cushing disease and hypophosphatasia are rare conditions that may be both responsible of an important impairment of bone metabolism with increased fracture risk. We reported for the first time a case of a 43-year-old woman that came at our attention for recent onset of alopecia and amenorrhea. At the anamnesis, she denied any past relevant events and no drug assumption. At the physical examination, she presented rubeosis and facies lunaris and central adipose distribution (waist circumference 130 cm). The preliminary laboratory tests showed increased free urinary cortisol in two subsequent measurements, high ACTH values and normal blood cortisol level. Furthermore, the 1 mg dexamethasone test was performed showing a lack suppression of cortisol (cortisol post-dexamethasone: 289 mmol/l) suggestive for hypercortisolism. Suspecting a Cushing's disease, a desmopressin test was done showing ACTH and cortisol response compatible with pituitary genesis of hypercortisolism. The pituitary MRI confirmed the presence of a suprasellar macroadenoma. Therefore the patient underwent transnasalsphenoid pituitary adenomectomy obtaining disease remission. The histological examination showed a papillary-like neoplasm with weakly and diffusely anti-ACTH antibody positive cells with Ki67 equal to 1%. In the screening evaluation of the patient, a bone densitometry was also performed showing no relevant abnormalities. In the mean time, the father of the patient was under our evaluation for multiple bone fractures resulting from low traumas. All secondary causes of osteoporosis were ruled out and hypophosphatasia was suspected based on high vitamin B6 levels (124 nmol/l with normal value: 19–55 nmol/l). The genetic analysis detected a germline mutation c1366G > A (p.Gly456Arg) in heterozygosity at the exon 12 of the alkaline phosphatase gene (ALPL), compatible with hypophosphatasia. Based on the father recent diagnosis, we tested total and bone alkaline phosphatase in our patient resulting low (18 U/l with normal value: 30–120 U/l; 3.7 microgr/l with normal value: 4.7–27 microgr/l, respectively) in association with increased vitamin B6 levels (118 nmol/l with normal value: 19–55 nmol/l). Although no clinical phenotype suggestive for hypophosphatasia (blue sclera, dental anomalies, hearing or cardiological problems, hystory of previous fractures) was present, the patient underwent to blood test examination for the genetical analysis showing the same father's mutation.

Conclusion

To our knowledge, this the first case of patient with Cushing Disease and Hypophosphatasia in absence of bone abnormalities. The clinical and radiological evolution of this phenotype is unclear and need periodical examination to detect possible future complications.

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P522

The effect of teriparatide on bone mineral density in a woman with severe lactation-related osteoporosis and multiple vertebral fractures

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Introduction

Lactation-related osteoporosis is a very rare entity, usually diagnosed with one or more fractures, during the early postpartum period. Due to the rarity of this condition, no consensus still exists with regard to thetype and optimal duration of treatment.

Case presentation

A 39-year old Caucasian female was presented at the outpatient clinic in December 2016 for evaluation and management of severely low bone mineral density (BMD) and multiple vertebral low energy fractures at the 5thto 7th(T5-T7) and 10thto 12ththoracic vertebrae (T10-T12). These fractures were diagnosed on occasion of severe back pain, following a weight-bearing activity, seven months after delivery. BMD assessed by dual-energy X-ray absorptiometry was markedly low, with absolute values of 0.783 g/cm^2 (T-score: −3.3, Z-score: −3.9) at lumbar spine (LS), 0.755 g/cm^2(T-score: −1.9, Z-score: −2.1) at femoral neck (FN) and 0.709 g/cm^2(T-score −2.4. Z-score: −2.7) at total hip (TH). Evaluation for causes of secondary osteoporosis (such as hyperthyroidism, hyperparathyroidism, celiac disease, hypercalciuria, renal or liver dysfunction) was negative, except for vitamin D deficiency (25-hydroxy-vitamin D concentrations: 12 ng/ml). Taking into account the patient's reproductive status and the unknown effect of bisphosphonates on fetal growth in future pregnancies (due to their long retention to bone), teriparatide was initiated (daily injections of 20 μg for 24 months). Cholecalciferol was also administered, at weekly doses of 50.000 IU for eight weeks, followed by a daily dose of 1000 IU combined with calcium carbonate (600 mg/daily). The patient reported significant relief in musculoskeletal symptomatology from the first 2–3 weeks of teriparatide treatment. BMD showed an increase of 13.1%, 7% and 11.5% in LS, FN and TH at 12 months and 19.1%, 15.7% and 16.5%, at 24 months, respectively. At the end of therapy, T- and Z-scores at LS, FN and TH were −2.1 and −2.3, −0.9 and −1, −1.4 and −1.6, respectively. Teriparatide was well-tolerated and the patient returned to her daily activities during the first 3–4 months of therapy. Except for a new vertebral fracture affecting the 9ththoracic vertebra at 12 months assessment, magnetic resonance imaging showed significant improvement in all fractured verterbral bodies at 12 and 24 months.

Conclusions

Teriparatide appears a quite effective and safe option in cases of lactation-associated osteoporosis, leading to a significant increase in both spinal and hip BMD. However, more data are needed to establish the optimal management and follow-up of these patients.

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P523

Relapse of primary hyperparathyroidism concurrent with a plasma cell proliferative disorder: report of a case

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Introduction

Primary hyperparathyroidism associated with multiple myeloma has been rarely reported to coincide, but relapse of previously remitted primary hyperparathyroidism concurrent with a plasma cell proliferative disorder has not been described.

Case report

A 76-year-old female was referred to the endocrine clinic for evaluation of primary hyperparathyroidism discovered incidentally during hospitalization for angina. She had a corrected calcium of 13.9 mg/dl (albumin 2.8 g/dl), phosphate 4.1 mg/dl (2,5-4,5), PTH 369 pg/ml, impaired renal function (eGFR 28,4 ml/min/1.73m^2), nephrotic syndrome (5gr protein/24h), hypercalciuria (503 mg/24h), alkaline phosphatase 87 U/L (30-120), uric acid 8.3 mg/dl, Ht 37.6%, Hb 12.7 g/dl, ESR 78 mm/1hr. Cervical ultrasound showed a large cyst at the lower right thyroid pole measuring 3.25 cm, suspicious for a parathyroid cyst. The diagnosis was confirmed by positive PTH (> 5000 pg/ml) in the aspirate. Skeletal survey was negative for pathologic fractures and lytic lesions, except for 'salt and pepper' skull. Serum free κ chains were 103mg/L (3.3–19.4) and λ chains 62.8 mg/L (5.71–26.3). There was no monoclonal band detected in urine or serum and results of bone marrow aspiration are pending. The patient's history was remarkable for a hospitalization with hypercalcemic crisis 5 years ago. At that time she had a calcium of 15 mg/dl and a PTH of 433 pg/ml and chronic renal impairment with an eGFR of 50 ml/min/1.73m^2 (CKD stage 3a). Sestamibi scintigraphy was negative. She was discharged after receiving supportive treatment, including an intravenous bisphosphonate. Past history was negative for kidney stones and osteoporotic fractures. She remained normocalcemic until the present illness, with interim documented calcium levels 9.9–10.1 mg/dl. The patient received an infusion of zolendronate and was started on cinacalcet 30 mg daily. A month later she had an uneventful parathyroidectomy. Conclusive diagnosis and treatment of the hematologic disorder is pending.

Conclusion

The classic CRAB criteria cannot be applied for the diagnosis of multiple myeloma and related disorders in the presence of primary hyperparathyroidism, because of common features shared between the two conditions, worsening each of them. Parathyroidectomy in these cases is desirable as it favorably affects treatment, follow up and perhaps prognosis of the hematologic disorder.

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P524

Diagnosis and treatment of an Argentine patient with severe primary hypoparathyroidism and 22q11.2 deletion syndrome

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Microdeletions or microduplications in the 22q11.2 region cause a variety of disorders, including DiGeorge syndrome (DGS; MIM 188400), velocardiofacial syndrome (VCFS; MIM 192430) and cat-eye syndrome (CES; MIM 115470). DGS and VCFS clinically overlap and are both caused by three million-base pair (Mb) deletions on the chromosome region 22q11.2, flanked by low copy number repeats (LCRs) labeled 'A-D'. The most common deletion, present in 85% of individuals, extends from A to D and includes *TBX1,* a gene deemed responsible for typically associated features, in particular conotruncal cardiac anomalies. The remaining 15% of affected individuals have atypical 'nested' deletions. Deletion of genes within the DiGeorge chromosome region (DGCR) is the only genetic abnormality known to be associated with 22q11.2. The 22q11.2 deletion syndrome is suspected in individuals with a range of findings including congenital heart disease (particularly conotruncal defects), palatal abnormalities, hypocalcemia, immune deficiency, learning difficulties, hearing loss and characteristic facial features, among other structural anomalies. We report a 24-year-old female patient with severe primary hypoparathyroidism (PHP), seizures during the 1st and 2nd year of life, intellectual disability, bilateral sensorineural hearing loss, microcephaly, dysmorphic facial features, severe myopia and recurrent infections. Heart ultrasound has not been performed yet. Her father is known to have hearing loss, intellectual disability, arthritis, myopia and astigmatism. The patient was diagnosed with PHP at 12 years old, when she required multiple hospitalizations in an Intensive Care Unit for symptomatic hypocalcemia resistant to oral treatment. She was medicated with calcium citrate 3.8 g orally per day, Calcium Carbonate 1.5 g orally per day and Calcitriol 3 ucg. She required weekly hospitalizations for hypocalcemia, receiving IV calcium gluconate with regular clinical and metabolic response and digestive intolerance. She started with recombinant PTH 1-84, 50 ucg diary, with a good clinical and biochemical improvement. We performed molecular diagnosis consisting of MLPA (multiple ligation probe amplification) employing the SALSA P250 MLPA kit. The analysis of copy number variations, revealed a deletion of 1.5 Mb in the 22q11 region ranging from LCR22-A to LCR22-B. Since the approximately 10 percent of cases is inherited, a molecular study was performed in the patient's parents with pending results.

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P525

The association between magnesium oxide and fracture- A nationwide population-based retrospective cohort study

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Background
Magnesium oxide is widely used for constipation and antacid. Some studies showed another antacid, proton pump inhibitor increased the risk of fracture. The association between laxative and the risk of fracture was limited. Our study aimed to evaluate the association between: usage of Magnesium oxide and fracture.
Design
Nationwide population-based retrospective cohort study.
Setting
Taiwan's National Health Insurance Research Database.
Participants
Individuals with usage ($n=3,273$) and without usage ($n=13,092$) of Magnesium oxide.
Measurement
Individuals with and without Magnesium oxide were matched 1:4 for age, sex, and index year. Those with fracture were further divided into hip fracture, vertebral fracture and other fracture. Incidences and hazard ratios (HR) for risks of developing fracture were calculated using Cox proportional hazard regression models.
Results
During mean follow-up of 4.8years, 567 participants in the usage cohort and 1859 participants in the non-usage cohort developed fracture events. Having usage of Magnesium oxide was significantly associated with risk of developing fracture events (adjusted HR (aHR) $=1.2$, 95% confidence interval (CI) $=1.09–1.32$, $P<0.001$, hip fracture: aHR $=2.14$, 95% CI $=1.63–2.81$, $P<0.001$, vertebral fracture: aHR $=1.68$, 95% CI $=1.38–2.04$, $P<0.001$)). But, there was no associated with risk of developing other fracture.
Conclusion
Magnesium oxide was independently associated with increased risks of fracture, especially over hip and vertebral fracture.

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Diabetes, Obesity and Metabolism 2

P526

Hypoglycemia as a first symptom of fructosemia, complicated by gestational diabetes in III pregnancy and 26 years of delayed final diagnosis: a case report

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Introduction
Fructosemia is a rare autosomal recessive genetic metabolic disorder, caused by mutations in the *ALDOB* (9q22.3) gene, encoding the enzyme aldolase B. This case shows that fructosemia typically causes hypoglycemia. This disorder should be included in differential diagnosis. Prevalence of GDM in women with fructosemia is unknown, but it is a rare condition[1].
Case
Five month old female baby arrived in 1976 to the Hospital of Lithuanian University of Health Sciences, Kauno klinikos with symptoms of fever, vomiting, diarrhea, seizures, when vegetables and sugar were included in child diet. Diagnostic tests showed hypoglycemia. Intravenous glucose admitted and symptoms disappeared but the cause of the hypoglycemia was unknown. In abdomen ultrasound liver was enlarged. Tolerance tests were performed – with glucose, galactose and fructose. The last test showed severe hypoglycemia to 1 mmol/l. Urine test showed excessive amount of fructose (3+). Liver biopsy showed diffuse hepatocytes necrobiosis. Then diet without fructose was prescribed and symptoms disappeared. Patient eliminate products with sugar from diet, vegetables (e.g. carrots) and all fruits. After 26 years in 2001 analysis of aldolase B gene was performed for this female patient and her 2 month old son. They both were homogeneous for the most frequent mutation for aldolase B gene A149P. Fructosemia diagnose was confirmed and the only treatment was eliminate fructose from diet. In 2014 women gave birth twins from another man and they were heterogeneous in aldolase B gene, and has no symptoms of fructosemia. In June of 2018 patient gave birth for a female baby and she has no symptoms for now, but the genetic examination is not performed for the aldolase B gene mutation. Third gestation was complicated by gestational diabetes mellitus. Glucose tolerance test (GTT) was performed during 29 week of third labor. Test results showed GDM: fasting glucose – 4.98 mmol/l, 1 hour after 75 g glucose load – 11.2 mmol/l, after 2 hours – 8.04 mmol/l. There was only dietary treatment needed to treat this condition. After gestation GTT were not performed, but glucose concentration in blood is normal.
Conclusion
Fructosemia is a rare genetic condition, which occurs in infants when fructose is added to the diet. There are no official fructosemia diagnostic or treatment guidelines. Its need to figure in this disease to our differential diagnosis when there is unclear hypoglycemia or digestive tract symptoms.
Literature
1. Baker P, *et al.* Hereditary Fructose Intolerance. Genes reviews, 2015 Dec 17.

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P527

Artificial intelligence for the remote evaluation of gestational diabetes using a smartphone application (Sinedie©): Study design.

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Background
Gestational diabetes (GD) prevalence is increasing as the obesity epidemic continues. Its management involves hospital visits every 1–2 weeks. In 2016 our team developed a web-based telemedicine platform (SineDie©). This tool operated as a clinical decision support system designed to manage the treatment of patients with GD. SineDie© automatically prescribed diet recommendations and identified the necessity of insulin treatment. We realized a randomized clinical trial that showed a 27.4% reduction of the time devoted by clinicians to patients' evaluation and the face-to-face visits per patient were reduced by 88.6%. The program detected all situations that required a therapy adjustment and all the generated recommendations were safe (Caballero-Ruiz E *et al*. *Int J Med Inform* 2017). Since today most people use smartphones and in order to enable the use of the tool, we have developed the mobile version. The aim of this communication is to present the app SineDie© and the ongoing clinical study design.
Methods
SineDie©app has been developed by the UPM bioengineering and telemedicine group and the Hospital Parc Taulí endocrinology department. The application can be installed in Android smartphones. SineDie©uses artificial intelligence to automatically classify and analyze the data, making therapy adjustment recommendations. The pregnant woman enters diet transgressions, exercise and ketonuria in the app. Blood glucose values are transferred from the glucometer (Accu-Check® Aviva Connect/Contour® next ONE) to the application with Bluetooth® connectivity. SineDie© analyzes the data introduced and, if necessary, makes dietary changes with an automatic notification to the patient. Recommendations regarding insulin treatment are notified through the professional version of the app SineDie© to the physicians, who decide to accept them or not. The system allows checking number of connections and the time spent for each user. The study, recently initiated, is a randomized trial 2:1 (SineDie© intervention versus standard care) that will include 84 patients. The goals are to evaluate the effectiveness and safety of the intervention and its impact in the professionals' workload, as well as patients' compliance and satisfaction.
Results and conclusions
The app SineDie© may be a good tool to prevent unnecessary hospital visits while keeping the best quality healthcare.

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P528

Adolescent type 1 diabetes self-management: what about dietary regimen?

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Introduction
Nutritional management and adequate food intake is one of the fundamental cornerstones in the treatment of Type 1Diabetes Mellitus (Type 1 DM) to achieve optimal diabetes control, and reduced risk of micro vascular complications. Despite this emphasis on the importance of dietary education and management, the actual dietary intake of Tunisian adolescents with diabetes is not well documented.
Aim
The aims were to describe the food and nutrient intakes in adolescents with Type 1 diabetes, to assess the importance of the dietary regime in the diabetes self-management and finally, to investigate associations between dietary intake and glycemic control.
Patients and Methods
We conduct a cross-sectional study including 33 adolescents with type 1 diabetes. Dietary intake was assessed with three 24-h recall interviews with each participant. We used *The Summary of Diabetes Self Care Activities questionnaire in Arabic version. (SDSCA-AR)* as a reliable and valid self-report measure of diabetes self-managementto evaluate the dietary regim self-care activities.
Results
General diet and specific diet were the gaps in specific self-care activities among adolescents with type 1 DM. The total energy intake of the adolescents is more than recommended in (63.6%). Carbohydrate and protein intakes was less than recommended in respectively 57.6% et 80.80% of the participants. However, lipid intake exceed the recommendation in 72.7% of the patients. The intake of fruits vegetables, and milk were insufficient. Nerveless the consumption of cereals are above the recommendation. Pastries and sweets were consumed by (84.4%) of the included patients. The glycemic control (HbA1C) was significantly associated with energy intake ($P=0.01$), (Body mass Index) BMI ($P=0.02$) and the age at the moment of the diagnosis of the diabetes. However, there was no relation between HbA1c and the nutrient intake.
Conclusion
Adolescents with type 1 diabetes pray less attention to the diet in the self-management activities. They did not met the dietary requirements. The food consumption can affect metabolic control. The nutrition therapy and promoting the dietary in the self-care activities of this population is very important and need to be regular and updated.

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P529

Epicardial fat accumulation in non-alcoholic liver disease and impaired glucose metabolism

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Patients with impaired glucose metabolism, either prediabetes (preD) or type 2 Diabetes (T2D), and non-alcoholic fatty liver disease (NAFLD) have a higher prevalence of cardiovascular events. Recent studies have shown a relationship between epicardial fat and myocardial ischemia.
Objective
To determine whether hepatic fibrosis assessed by liver elastography (LE) or Fibrosis-4 (FIB-4) score correlates with epicardial fat volume quantified by computed tomography (CT), as a risk marker of cardiovascular disease.
Methods
Cross-sectional study in patients with preD or T2D and NAFLD. Clinical data, serum markers and imaging studies (CT and LE) were obtained between May 2016 and December 2017. Patients with other causes of liver disease were excluded. Epicardial fat was quantified semiautomatically including voxels with attenuation values between -45 to -190 Hounsfield units. In LE, an increased liver stiffness was considered if ≥ 8.2 kPa. A FIB-4 Score (age in years$\times$AST) (platelet count$\times\sqrt{\text{ALT}}$) ≥ 2.67 was considered as possible fibrosis.
Results
Twenty-five patients met inclusion criteria. 84% (21/25) were men with an average age of 61.52 ± 13yo, BMI of 31.44 ± 3.15 kg/m^2 and body fat (CUN-BAE) of 36.04 ± 4.75%. 72% (18/25) had hypertension, 76% (19/25) dyslipidemia, 36% (9/25) SAOS, 20% (5/25) hyperuricemia and 60% (15/25) were ex-smokers or current smokers. Moderate-severe insulin resistance was observed (HOMA-IR of $9.47\pm5{,}263$). 52% (13/25) had T2D with an average glycosylated hemoglobin of 6.68 ± 1.67%. A 24% (6/25) presented increased liver stiffness assessed by LE. A significant positive correlation was found between epicardial fat and liver stiffness measured by LE ($r=0.45$, $P=<0.05$), as well as between epicardial fat and FIB-4 Score ($r=0.410$, $P=0.05$). Patients with increased liver stiffness had higher epicardial fat compared to patients with liver stiffness <8.2 kPa (289.83 ± 119.93 cm^3 versus 171.89 ± 98.72 cm^3, $P=0.023$). Additionally, a positive correlation was found between epicardial fat and AST levels ($r=0.411$, $P=<0.05$), triglycerides ($r=0.49$, $P=<0.05$), the presence of dyslipidemia, obesity and the occasional alcohol consumption ($r=0.429$, $P=<0.05$, $r=0.468$, $P=<0.05$ and $r=0.708$, $P=<0.01$, respectively). A significant negative correlation was found between epicardial fat and HDL levels ($r=-0.434$, $P=<0.05$).
Conclusions
In patients with impaired glucose metabolism, liver fibrosis assessed by LE or FIB-4 Score correlates positively with epicardial fat volume. The early identification of these situations allow us to establish preventive measures to reduce cardiovascular risk.

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P530

Vitamin B12 and gestational diabetes mellitus

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Objective/Design
Gestational diabetes mellitus (GDM) has been associated with serious complications for both the pregnant woman and the newborn. Vitamin B12 is implicated in some important metabolic procedures such as methylation and one carbon cycle and its deficiency can cause serious health problems, such as hyperhomocysteinemia, defective synthesis of neurotransmitters and fatty acids and more. However, it is not known if there is a link between vitamin B12 deficiency and the risk of GDM. The purpose of this study is to systematically investigate and meta-analyze the evidence that exists up to date for this association.
Methods
A comprehensive research was conducted in PubMed, Scopus and Cochrane Central Register of Controlled Trials up to November 30th, 2018. Data are expressed as odds ratio (OR) with 95% confidence intervals (CI). The I^2 index was employed for heterogeneity.
Results
Six studies ($n = 1{,}810$ pregnant women, 309 GDM cases) fulfilled eligibility criteria for qualitative and two studies for quantitative analysis. Women with vitamin B12 deficiency were at higher risk for developing GDM when compared with those who were vitamin B12 sufficient: OR 1.81 (95% CI, 1.25–2.63, I^2: 0%). Due to the small number of studies, the role of potential confounders could not be clearly estimated.
Conclusions
Vitamin B12 deficiency seems to be associated with increased risk of GDM. The pathogenetic mechanisms for this association need to be clarified in future studies.

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P531

TRMA syndrome (thiamine-responsive megaloblastic anemia): a case report

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Introduction
Thiamine responsive megaloblastic anemia (TRMA) syndrome, also known Rogers ***syndrome*** is a rare autosomal recessive inherited disorder characterized by a triad features of megaloblastic anemia, sensorineural deafness and diabetes mellitus. TRMA manifestation is caused by mutations in the gene SLC19A2 encoding a high-affinity thiamine transporter, which disturbs the active thiamine uptake into cells.
Case Presentation
We report a case of TRMA syndrome in a 16-year-old boy now. He has been the third child of first degree consanguineous parents. He was born at full term after uncomplicated pregnancy. At the age of 7 months, megaloblastic anemia without thrombocytopenia was confirmed. A the age of 2 years, an audiogram revealed sensorineural hearing loss. Electrocardiography and echocardiography were normal. Diabetes mellitus of non-autoimmune etiology was diagnosed at the age of 4 years old. The patient was started on insulin therapy. On the basis of history, clinical examination and laboratory investigations the diagnostic of TRMA syndrome was made. The patient was started on oral thiamine therapy. Thiamine‘s effect was found to be quite remarkable on the hematological disorders. However there was no improvement in hearing disability and the patient is still on insulin therapy.
Conclusion
In children, TRMA syndrome should be kept in mind especially when diabetes is associated with megaloblastic anemia and/or neurosensorial deficits. Early introduction of high dose thiamine can reverse anemia and allow more glycemic control for diabetes.

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P532

Study on efficacy of long-term education for achieving compensation of type 1 diabetes mellitus in children Almaty region of Kazakhstan

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Background
Education is a basic component – to assess achievement of compensation in children and adolescents with type 1 diabetes mellitus within a 3-year period after training.
Aim
The work was initiated to assess level of knowledge and compensation degree in children and adolescents with type 1 diabetes mellitus in ‘Type 1 Diabetes School’.
Materials and methods
A five-day training course was conducted in ‘Type 1 Diabetes School’ at the Almaty regional children’s clinical hospital, Kazakhstan Republic. The training was conducted by means of a structured program containing all appropriate sections. Before and after training course all participants were tested with a questionnaire containing 30 key questions for self-control. On the basis of the findings children and adolescents with type 1 diabetes mellitus were divided into groups, trained and untrained. 18 of 68 children and 20 of 36 adolescents were preliminary trained, 14 children and 16 adolescents got no training. DCA Vantage Siemens (USA) was used to measure glycated hemoglobin (HbA1c) by means of latex agglutination inhibition. Certified by the National Glycohemoglobin Standardization Program this method became the reference one. It helps demonstrate the predicting role of HbA1c level as a criterion for assessment of compensation.
Results and discussion
Before training children gave right answers to 25% of questions only. In 3 years they could give right answers to 75% of questions, mean HbA1c in trained and untrained children was 7.7% and 9.8%, respectively. Children who got no training, those with low level of knowledge and motivation both in them and their parents were hospitalized at the intensive care units more frequently both before and after training. Within follow-up period they gave right answers to 15% of questions only. The trained adolescents with type 1 diabetes mellitus initially could give right answers to 25% of questions, in 3 years there were 70% of right answers. In the untrained adolescents, level of knowledge remained as low as it was before and after 3-year follow-up, mean HbA1c level was 8.4 and 10.3% in the trained and untrained adolescents, respectively.
Conclusions
In the group of children trained for 3 years HbA1c mean level was 7.7%, in those untrained it was 9.8%. In the groups of trained and untrained adolescents mean HbA1c was 8.4% and 10.3%, respectively. Better compensation and level of knowledge in children as compared with those among adolescents confirm the role of family in the type 1 diabetes mellitus control.

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P533

A novel oral pyruvate dehydrogenase kinase 4 inhibitor ameliorates various spectrum of metabolic diseases in mice

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Pyruvate dehydrogenase kinase 4 (PDK4) activation is associated with metabolic diseases including hyperglycemia, insulin resistance, allergies, and cancer. We report here a new series of allosteric PDK4 inhibitor modified from hit anthraquinone. A novel PDK4 inhibitor, namely compound 8c, improved glucose tolerance in diet-induced obese mice. PDH activity in muscle and liver was enhance d by compound 8c treatment. Given the importance of PDK4 in immune cells including mast cells, we studied the effect of compound 8c in a passive cutaneous anaphylaxis mouse model. Compound 8c successfully improved allergic reactions as evidenced by decreased Evans Blue extravasation in ears. Additionally, compound 8c exhibited anticancer activity by controlling cell proliferation, transformation, and apoptosis in colon cancer cell lines. PDK4 inhibitors could be widely applicable in a various spectrum of metabolic diseases including diabetes, allergies and obesity-related cancers.

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P534

Quality of life in patients undergoing bariatric surgery

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Aim
Evaluate results of bariatric surgery by using the Bariatric analysis and reporting outcome system (BAROS) scoring system
Patients and methods
Observational clinical study of consecutive cases of patients undergoing bariatric surgery in Reina Sofia University Hospital (Córdoba, Spain) and clinical follow-up in the Endocrinology service between January and December 2018. Statistical analysis performed with SPSS 24th version.
Results
152 patients were recruited for our study. Age: 48.64 ± 10.12 years. 78.3% women. As far a type of surgery patient underwent were gastric bypass (65.1%), of gastric sleeve (31.6%) and gastric banding (3.3%). Prior to surgery 31.6% of patients suffered from diabetes, 40.8% of HBP, 35.5% of dyslipidemia and 19.7% of obstructive sleep apnea. Time since surgery was 48.39 months. Percentage of excess weight loss (WLP) was 60.46 ± 18.80%. In BAROS scoring system, quality of life (QoL) is assessed by Moorehead-Ardelt questionnaire, which was reported as normal in 20.4% of patients, fair in 23% and very good in 54.6%. 2% (3 patients) had poor or very poor QoL. There were no statistically significant differences between QoL and type of surgery performed. Patients with very good QoL had a statistically significant higher WLP (64.29%) than patients with normal (57.39%) and good (57.12%) QoL. Although this difference was found among other groups, it did not reach the statistical significance.
Conclusions
In our experience, QoL of patients after bariatric surgery is good or very good in 77.6% of cases, without statistically significant differences between QoL and type of surgery performed. QoL is influenced by loss weight so that patients with a very good QoL showed statistically significant higher WLP than patients with normal and good QoL.

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P535

Metabolic encephalopathy secondary to diabetic ketoacidosis

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Case presentation
A 35-year-old man presented to the emergency department (ED) in a confused and agitated state. His past medical history was significant for poorly controlled type 1 diabetes, complicated by background diabetic retinopathy. He was taking basal/bolus insulin and had a history of diabetic ketoacidosis (DKA) eleven years prior. He also had multiple sclerosis however disengaged with neurology services and was non-compliant with interferon therapy. Prior to admission he worked as a caretaker in a school, smoked ten cigarettes per day, took excess alcohol and smoked cannabis twice per week. Following initial investigations, he was found to be in DKA. Unfortunately, despite timely and appropriate management his neurological symptoms and behavioural disturbance persisted. Biochemistry revealed DKA (pH 7.17, blood ketones 8 mmol/l and blood glucose 26 mmol/l). Alcohol levels were undetectable, urine and serum toxicology screens were negative. Excluding ketosis, acidosis and hyperglycaemia there were no significant abnormalities in other biochemical or haematological investigations. HbA1c was 70 mmol/mol (8.5%). Analysis of cerebrospinal fluid (CSF) on the second day of admission revealed an elevated protein at 61 mg/dl with normal glucose 6.3 mol/l, erythrocytes 86 u/l and leucocytes 1/uL. Serum and CSF extended viral PCR was negative. Neuroimaging revealed temporal lobe abnormalities consistent with an encephalopathic process. The patient underwent extensive investigation looking for evidence of autoimmune, infective, metabolic, toxic and paraneoplastic encephalopathy, with no obvious cause demonstrated. Temporal lobe biopsy showed marked astrocytic gliosis without evidence of vasculitis, inflammation, infarction or neoplasia. Electroencephalogram was consistent with an encephalopathic process. A diagnosis of metabolic encephalopathy secondary to DKA was reached.
Results and treatment
In addition to his initial treatment for DKA followed by basal/bolus insulin, the patient was also given high dose intravenous thiamine and a reducing regimen of chlordiazepoxide. He received empiric antiviral treatment and folic acid supplementation. Subsequent treatment was largely supportive, involving a multidisciplinary team of occupational therapy, physiotherapy, social care and neuropsychology. Despite neuro-rehabilitation, the patient's cognitive function remained impaired up to 18 months post presentation and he ultimately required residential care.
Conclusion and points for discussion
DKA poses a serious and significant neurological risk to patients with diabetes mellitus. To our knowledge this is the second case report of metabolic encephalopathy as an acute complication of DKA. The aims of this report are to highlight metabolic encephalopathy as a complication of DKA and to explore the current research in diabetic related brain injury.

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P536

Maternal weight status and gestational diabetes

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Introduction
Gestational diabetes and maternal obesity have long been regarded as risk factors for pregnancy. The amount of weight gained during pregnancy can affect the immediate and future health of a woman and her infant [1]. The objective of our study is to evaluate the impact of maternal weight status on the glycemic profile of women followed for gestational diabetes.
Materials and methods
This is a retrospective study over three years, including 25 patients hospitalized for gestational diabetes in Endocrinology-Diabetology Department of University Hospital Center in Oujda, Morocco.
Results
The mean age of our patients was 33 years ±6.08 (21 to 44 years). Mean gestational age of GD discovery was 27.27 weeks of amenorrhea. Mean pre-gestational BMI was of 27.45 ± 2.42 kg/m^2. The average weight gain was 7.33 ± 2.08 kg. According to the pre-pregnancy BMI, 4.9% were underweight, 44% were of normal weight, 46.1% were overweight and 5% were obese. Pre-pregnancy BMI was higher in women with excessive gestational weight gain (32.23 ± 2.81 kg/m^2) and overweight gestational weight gain (GWG) (27.99 ± 1.62) than in women with adequate weight (22.9 ± 1.2 kg/m^2). The level of glycated hemoglobin was higher in women with excessive GWG (5.46 ± 0.92%) than in women with overweight gestational weight gain (4.5 ± 0.23). After delivery, 14.8% newborns of excessive gestational weight gain were macrosomes with neonatal hypoglycemia in one newborn.
Discussion
Maternal, perinatal and neonatal complications are strongly associated with gestational diabetes mellitus. Women who are followed for gestational diabetes are at risk of maternal and neonatal complications during pregnancy. And the association of pregestational overweight or obesity with excessive gestational weight gain may aggravate this risk. In addition, compared with GWG within the Institute of Medicine (IOM) recommendations, excessive GWG increased the incidence of cesarean section and infant macrosomia, while inadequate GWG decreased the incidence of LGA [2].
References
[1] Siega-Riz AM, Viswanathan M, Moos MK, Deierlein A, Mumford S, Knaack J, *et al*. A systematic review of outcomes of maternal weight gain according to the Institute of Medicine recommendations: birthweight, fetal growth, and postpartum weight retention. *Am J Obstet Gynecol* 2009;201:339.e1–14
[2] Weight gain during pregnancy. Committee Opinion No. 548. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2013;121:210–2.

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P537

Diabetic retinopathy: Prevalence and risk factors

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Intoduction
Diabetic retinopathy remains one of the major causes of blindness. The management of the diabetic patient is multidisciplinary. The objective is to

study the prevalence of retinopathy in a group of type 2 diabetic patients and to update the risk factors.
Patients and methods
This is a cross-sectional study during 3 years of 129 type 2 diabetic patients followed up for endocrinology and metabolic diseases at the Mohammed VI University Hospital of Oujda, who received an ophthalmological evaluation.
Results
The average age of the patients is 58.2 years, with a female predominance. The reason for hospitalization was dominated by diabetic imbalance. One-third of the population had a high blood pressure. The fundoscopic exam revealed a diabetic retinopathy in 44.5% of cases, with a non-proliferative type in 67.4% of cases and a proliferative type in the 32.6% other. Diabetics with retinopathy had a duration of diabetes more than 10 years in 60.4% of cases, and a poor glycemic control (HBA1C> 8%) in 76.2% of cases. There is a significant correlation between retinopathy and dyslipidemia (63.15% of cases) (*P* 0.009). Diabetic retinopathy was associated with arterial hypertension in 47% of cases, and nephropathy in 18% of cases.
Conclusion
Our study showed that the glycemic imbalance, the age of diabetes and dyslipidemia predisposed to retinal damage, hence the importance of optimal glycemic control at the discovery of diabetes and regular monitoring by fundoscopic exam.

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P538

Efficacy of plasmapheresis in the management of severe hypertriglyceridemia

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Objective
Severe hypertriglyceridemia is one of the leading causes of acute pancreatitis which is associated with increased mortality and morbidity. Here we evaluate the effectiveness of plasmapheresis on triglyceride levels in our group of patients who had plasmapheresis in our endocrinology clinic.
Method
We retrospectively evaluate clinical and laboratory reports between 2016–2018, for demographic parameters and the lipid levels before and immediately after the plasmapheresis session. Same double filtration plasmapheresis machine and same blood purificationand plasma seperator sets were used for all plasmapheresis sessions. Serum triglyceride, total cholesterol and HDL levels were measured with spectrophotometric analysis.
Results
We are presenting the results of 8 patients (F/M:4/4) and 31 session of plasmapheresis. All patients had severe hypertriglyceridemia, above 1000 mg/dl. Mean age was 43.5 years. 5 patients admitted to emergency clinic with acute pancreatitis and had plasmapheresis treatment. Two patients were pregnant, one of them admitted to emergency with pancreatitis and one of the pregnant patients was referred to our outpatient clinic with severe hypertriglyceridemia and had repetitive plasmapheresis up to delivery. One patient who had a history of 9 pancreatitis attack was taken to routine plasmapheresis program every 3 weeks. Mean serum triglyceride levels before and after plasmapheresis were 3399 ± 1687 mg/dl and 2509 ± 1559 mg/dl and there was a significant difference (*P*: 0.032). Mean serum HDL was 89.5 ± 64.8 mg/dl before plasmapheresis and 70.4 ± 58.7 mg/dl after plasmapheresis. Mean total cholesterol was 449 ± 217 mg/dl before plasmapheresis and 370 ± 208 mg/dl after plasmapheresis. The decrease in HDL and total cholesterol levels before and after plasmapheresis was not significant statistically. The mean decrease in triglyceride levels with plasmapheresis in this 31 session was % 24.5. Only in 5 session triglyceride levels decreased 50% or more. In 2 session we had triglyceride level <500 mg/dl after plasmapheresis.
Conclusion
We observed mild to moderate decrease in serum triglyceride levels after plasmapheresis in severe hypertriglyceridemia patients. Further clinical trials are needed to assess the effectiveness of plasmapheresis in managing hypertriglyceridemia and triglyceride induced acute pancreatitis.

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P539

Insulin pump therapy in patients with type 1 diabetes in Morocco

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Introduction
Strict metabolic control is the main purpose in the management of type 1 diabetes in order to prevent patients from macro or microvascular complications. The therapy of type 1 diabetes was optimized by the basal-bolus regimens with multiple daily injections in addition to the educational programs such as flexible insulin therapy. Nevertheless, despite all those therapeutic approaches, the metabolic control is not always obtained. The specific aim of our study is to demonstrate the effectiveness of insulin pump therapy in improving the metabolic control of patients with type 1 diabetes in Morocco.
Methods
In the Department of Endocrinology, Mohammed VI Hospital, Medical School, Mohamed the First University, Oujda, Morocco, we describe a prospective study collecting six moderately controlled patients with type 1 diabetes (HbA1c $\geq 7.5\%$), previously educated to insulin flexibly. Those patients were treated by the subcutaneous infusion pump in order to improve their metabolic control. Over a 3 months period of the study, the data collected: HbA1c, the rate of hypoglycemic events and the insulin requirements of the basic rate.
Results
The mean age was 20.1 ± 5.9 years old, 5 girls and 1 boy. The average diabetes duration was 5.5 ± 2 years. Over a 3 months period of the study, the frequency of the mild hypoglycemia decreased from 10 ± 4.1 episodes/month to 1 ± 0.5 episodes/months and the HbA1c decreased from 8.4% to 7% Δ 1.4%. The insulin basal requirements were reduced in 2/3 of patients by 0.04ui/24h and the adaptation of basal rates allowed the correction of the dawn phenomenon
Conclusion
The basal-bolus regimens with multiple daily injections or insulin pump were recommended for therapy of type 1 diabetic patients. In Morocco, the opportunity to be treated by the insulin pump therapy is not possible for all our patients with type 1 diabetes especially due to economic reasons. In our Department, we were able to offer to our poorly controlled patients the possibility to benefit from this approach.

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P540

Role of proinflammatory cytokines TNF-α and IL-6 in pathogenesis of type 2 diabetes mellitus in persons exposed to ionizing radiation after the Chernobyl NPP accident

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Contemporary research data indicate that pancreatic beta cells are sensitive to ionizing radiation. Our recent studies showed a significant (2–3-fold) increase in the type 2 diabetes mellitus (T2DM) incidence in adults exposed to ionizing radiation in a young age within 1986–1990 time period compared to the entire population of Ukraine. Currently there are no data on the time pattern of content of proinflammatory cytokines TNF-α and IL-6 in the clean-up workers of Chernobyl nuclear power plant accident (ChNPPA), while both cytokines are critical for pathogenesis and clinical course of T2DM. The clean-up workers of ChNPPA ($n=111$) participated in emergency works in the 'acute iodine period' within first months upon accident were involved in the study. The 66 of them were T2DM patients. The 30 persons were admitted as a control group. Higher concentrations of circulating TNF-α and IL-6 were established in the clean-up workers having T2DM. There was a significant correlation found between the TNF-α serum concentration and increased body mass index (BMI). However, it was not reliable ($r=0.224$; $P>0.05$). A direct average correction with a high level of statistical significance ($r=0.525$; $P<0.001$) was found between the IL-6 concentration and BMI. A consistent pattern of the reduction of cytokine concentration along with perfect clinical and metabolic compensation of T2DM was revealed. There was no dependence of the level of proinflammatory cytokines on the duration of the T2DM. Thus, the increased concentrations of TNF-α and IL-6 proinflammatory cytokines highlighting an activation of humoral component of immune response were found in the clean-up workers of an 'acute iodine period' of ChNPPA having now the T2DM. Concentration of proinflammatory

cytokines is linked to the indices of glycemic control and body weight. The increased risk of T2DM and cardiovascular disease should be considered when managing patients e.g. having thyroid cancer, in which some medical radiological procedures are indicated, including the radionuclide diagnostics or treatment.

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P541

A case of DRESS syndrome associated with autoimmune type 1 diabetes

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Introduction
DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome is a severe multiorgan drug reaction, often associated with the development of autoimmune diseases. Pathogenically it has been related to the reactivation or the primary infection of different herpes virus.
Clinical case
A 33-year-old woman with a history of residual epilepsy, after resection of a cerebellar pleomorphic xantoastrocytoma, started treatment with Levetiracetam and after 3 months presented oral aphthous lesions and fever followed by a generalized erythematous skin rash. Laboratory findings showed: leukocytosis with eosinophilia, altered liver profile, impaired renal function and eosinophiluria related to an immunoallergic nephritis, negative serologies for VIH, VHB, VHC, negative autoimmunity (ANCA, ANA and complement) and negative result for Paul Bunnel, HHV-6 and HHV-7. The abdominal-pelvic TC did not present significant findings whereas skin biopsies found a dense lymphocytic infiltration with effacement of the dermoepidermal interface and dermal eosinophilia suggestive of toxicodermia in relation to the development of DRESS syndrome. We suspended treatment with Levetiracetam and started high doses of corticosteroids treatment with mycophenolate, experiencing a progressive clinical improvement of the patient. After about 4 weeks from starting corticosteroid therapy our patient developed a diabetes mellitus with hyperglycemia of 687 mg/dl (Normal 70–110 mg/dl), ketoacidosis symptoms, cetonuria and fluctuating insulin requirements. Analytically highlighted an undetectable C-peptide <0.02 ng/ml (Normal 1.0-4.0 ng/ml) and positive pancreatic autoimmunity with antibodies: Anti-GAD65 21.3 lU/ml (Normal ≤ 5), Anti-Tyrosine phosphatase IA2 19 U/ml (Normal ≤ 10), Anti-Insulin 2.81 (Normal ≤ 18.0), Anti-Zinc 8-transporter 1.57 U/ml (Normal 0.00–15.00). After correction of ketoacidosis by fluids and intravenous insulin treatment, a bolus-basal subcutaneous insulin regimen was initiated. The patient was followed in the ambulatory with great difficulty to achieve optimal glycemic control mainly due to the variability in the subcutaneous absorption of insulin depending on cutaneous status.
Discussion
In Endocrinology, DRESS syndrome has been related to the development of fulminant diabetes mellitus (a subtype of diabetes with negative autoimmunity and massive destruction of pancreatic beta-cells) as well as with Hashimoto's thyroiditis and Graves-Basedow disease but there are few cases reported in literature of diabetes mellitus with positive pancreatic autoimmunity. It is important to know the possible associations with endocrine pathologies of DRESS syndrome since they can modify the management, follow-up and the multidisciplinary approach of the patient.

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P542

Examination of the care pathways of adults with diabetes undergoing haemodialysis for end stage renal failure

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Background
Management of diabetes in patients with End Stage Renal Failure (ESRF) is complex, requiring intervention from multiple disciplines. The Joint British Diabetes Societies and Renal Association published the first ever guidelines for the management of patients with diabetes undergoing haemodialysis for ESRF in 2017.
Aims and objectives
Assess Current Care Pathways of all patients with Diabetes undergoing Haemodialysis in Cork University Hospital, Ireland to establish whether management is concordant with the Guidelines of the Joint British Diabetes Societies and Renal Association.
Methods
Structured patient interviews to assess availability and utilisation of diabetes-specific services. Structured interviews with medical, dietetic and nursing staff to assess therapeutic management interventions. Review [HbA1c] over a six month period. The findings were compared with the designated Guidelines.
Results
49/51 patients took part in interviews. 73% had not attended their G.P. for diabetes specific care in previous 6-months. 35% have never attended a Hospital Diabetes Clinic. 37% had not undergone a foot examination in previous 12 months. 80% followed Renal and Diabetes diets. 84% attended regular retinal screening. Management of Glycaemic Control: diet alone ($n=12$), oral hypoglycemic agents/insulin ($n=39$). Recommended [HbA1c] is 58-68mmol/mol. 67% of patients had mean [HbA1c] <58 mmol/mol. 5% had mean [HbA1c] >80 mmol/mol. Interviews with health care staff revealed: 1) an annual review of each patient by disciplinary teams involved in care was not available as recommended by guidelines. 2) absence of routine foot inspection of this high-risk patient group.
Conclusion
Overall, the current Care Pathways do not effectively manage the complex needs of this group. Dietary and ophthalmic management is concordant with recommendations. However, management of glycaemic control and foot complications remain fragmented. The absence of a standardized foot screening care pathway for this patient population is significant and may have an impact on patient outcomes. Furthermore, the HbA1c levels of two thirds of this patient population are below the recommended range of 58–68 mmol/mol. This may indeed highlight that the current therapeutic management of glycaemic control in this patient population may be too tight. The implications of tight glycaemic control in this patient population has not been extensively investigated. Certainly, the findings of this study would suggest that the outcomes of patients with tight glycaemic control should be evaluated further.

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P543

Exploratory study into communication styles of diabetes healthcare professionals according to their patients numerical ability

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Background and aims
Type 1 diabetes mellitus (T1DM) requires daily self-management to mimic endocrine function, using numerical skills such as carbohydrate counting and interpreting nutritional information. Healthcare professionals (HCPs) rely on effective communication to relay information to people with T1DM to enable good self-care. Curricula for diabetes self-management education (DSME) courses require high-school level numerical skills. Eighty percent of adults in the United Kingdom are functionally innumerate therefore an access gap exists: those with low numeracy may be unable to access DSME course content and optimise self-management. There has been no research studying HCP communication with patients with T1DM and low numeracy. Our study aimed to assess HCP perception of their patient's numeracy and the effect this has on their communication approaches.
Materials and methods
This pilot, double-blinded, cross-sectional observational study recruited adults with T1DM attending specialist outpatient clinics in South London to complete a validated Diabetes Numeracy Test (DNT-5). Consultations were observed, using two checklists to measure HCP use of verbal and non-verbal communication techniques and information relayed by the HCP. Following consultation, HCPs (doctors or diabetes specialist nurses) estimated patient's DNT-5 score. Analysis included descriptive statistics and Pearson correlation.
Results
Fifty-eight patients completed the DNT-5 test. 5 patients (9%) had low numeracy (scoring $<3/5$) and 53 patients (91%) had adequate numeracy (scoring $\geq 3/5$). Mean $\pm$ SD DNT-5 score achieved by patients was 4.17 ± 1.02. The average HCP-perceived score was 3.72 ± 1.20, with a significant relationship between the two ($r=0.339$, 95% CI 0.088 to 0.549, $P < 0.05$). The relationship between HCP perceived level of numeracy and filtering of diabetes information ($\chi^2=9.04$, $P=0.94$) and communication methods used by HCPs ($\chi^2=14.50$, $P=0.88$) did not reach significance. The commonest information conveyed was insulin dose adjustment for carbohydrate intake (48/58 [83%]) and explaining/changing dose of medication (46/58 [79%]).

Conclusion
Diabetes specialist HCPs are able to identify patients with low numeracy. They did not filter diabetes information ensuring equity of information provided. However, they did not tailor their communication methods to ensure that those with low numeracy understood the given information. This exploratory study provides a methodology for assessing the support available to people with low numeracy. We propose that HCPs require additional communication training so patients with low numeracy are able to understand all information provided. Further studies are required to confirm a resultant difference in patient recall following consultation.

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P544

Enterotypes of the gut microbiome in Russian population and their metabolic activity

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Background
Network analysis of species abundance across different individuals suggested that the overall structure of the human gut microbiota in each individual conforms to discrete and distinct patterns defined by interactions within community members. This hypothesis was investigated using a dataset of metagenomic sequences from American, European and Japanese individuals. Multidimensional cluster analysis and principal component analysis revealed that all individual samples formed three robust clusters, which have been designated as 'enterotypes'.
Aims
To determine the enterotypes of gut microbiome and their metabolic activity in Russian population.
Materials and methods
To determine the phylogenetic and functional basis of the enterotypes, we investigated in detail their differences in composition at the phylum, genus, gene and pathway level as well as correlations in abundance of co-occurring genera. We analyzed gut microbiota in 92 patients with various glucose tolerance: normal glucose tolerance ($n=48$), prediabetes ($n=24$) and type 2 diabetes (T2D) ($n=20$). Metagenomic analysis was performed using 16SrRNA sequencing.
Results
The dominant bacteria in total samples composition were two main phyla: Bacteroidetes ($12.7\pm9.86\%$) and Firmicutes ($57.09\pm13.6\%$). Taxonomic analysis of the sample revealed two clusters with average silhouette value 0.22. After the clustering into enterotypes the Prevotella, Oscillospira, Flavobacterium, Sphingobacterium, Parabacteroides abundance turned to be higher in the first cluster, and the Ruminococcus, Peptoniphilus, Thiothrix, Legionella in the second cluster ($P<0.004$). There were no sex and age differences in the clusters, but the T2D prevalence was higher ($P=0.016$) in the second cluster. The relative abundances of the different species making up the samples' richness are defined as 'evenness'. The Shannon-diversity index relates both, OTU richness and evenness. We found that the microbial diversity (alpha diversity) ($P=8.089e-05$) and the percentage of pathways for the synthesis of vitamins B9, B2, B6, K were significantly less, but the percentage of pathways for the synthesis of vitamin B12 significantly higher in the second cluster. The second cluster had a smaller representation of enzymes that convert butyryl-CoA into butyrate.
Conclusions
Despite the absence of high confidence taxonomic clustering, we found two enterotypes in the gut microbiota of Russian population that vary in species, functional composition, T2D prevalence and are sex and age independent.

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P545

Lipid profile and cardiovascular risk in ankylosing spondylitis

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Introduction
Ankylosing spondylitis (AS) is a chronic systemic inflammatory disorder which affects the sacroiliac joints, the axial skeleton, peripheral joints as well as other organs. It develops in young adults causing significant mobility and functional disorders, with associated severe dysfunction or disability. Ankylosing spondylitis has serious adverse effects on the ability to work and quality of life. Biologic agents are used for the treatment of AS, this effect having multiple effects on lipid profile and cardiovascular risk.
Aim
The aim was to follow-up a group of AS patients as far as their mobility and functional ability, as well as to evaluate comorbidities, lipid profile and cardiovascular risk and to evaluate the effect of treatment on these parameters.
Methods
Questionnaires were used for the estimation of function and mobility, namely BASDAI, BASFI, BASMI, health indices, namely BAS-G, ASAS-Health Index and a questionnaire of productivity and work-related productivity, namely WPAI:GH was utilized. The inflammation indices ESR and CRP were measured, as well as blood total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides. The 10-year cardiovascular risk was evaluated using SCORE.
Results
BASDAI index decreased from 3.91 ± 0.67 before to 2.51 ± 0.47 (mean $\pm$ S.E.M.) after treatment in AS patients ($P<0.001$, Student's t test), BASFI from 4.05 ± 0.68 to 3.17 ± 0.61 ($P<0.001$), BAS-G from 4.25 ± 0.69 to 3.29 ± 0.57 ($P<0.001$), ASAS-Health Index from 7.29 ± 1.23 to 5.23 ± 0.93 ($P<0.001$) and ESR from 16.12 ± 3.4 mm/h to 12.41 ± 2.9 mm/h ($P<0.001$). Total cholesterol increased from 113.52 ± 20.26 mg/dl before to 193.41 ± 8.81 mg/dl ($P<0.001$) after treatment, HDL cholesterol from 25.37 ± 4.64 mg/dl to 54.06 ± 4.74 mg/dl ($P<0.001$), LDL cholesterol from 69.52 ± 13.02 mg/dl to 112.5 ± 8.67 mg/dl ($P<0.001$) and triglycerides from 86.97 ± 22.21 mg/dl to 138.65 ± 23.91 mg/dl ($P<0.001$).
Conclusions
It appears that in AS indices of function and mobility as well as health indices improve after treatment, whereas the lipid profile is altered, without, however, an adverse effect on atherogenesis and cardiovascular risk.

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P546

Diagnostics of carbohydrate metabolism according to the regularity of menstrual cycle

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Objectives
To analyze the presence of correlation between DHEA-S level and glycemic indices at CGMS of intercellular fluid according to the regularity of menstrual cycle of women with type 1 diabetes mellitus.
Methods
The study of daily dynamics of glucose has been performed with continuous glucose monitoring system (CGMS) Medtronik MINIMED company, the USA. The study involved 155 patients with type 1 diabetes mellitus. The patients were divided into 2 groups: group 1 - women with regular menstrual cycle ($n=117$), group 2 - women with abnormal menstrual cycle ($n=38$). The groups were compared in mean age (28.59 ± 7.10 years) and duration of type 1 diabetes mellitus (10.46 ± 7.67 years).
Results
In the first group, significant negative correlations were found between the level of DHEA-S with the duration of the hyperglycemia period ($r_s=-0.19$), the duration of DM type 1 ($r_s=-0.23$) and a positive correlation with the duration of the normal glycaemia period ($r_s=0.24$). In the second group, significant negative correlations were found between the DHEA-S level and the HbA_{1C} level ($r_s=-0.50$), the mean glucose level in the ICF ($r_s=-0.40$), the maximum glucose level in the ICF ($r_s=-0.44$) with the duration of the hyperglycemia period ($r_s=-0.41$) and a positive correlation with the duration of the normal glycaemia period ($r_s=0.39$).
Conclusions
1. Regardless of the regularity of the menstrual cycle, hyperglycemia is accompanied by a decrease in the DHEA-S level.
2. Decrease in the DHEA-S level has been noted in the onset of DM type 1 with a regular menstrual cycle.

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P547

Clinical characteristics and foot amputations rate in patients treated in a multidisciplinary diabetic foot unit

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Objective
This study reviews the clinical characteristics of patients treated in a Multidisciplinary Diabetic Foot Unit (MDFU) and analyzes the rate of diabetic foot amputations and the risk factors associated.
Design and methods
A retrospective cohort study including data from all patients who attended the MDFU during December 2017-October 2018 period. The patients were followed until January 2019. Clinical, anthropometric, and biochemical parameters (HbA1c, LDL-c) were determined. A descriptive analysis, cumulative incidence of foot amputations, and a correlation analysis (significance <0.05) was performed.
Results
A total of 118 subjects with a median age of 65 ± 11 years were included. Of these, 77% were males and 93% had type 2 diabetes mellitus (diabetes evolution time 19 ± 11 years). 52% of patients were in secondary prevention (of these, 41% had history of lower-extremity amputation). Clinical form: at-risk foot (without pre-ulcerative signs) 40.7%, neuropathic ulcer 20.4%, neuro-ischemic ulcer 14.8%, infected foot 13%, neuropathic arthropathy 3.7%, and risk-free foot 7.4%. The severity of foot ulcers according to the Wagner's ulcer classification scale was: grade 1, 22%; grade 2, 5%; grade 3, 13%; grade 4, 2%; and grade 5, 1%. Subjects were characterized as patients with high prevalence of chronic complications: sensory neuropathy 77%, retinopathy 46%, peripheral artery disease 46%, nephropathy 30%, ischemic heart disease 25%, and cerebrovascular disease 16%. Mean values of the biochemical and anthropometric parameters: HbA1c 8%$\pm$2, LDL-c 110 mg/dl$\pm$38, BMI 30 kg/m$^2\pm$5. The average time follow-up was 9.4 ± 4 months. Incidence of foot amputations was 14% (25% major amputation); 63% occurred in patients with history of lower-extremity amputation. Median time to the amputation was 6 ± 5 months. Correlation analysis showed retinopathy ($P=0.04$), peripheral artery disease ($P=0.002$), sensory neuropathy ($P=0.086$), smoking ($P=0.01$) and alcoholism ($P=0.03$) to be factors related to foot amputation; but not glycosuric drugs (28 subjects, $P=0.6$). HbA1c value showed a reduction in 1.7% ($P=0.01$) at the end of the follow-up.
Conclusions
Patients attended in MDFU are characterized by high morbidity with secondary prevention being the most frequent cause of medical care. Retinopathy, peripheral artery disease, sensory neuropathy, smoking and alcoholism were factors related to foot amputation incidence. Primary prevention should be a priority in MDFU. It is necessary to implement a new preventive comprehensive foot care program.

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P548

Microbiota changes in type 2 diabetes patients intolerant to metformin after drug reintroduction

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Introduction and objectives
Metformin (MTF) is the most used oral antidiabetic drug for the treatment of type 2 diabetes (T2D). However, intolerance to drug is frequent and limits its use. There are controversies about the cause of this problem, the gut microbiota has been proposed to be responsible. The gradual introduction of MTF could exercise an adaptation of gut microbiota that would facilitate tolerance to MTF. In this study we evaluate the metabolic changes and gut microbiota when introducing MTF in T2D patients with a history of intolerance.
Material and method
Prospective study, MTF 850 mg was introduced progressively (increasing doses every 2 weeks) to 40 patients. Those who tolerated the final dose were classified as tolerant. The subjects who presented digestive symptoms, to the introduction or dose progression, were classified as intolerant. Blood analysis and DNA extraction from faecal samples were made.
Results
Mean age 62.8 ± 10.5 with 11.39 ± 8.1 years of evolution of DM2. 70% of the patients were male. Diabetes complications: 15% microalbuminuria, 15% retinopathy and 5% neuropathy. Physical examination: weight 82.6 ± 17.2 kg with BMI 32.2 ± 6.7 kg/m^2. Baseline analysis: Hb1Ac 7.38 ± 0.9%, glucose 149.3 ± 41.41 mg/dl, Cr 0.9 ± 0.31 mg/dl, LDL 95 ± 31 mg/dl, HDL 51 ± 12.2 mg/dl, total cholesterol 180.9 ± 39.8 mg/dl, triglycerides 175 ± 98 mg/dl, microalbuminuria 60 ± 160 mg/l. After the introduction 31.3% ($n=10$) were classified as tolerant to MTF. Nine samples of microbiota extracted at the end of the study were sequenced; five tolerant and four intolerant. We analysed the proportion of phyla, biodiversity and homogeneity of the samples with Shannon and Pielou indices.

Proportion phyla ($n=9$)	Tolerants ($n=5$) Mean$\pm$S.D.	Intolerants ($n=4$) Mean$\pm$S.D.	Kruskal-wallis test *P* value
Actinobacteria	14.4725$\pm$24.43	2.628$\pm$2.495	0.6
Bacteroidetes	36,2625$\pm$9.61	47.364$\pm$7.79	0.086
Cyanobacteria	0.08754$\pm$0.098	0.092 $\pm$0.142	0.53
Firmicutes	37,4375$\pm$17005	37.64$\pm$9.02	1
Fusobacteria	0.0950$\pm$0.19	0.00$\pm$0.00	0.26
Lentisphaerae	0.0075$\pm$0.00957	0.04$\pm$0.058	0.78
TM7	0.00$\pm$0.00	0.00$\pm$0.00	1
Tenericutes	0.025$\pm$0.33	0.032$\pm$0.056	0.89
Verrucomicrobia	0.00$\pm$0.00	0.05$\pm$0.07	0.18
Proteobacteria	23.25$\pm$22.9	12.01$\pm$7.1	0.62
Others	0.5$\pm$0.895	0.13$\pm$0.15	0.9

Conclusions
No differences were seen in intestinal microbiota profiles at the phyla level among patients tolerant and intolerant to MTF after the reintroduction of the drug. The small sample size could limit our results. The remaining samples are being analyzed to clarify possible changes in the main phyla.

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P549

PRIMAVERA study: sibutramine therapy safety monitoring in patients with obesity

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Objective
The aim of the study was to assess the effectiveness and safety of long-term sibutramine therapy in routine clinical practice.
Materials and methods
In total, 98 774 patients (82.3% women, 17.7% men), from 142 cities of the Russian Federation were enrolled in the PRIMAVERA program. The mean age of the patients was 39.39 ± 10.38 years, the mean body weight was 99.1 ± 14.28 kg, and the mean BMI was 35.7 ± 4.41 kg/m^2. Physicians determined the duration of the sibutramine therapy taking into consideration clinical conditions: 59.3% of patients took the drug for six months, the treatment course of 37.7% of patients was 12 months, and 3% of patients had treatment for three months.
Results
BMI reduction correlated with the treatment duration: 3.4 ± 1.53 kg/m^2 after three months of therapy, 5.4 ± 2.22 kg/m^2 after 6 months, and 7.2 ± 3.07 kg/m^2 after 12 months. The body weight reduction after 3, 6 and 12 months of treatment was 9.5%, 15.1%, and 19.7%, respectively. The body weight loss associated with the sibutramine treatment was accompanied by a slight decrease in blood pressure and did not lead to any significant increase in the heart rate (HR).
Conclusions
The results of the PRIMAVERA study confirmed the lack of increased risk of using sibutramine in routine clinical practice in patients without underlying cardiovascular disease and low rate of adverse events.

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P550

Does therapeutic education really prevent lipodystrophy?

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Introduction
Therapeutic education (TE) on injection techniques and zooning is a key step for any insulin-treated patient. Our study's objective was to evaluate the role of ET and the number of sessions required to prevent lipodystrophies (LD).
Materials and methods
We conducted a prospective study including any diabetic insulin-treated patient for more than 6 months, followed in our unit between February 2015 and June 2017. Patients responded to a questionnaire regarding the number of zooning therapeutic education sessions and the characteristics of these sessions. The clinical examination examined for the presence of LD. The statistical analysis was performed by the SPSS software.
Results
During the period mentioned, 1000 insulin patients were included, with a sex ratio of 2F/1H. The average age was 42 ± 20 years. The average age of diabetes was 9.6 years (from 6 months to 37 years). The average duration of insulin therapy was 5.7 years (6 months to 37 years). The types of diabetes were: type 2 diabetes in 60% of patients, type 1 diabetes in 38% of patients and 2% slow type 1 diabetes. The prevalence of LD was 48%. Regarding S.D., 90% of patients received sessions with a number of one to two sessions in 55% of patients, 3 to 4 sessions in 30% of patients, and 5% more than 4 S.D. sessions. Among patients who received 1 to four education sessions, 45% had LD with $P = 0.33$, while in patients receiving more than 4 sessions, LD was objectified in only 35% with $P = 0.008$.
Conclusion
Therapeutic zooning education is essential when starting insulin therapy, but in order to prevent LD, at least 4 S.D. sessions are required, hence the need to reassess knowledge at each consultation.

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P551

Insulin injection techniques: what do moroccan diabetic patients do?

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Introduction
A good injection technique is crucial to ensure that insulin is properly administered into the subcutaneous tissue and then released at the right time, to avoid some common complications such as lipodystrophies (LD). The objective of our study is to evaluate injection techniques in Moroccan diabetic patients.
Materials and methods
We conducted a prospective study including any diabetic insulin-treated patient for more than 6 months, followed up at the service between February 2015 and June 2017. Patients completed a questionnaire and were analyzed according to their injection techniques. Variables studied were the vectors used, injection techniques, the injection sites. The statistical analysis was performed by the SPSS software.
Results
During the period mentioned, 1000 insulin patients were included, with a sex ratio of 2F/1H. The average age was 42 ± 20 years. The average age of diabetes was 9.6 years (from 6 months to 37 years). The average duration of insulin therapy was 5.7 years (6 months to 37 years). The types of diabetes were: type 2 diabetes in 60% of patients, type 1 diabetes in 38% of patients and 2% slow type 1 diabetes. The vector used was an insulin syringe in 92% of patients and insulin pens in 8% of patients. Only 12% used the antiseptic before the insulin injection. The injection fold was performed in 43% of patients and released in 15% of patients. Needle retention after injection was observed in 41% of cases. Rotation of injection sites was noted in 55% of patients. All patients reported reusing the needle and 97% used it more than four times.
Conclusion
Our study shows a number of gaps in knowledge of injection techniques, which points to the importance of regular verification of prior learning and regular reminder of key points of the injection technique at each consultation.

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P552

The reuse of insulin needles: a problem with consequences (about 1000 cases)

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Introduction
Changing needles and syringes when injecting insulin is often included in recommendations on injection techniques and in education sessions. The objective of our study was to evaluate the rate of insulin needle reuse and its consequences.
Materials and methods
We conducted a prospective study including any diabetic insulin-treated patient for more than 6 months, followed up at the service between February 2015 and June 2017. Patients responded to a questionnaire about the habit needle use. The variables studied were: the vectors used, the number of uses, the number of hypoglycemias. The clinical examination examined for the presence of lipodystrophies. Hypoglycemia has been defined as blood glucose less than or equal to 0.70 g/l. The statistical analysis was performed by the SPSS software.
Results
During the period mentioned, 1000 insulin patients were included, with a sex ratio of 2F/1H. The average age was 42 ± 20 years. The average age of diabetes was 9.6 years (from 6 months to 37 years). Insulin therapy's average duration was 5.7 years (6 months to 37 years). Diabetes types were type 2 diabetes in 60% of patients, type 1 diabetes in 38% and LADA in 2%. The most commonly used vector was the insulin syringe in 92% of patients, followed by the pen in only 8%. Regarding the number of needle use: 3% of patients used the needle less than 4 times, 43% between 4 and 6 times, 42% between 6 and 10 times, and 11% of patients 10 times or more. The rate of needle use was correlated with the presence of lipodystrophies; 61% of patients with lipodystrophy used needles more than 6 times with $P = 0.0000004$, this lipodystrophy was correlated with the rate of hypoglycemia with $P = 0.00000001$.
Conclusion
Needle reuse is a risk factor for lipodystrophy and hypoglycemia, hence the need for therapeutic education on needle change.

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P553

Polymorphisms of genes GNB3, SERT, NET, TPH2 and results of obesity treatment with sibutramine

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Introduction
Results obtained from PRIMAVERA study have demonstrated that 7.5% of obese individuals does not respond to sibutramine therapy. The aim of the study was to evaluate if *GNB3, SERT, NET, TPH2* genes polymorphisms are associated with the results of obesity treatment with sibutramine.
Methods
69810 obese patients took sibutramine for at least 3 months. According to the results of 3 months therapy, we formed two groups of patients: 1) $< 5\%$ of body weight reduction – non-responders ($n = 52$, mean age 43.6 years) 2) clinically significant weight loss $\geq 5\%$ -responders ($n = 66$, mean age 43.7 years). The second group was elected by paired comparison method from PRIMAVERA database. Also *GNB3, SERT, NET, TPH2* genes polymorphisms were assessed.
Results
We did not find significant correlations between *SERT, NET* and *TPH2* genes polymorphism and body weight loss. *GNB3* TT genotype was more frequent in significant weight loss group (responders) ($P = 0.022$). We evaluated body weight loss and BMI change in patients with different genotypes of *GNB3* C825T polymorphism in the whole group ($n = 118$). Sibutramine treatment resulted in significantly greater weight loss in patients with TT genotype than in CC/CT genotype carriers (-9.35% vs -6.45%, $P = 0.03$).

Table 1 Body weight loss in patients with genotype TT and allele C of polymorphic marker C825T of *GNB3* gene

	Body weight loss			
Genotypes	**%**	**P**	**kg**	**P**
CC and CT genotypes (*n*=93)	−5.1 (−8.75; −2.91)	0.034*	−5 (−8; −3)	0.018*
TT genotype (*n*=25)	−8.24 (−10.34; −6.12)		−8 (−12; −5)	

Conclusions
1. *GBN3* gene TT genotype was associated with more effective weight loss during sibutramine treatment; 2. Treatment results were not effected by *SERT, NET and TPH2* genes polymorphisms.

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P554

Microcirculatory disorders in adolescents with tipe 1 diabetes mellitus

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Microcirculatory disorders play important role in pathogenesis of diabetic vascular complications.
Aim
To study peculiarities of microcirculatory haemostasis (tromboresistance of vessel wall and functional activity of thrombocytes) in adolescents with type 1 diabetes mellitus (T1DM).
Patients and methods
80 adolescents (42 boys, 38 girls) 11–16 y.o. with T1DM were examined. The duration of the disease was: less than 1 year - in 27 patients (HbAc1 7.1 ± 0.4%) – group 1, from 1 to 5 years - in 23 patients (HbAc1 8.7 ± 1.2%) – group 2, more then 5 years - in 30 patients (HbAc1 10.2 ± 1.1%) – group 3. Control group: 50 healthy adolescents 11–16 y.o. The indexes of tromboresistance of vessel wall (antiaggregating, anticoagulating, antifibrinolytic activity) measured by manjetic method. The indexes of trombocyte aggregation (degree, speed and time of aggregation) measured by laser method with different inductors (ADP, adrenalin, kollagen) and intravascular aggregation were evaluated.
Results
Tromboresistance of vessel wall was normal in group 1 in comparance of control group ($P<0.05$). Levels of ADP- and adrenalin-stimulating aggregation, intravascular aggregation of thrombocytes were increased in this group ($P<0.05$). Tromboresistance of vessel wall was decreased in group 2 ($P<0.05$). Levels of ADP- and kollagen-stimulating aggregation ($P<0.05$) and intravascular aggregation ($P<0.05$) were also increased in group 2. Decrease of aggregation time was revealed in this group ($P<0.05$). Decrease of tromboresistance of vessel wall ($P<0.001$), increase of all indexes of functional activity of thrombocytes ($P<0.05$) and intravascular aggregation ($P<0.001$) were found in patients of group 3 in comparance of control group.
Conclusions
Microcirculatory disorders in adolescents with T1DM correlated with duration of the disease and may demand treatment.

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P555

Therapeutic and nutritional compliance in diabetic patients in the Endocrinology-Diabetology-Nutrition Department of Mohammed VI University Hospital Center in Oujda

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Introduction
The non-compliance to treatment is defined as the lack of adequacy between patients' behaviors in taking medication, following a diet, and/or executing lifestyle changes, and medical prescriptions. It is a major cause of therapeutic failure that puts into question the real efficiency of medical care. The objective of this study was to evaluate the therapeutic compliance degree in diabetic patients and to determine the different factors and issues complicating compliance to treatment.
Materials and methods
It is a descriptive and prospective study conducted in the Endocrinology-Diabetology Department of Oujda's University Hospital Center, including 60 patients with type 1 and type 2 diabetes mellitus, who have been evaluated on their therapeutic compliance, using the Morisky scale. The analysis was performed by SPSS 20 software.
Results and discussion
The mean age was 41 years with a female predominance. 43% of patients were on oral hypoglycemic agents and 57% were on injectable treatment. Non-compliance was found in 59% of the patients. They were older (mean age was 65 years vs. 31 years in observing patients [OP] $P=0.04$), more unstable (mean HbA1c was at 8.9% vs. 7.4% in OPs) with a lower socio-cultural level ($P=0.06$). The other non-compliance factors were numerous: the lack of education (56%), the occurrence of undesirable effects (36%), the non-availability of treatment at health centers (22%), 20% of cases due to work constraints, and 20% owing to illness and depression denial.
Conclusion
Non-compliance to therapy is common within diabetic patients and is often related to age, disease denial, and low socioeconomic status. Personalized education can be a factor in improving adherence to medication.

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P556

Diabetes increases liver fibroscan value regardless of steatosis

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Background
Fibroscan is a noninvasive medical dispositive for the evaluation of hepatic fibrosis based on the technique of pulse elastography. However, the interpretation of its value depends on several parameters.
Objective
The purpose of our work is to study the impact of diabetes on the value of liver fibroscan and to identify possible factors influencing this value in diabetics.
Materials and methodes
Our work is a cross-sectional comparative study with a prospective collection of data including diabetics and healthy controls between 1st August 2016 and 31 July 2018. Subjects with clinical, biological or radiological signs of liver disease were excluded. Among the controls, subjects with hepatic steatosis were excluded. A fibroscan, an hepatic ultrasound and a blood sampling (liver enzyme) were realised to our subjects. The measurement of the fibroscan value was performed by a single operator. We compared fibroscan values in diabetic patients against healthy controls.
Results
We recruited 91 healthy controls and 38 diabetics, 13 of whom were excluded due to the impossibility of performing fibroscan. The mean value of fibroscan was significantly higher in diabetics (4.9 ± 1.25 Kpa VS 4.3 ± 1 Kpa, $P=0.045$). The rate of steatosis in diabetics was 36%, the majority (55.5%) was with grade 1. The mean value of fibroscan was not influenced by the presence of steatosis (4.8 ± 1.4 Kpa Vs 4.9 ± 1.2 Kpa, $P=0.9$). Similarly, among diabetic patients, there was no correlation between fibroscan values and their age ($P=0.14$), sex ($P=0.19$) or BMI ($P=0.06$). The presence of overweight ($P=0.2$) or a recent change in weight ($P=0.1$), the presence of hypertension ($P=0.9$), kidney failure ($P=0.5$) or metabolic syndrome ($P=0.9$) did not influence the value of fibroscan in diabetics. However, the mean value of fibroscan was significantly higher in diabetic patients with dyslipidemia ($P=0.09$). There was no influence of diet, Hb A1c, or physical activity on the value of fibroscan in these patients. A negative correlation was found between the age of diabetes and the value of fibroscan liver ($r=49\%$, $P=0.012$).
Conclusion
Our data shows that diabetes increases the value of liver fibroscan regardless of the presence of steatosis. In diabetics, fibroscan values increase with dyslipidemia and are negatively correlated with the age of diabetes.

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Tobacco and diabetes: a comparative study of smoking diabetic patients and non-smoking diabetic patients in the Endocrinology-Diabetology-Nutrition Department of Oujda's University Hospital in Morocco

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Introduction
Smoking is considered to be a cardiovascular risk for diabetic patients, as for the overall population. Its presence in diabetic patients increases significantly the risk of micro and macro vascular diseases. This study purpose is to compare and analyze the occurrence rate of degenerative complications in diabetic patients who smoke and those who don't.
Materials and methods
It is a descriptive and comparative study carried out in the Endocrinology-Diabetology-Nutrition Department of Oujda's Mohammed VI University Hospital Center in Morocco. The study population included 66 diabetic patients divided into 2 groups: smokers and non-smokers.
Results
The study population consisted of male patients only. Among the patients, 20 were smokers (30.4%) while the other 46 were not (69.6%). The mean age of the participants was 56.5 years for smokers versus 62.5 years for non-smokers. The average duration of diabetes was 11.25 years for diabetic patients who smoke versus 12.23 years for those who don't. Mean HbA1c value was at 8.05% for smokers compared to 7.83% for non-smokers. The macro vascular diseases included: myocardial infarction in 61.2% of smoking patients versus 55.5% of non-smoking patients ($P=0.055$), peripheral arterial disease in 12.3% of smokers versus 11.1% of non-smokers ($P=0.820$) and stroke in 10.4% of smokers versus 5.6% of non-smokers ($P=0.09$). Diabetic retinopathy was found in 55% of smokers and 22.2% of non-smokers ($P=0.302$). Diabetic smoking patients were more likely and significantly to develop a diabetic kidney disease ($P=0.05$). 13.4% of smoking diabetic patients experienced diabetic neuropathy versus 11.1% of non-smoking patients ($P=0.212$).
Conclusions
Smoking is, together with diabetes mellitus, one of the main risk factors of insulin resistance and degenerative complications. Smoking cessation is of vital importance for management of diabetes, because it improves glycemic control and prevents the development of degenerative complications.

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P558

Endocrinopathies and diabetes: cardiovascular risk assessment

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A large number of endocrine pathologies can be associated to abnormalities in carbohydrate tolerance up to diabetes. The latter participates in the high risk of cardiovascular morbidity and mortality during these pathologies. The aim of our study was to assess the cardiovascular risk in a diabetic population suffering from an endocrine pathology. This is a retrospective study conducted in the department of endocrinology at Charles Nicolle Hospital involving 54 patients hospitalized between 1985 and 2015. Our population includes diabetic patients: 22 cases of Cushing's syndrome, 12 of acromegaly, 09 of pheochromocytoma and 11 of primary hyperaldosteronism. The average age of our population was 44.85 ± 12.74 years old. The majority were female (72.2%). 27.8% were smokers. Obesity was present in 37% of cases. Almost all of our patients had high blood pressure (92.6%). The lipid profile showed hypercholesterolemia in 48.1% of patients, hypoHDLemia in 45.5% and hypertriglyceridemia in 53.8%. After healing of endocrinopathy, we found a remission of diabetes in 37% of cases. High blood pressure disappeared in 33.3%. Total cholesterol and HDL cholesterol were significantly improved ($P=0.001$ and $P=0.05$). On the other hand, the triglycerides have not been modified. Patients suffering from endocrinopathy are at high cardiovascular risk. Diabetes increases this risk and increases cardiovascular morbidity. The healing of endocrinopathy significantly improves the cardiovascular prognosis of these patients.

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P559

Inflammation and adipocytokines in overweight and obesity

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Introduction
In obesity and overweight, inflammation is associated with a progressive infiltration of immune cells causing cytokine secretion into adipose tissue. Objective. Evaluation of adipocytokines derived from adipose tissue and immune cells (adiponectin, resistin, TNF-α and IL-6). Materials and methods. 150 adults divided up in 3 groups; obese, overweight and controls. Adipocytokines (adiponectin, resistin, TNF-α and IL-6) were quantified by ELISA, serum insulin concentrations were assessed by RIA, and were used to calculate HOMA-IR, metabolic parameters (glycemia, triglycerides, HDLc, LDLc, cholesterol) by spectrophotometry. Results. In overweight and obese subjects, a very pronounced state of insulin resistance has been observed associated with hyperinsulinism and an imbalance in the level of pro-/anti-inflammatory adipocytokines, characterized by an increase in TNF-α, IL-6 and resistin and a decrease in adiponectin. Conclusion. The imbalance in adipocytokines levels is a biomarker of inflammation and characterizes overweight and obesity.

Keywords: resistin, adiponectin, overweight, obesity, insulin resistance
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Free T3 correlates with iron metabolism indexes in patients with type 1 diabetes and diabetic kidney disease

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Aims
Thyroid status disturbances are not rare among DKD patients. It is known that the genesis of anemia in DKD has a multifactorial nature, and the combination of DKD and anemia significantly impairs quality of life. In addition, anemia in diabetic patients with DKD occurs earlier and tends to be more severe compared with CKD patients without diabetes. The purpose of the study was to investigate potential relationship between thyroid status and iron metabolism profile in patients with type 1 diabetes (T1D) and DKD.
Materials and methods
We recruited 166 patients with T1D. GFR was estimated by CKD-MDRD formula. Kidney injury was assessed using NGAL. All patients were divided into 2 groups: the group 1 comprised 79 patients with GFR >60 ml/min; group 2–87 patients with GFR <60 ml/min. Biochemical parameters, HbA1c, thyroid hormones, NGAL, iron homeostasis parameter were measured. Nonparametric statistical methods were used. A P-value <0.05 was considered significant.
Results
Groups were matched by gender, age of T1D manifestation, HbA1c, BMI. Age, duration of T1D, NGAL differed by groups. Comparative analysis of patients in the subgroups revealed reliable differences in fT3 ($P=0.012$), AbTSH-R ($P=0.003$). Groups did not differ by TSH, fT4, AbTPO, TG. Correlation of fT3 and Hb ($\rho=0.312$ $P<0.05$), erythrocytes ($\rho=0.329$, $P<0.05$) was observed in group 1. Levels of serum iron correlates with fT3 ($\rho=-0.267$, $P<0.05$) in group 2. When the study sample was divided into groups according fT3 levels: the values in the reference range and low fT3, the groups were matched by age, BMI, duration of T1D and DKD, lipid profile and NGAL. However, significant differences were found in Hb levels ($P=0.023$), erythrocytes ($P=0.005$). In low fT3 group these parameters were statistically significantly lower than in patients with normal values of fT3. Risk of developing anemia (Hb <120g/l) was 1.51 times higher (OR 1.59, 95% CI (0.74–3.07)) in patients with T1D and low fT3 than in patients with normal values of fT3.
Conclusion
Since the serum parameters of iron homeostasis are important determinants of anemia, therefore, the presence of additional influencing factors such as fT3 associated with the development of anemia, regardless of the stage of DKD, may be of fundamental importance in predicting the risks of anemia, as well as discovering therapeutic window for iron profile correction.

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Features of type 2 diabetes mellitus in the elderly (Minsk)

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The article is devoted to one of the most pressing medical problems – diabetes mellitus type 2.
Objective
To study the peculiarities of the course of diabetes mellitus type 2 in persons over 65 years of age; to evaluate the effectiveness of different therapy regimens for the level of HbA1C.
Material and methods
The retrospective study included 100 patients with type 2 diabetes (T2D). The age of the patients: 65 to 82 years. The effectiveness of the prescribed treatment was assessed by the level of HbA1C. The compensation criterion for T2D was chosen to reach the level of HbA1C $<$ 7.5% (for patients aged $<$ 75 years) and HbA1C $<$ 8.0% (for patients over 75 years).
Results
Patients were divided into two age groups: 65–75 years old (80 people, 80%) and 75 years old and older (20 people, 20%). It was determined that the recommended HbA1C values were not observed in elderly and senile patients with different frequencies: they exceeded the recommended level of incidence (7.5%) - 75% of patients in the age group 65–75 years old and 40% of patients in the group over 75 years old (threshold HbA1C = 8.0%). The grouping of patients according to the modes of therapy (monoinsulin therapy and combination therapy) showed that the group of monoinsulin therapy with the target level of HbA1C exceeded 7.5% (65–75 years) was 22 people. (37.9%) and HbA1C exceeded 8% (over 75 years of age) by 4 people. (80%), and in the group of combined therapy such patients were 36 people. (62%) and 4 people. (50%) was responsible. Thus, the total number of patients who exceeded the recommended level was 66 people. (66%). The analysis has shown that in combination therapy insulin is prescribed in doses that do not provide adequate control of glycaemia. More than half of the patients have high levels of HbA1C, and, therefore, an increased risk of development and progression of late complications of the disease. In our study, all 100% of patients had chronic complications with diabetes mellitus.
Conclusions
1. Excess of the recommended level of HbA1C is more frequent in patients aged 65–75. 2. Patients over 75 years of age are compensated in 60% of cases; 65–75 years of age are compensated in only 25%.

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P562

The role of glucagon like peptide - 1 (GLP-1) receptor agonists in the treatment of type 2 diabetes mellitus

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Background and Aims
Type 2 diabetes mellitus (T2DM) is multifactorial, affected by obesity, blood pressure (BP) and cardiovascular disease (CVD). The therapeutic effects of GLP-1 in managing BP and increasing satiety promoting weight loss prove beneficial against these risk factors. This literature review aims to assess current evidence on the efficacy of GLP-1 receptor agonists (GLP-1RA) for T2DM treatment.
Methods
A PubMed literature search over the preceding 5 years was carried out using keywords including GLP-1 receptor agonists and obesity, hypertension and CVD. A total of 7 studies were analysed.
Results
Obesity: A meta-analysis showed a 3 kg weight reduction by GLP-1RA compared to other active therapies. The SCALE diabetes study confirmed that Liraglutide 3.0mg brought about a 6.0% weight reduction. Liraglutide use sufficiently reduced HbA1c (-1.3) that 57.0% of patients achieved target HbA1c of $\leq$6.5% compared to placebo (-0.3 HbA1c reduction, 15.0% HbA1c $\leq$6.5%), and significantly reduced the use of other antiglycaemic drugs also.
BP control: Mice studies showed atrial GLP-1 receptor stimulation promoted secretion of atrial natriuretic peptide and lowering of BP. A 12 week treatment of Liraglutide in obese T2DM patients also lowered BP (-5.30; 95% CI, -7.90 to -2.60; $P<0.001$) and increased weight loss (-5.03; 95% CI, -5.81 to -3.80; $P<0.001$).
CV effects: ELIXA study showed no significant change ($P=0.81$) in heart failure risk with Lixisenatide (hazard ratio 0.96; 95% CI, 0.89 to 1.17) or rate of death (hazard ratio 0.94; 95% CI, 0.75 to 1.23) compared to placebo. LEADER and SUSTAIN-6 studies showed significant reductions in CV risk using Liraglutide (0.87; 95% CI, 0.78 to 0.97; $P=0.01$) and Semiglutide (0.74; 95% CI, 0.58 to 0.95; $P<0.001$) respectively, along with reductions in HbA1c, body weight and BP therefore providing cardiac protection.
Conclusion
GLP-1RA, by appetite regulation and BP control, could slow down progression of T2DM and death by CVD. The studies explored in this review suggest that GLP-1RA could have a place much earlier in T2DM treatment than where current guidelines suggest. Further research to assess long term outcomes is recommended.

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P563

Autoimmune diabetes mellitus adult patients having latent autoimmune diabetes of adulthood (LADA) form exhibit different prevalence of accompanying autoimmune diseases than patients with conventional (juvenile) autoimmune type 1 diabetes: Furthermore, anti-GAD autoantibodies are strongly associated with accompanying autoimmune diseases in patients with autoimmune diabetes mellitus

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Introduction
Autoimmune diabetes mellitus patients, either with Latent Autoimmune Diabetes of Adults (LADA) form or with conventional (juvenile) autoimmune type 1 diabetes (T1D) form, exhibit a higher prevalence of Accompanying Autoimmune Diseases (AADs). The aim of this study was to investigate possible differences in AADs, Familial Autoimmune Diseases (FADs) and metabolic profile between patients with LADA and T1D and between patients with or without anti-GAD (Anti-Glutamic Acid Decarboxylase) antibody titers.
Methods
We Retrospectively investigated 160 adult patients with autoimmune diabetes mellitus (114 with T1D and 46 with LADA), mean $\pm$ SD 40.36 $\pm$ 15.89 years, 81(50.63%) males. Personal and familial medical history was recorded for AAD and FAD respectively. Antibody titers were measured for anti-GAD, IA2(islet tyrosine phosphatase 2), ICA(islet cell antibodies) and other organ specific antibodies. Basic biochemical and hormonal parameters were also evaluated.
Results
In overall sample there was a significant correlation between total number of AADs and FADs (rho = 0.16, $P=0.039$). Patients in LADA group had a higher prevalence of AADs (73.9% vs 51.7%, OR = 2.64, $P=0.01$), while the total number of AADs was associated with LADA (for 1 AAD OR = 2.29, $P=0.05$, for 2 AADs OR = 3.56, $P=0.006$). There was no association between LADA and FADs (43.5% vs 35.9%, $P=0.23$). Patients with LADA had a higher prevalence of autoimmune thyroiditis (58.6% vs 39.4%, OR = 2.17, $P=0.027$) and gastric autoimmunity (43.4% vs 19.2%, OR = 3.21, $P=0.002$), whereas all patients with celiac disease had T1D (0% vs 5.2%, $P=0.041$). Patients with LADA had a greater proportion of anti-GAD titers (83.7% vs 64.8%, OR = 2.78, $P=0.025$), ICA titers (85.2% vs 62%, OR = 3.54, $P=0.018$) and anti-pancreatic titers in general (95.3% vs 79.3%, OR = 2.78, $P=0.017$). Anti-GAD titers were found in 134(83.75%) patients. Those patients had a higher prevalence of AADs (70.6% vs 41%, OR = 3.43, $P=0.0015$), higher prevalence of autoimmune thyroiditis (55.7% vs 33.3%, OR = 2.52, $P=0.017$) and gastric autoimmunity (35.7% vs 17.9%, OR = 2.54, $P=0.036$). There was no association between anti-GAD and FADs (38.9% vs 43.5%, $P=0.37$). After controlling for the effect of LADA anti-GAD remained a significant predictor of AADs.
Conclusions
Patients with LADA have a higher prevalence of AADs. Even if diabetes mellitus phenotype of LADA patients is similar to that of conventional autoimmune type 1 diabetes, the underlying autoimmune pathophysiology may differ. LADA patients may be characterized by a stronger, generalized and multiple autoimmune disorder. Anti-GAD are also associated with a higher prevalence of AADs, thus possibly considered to be a marker of further self-autoimmunity.

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P564

Erythrocytes glucose uptake increases in rats with experimental induced obesity, diabetes and hyperinsulinemia

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Introduction
As were previously shown the erythrocytes glucose uptake is impaired in patients with the Diabetes Mellitus, obesity and polycystic ovarian syndrome due to insulin resistance. For further, study whether the erythrocytes glucose uptake will be impaired in rats with experimental metabolic syndrome were observed gradually.
Material and methods
The 40 adult white male rats separated into 4 groups. In 10 rats diabetes were induced by injection of 200 mkg/kg alloxan (AID), in other 10 rats obesity were induced by diet (DIO), in other 10 rats hyperinsulinemia induced by daily sc injection of insulin 0.1 mU/kg during one month (HIR) and another 10 rats were stay intact as a control group (N). Rats body weight (BW), glycemia, HbA1c level and erythrocytes glucose uptake (EGU) observed weekly during 2 months and compare to initial data in the beginning (ID) in each group.
Results
Final BW were significantly increased in DIO group by 20.14%, $P<0.01$ and in HIR by 17.62%, $P<0.05$ than ID. The fasting glycemia level were increased only in AID by 2 times ($P<0.05$), whereas HbA1c level were increased by 62% ($P<0.01$) in AID, by 44% ($P<0.01$) in HIR and 26% ($P<0.05$) in DIO. Interestingly, EGU level were increased by 109% ($P<0.01$) in AID, by 130% ($P<0.01$) in HIR, by 58% ($P<0.05$) in DIO group than ID and show the strong linkage with HbA1c level in all groups. Analysis in dynamics shown gradually increasing of the EGU in AID in the first week, in DIO in the 2nd week and in HIR in the 3rd week of experiment.
Conclusion
EGU were increased in rats with experimental models of metabolic syndrome AID, HIR, DIO, dependent from HbA1c level and can be used as a marker in early diagnosis.

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P565

Giant prolactinoma associated with alopecia universalis (AU): a case report

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Introduction
Giant prolactinomas are rare tumours, they represent range from 0.5 to 4.0% of all pituitary tumours. We are presenting a patient with giant prolactinoma without visual field defects and any obvious clinical symptoms related to hyperprolactinemia and probably associated with alopecia universalis.
Case
32 years old man has visited outpatient department of our hospital, complaining of severe headache for the last three years. He underwent brain CT scan and 4.8×5.8 cm pituitary macroadenoma was revealed. The first prolactin measurement (RIA) was 4409.0 mU/L (NR: 38–379 mU/L). Further evaluation revealed episodically lower testosterone levels (from 8.85 up to 12.6 nmol/L (NR: 9.26–35.1 nmol/L), and IGF-1 was near lower normal limit: −20.5 nmol/L (NR: 20.2–25.4 nmol/L). Other hormones were at normal range and neuroophthalmological assessments were without any pathological signs for all time of observation. Physical examination revealed AU and family history was confirmed - patient's mother also suffered from AU. Treatment was started with cabergoline 2 mg per week and after two weeks the dose was increased to 3 mg per week. After one month of treatment prolactin decreased to 948.0 mU/L, after 3 months the prolactin concentration reached the normal range- 321.0 mU/L. The dose of cabergoline was increased further to 4 mg per week. After 6, 12 and 24 months of treatment concentrations of prolactin were 171.0 mU/L, 77.0 mU/L and 48.0 mU/L respectively. The patient was treated with dose 4 mg per week for another 12 months and the prolactin concentration remained suppressed. One month after start of the treatment, the MRI scan was performed: the size of pituitary adenoma was decreased to 2.7×2.1×4.2 cm. The positive dynamics on the MRI scans steadily persisted after 3, 12 and 28 months, according to the last MRI the size of macroadenoma was reduced to 2.5×2.6×2.8 cm. Just after two weeks of treatment, the patient's well-being improved, after two months of treatment the headache disappeared. Alopecia remained unchanged. Genetic investigation with the aim to find possible genetic associations between giant prolactinoma, AU and primary hypopituitarism was started.
Conclusion
Giant prolactinoma with hypopituitarism (lower testosterone level, LH and IGF-1 lower normal level) possibly are independently associated with alopecia universalis in our case, comprehensive genetic testing is required. This clinical case demonstrates that cabergoline could be highly effective for the treatment of giant prolactinoma.

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P566

Evaluation of the improvement in vascular endothelial function from raphanus sativus via activation of PI3K/Akt pathway

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This study investigated the role of muscarinic receptors and endothelial signaling pathways in the vascular relaxation promoted by *Raphanus sativu.* In our research for active constituents in *Raphanus sativus* with the potential for improving the vascular system, we evaluated the effect of *Raphanus sativus* on NO production in vascular endothelial cells. In the result, we found that the underlying mechanism for stimulating NO production by *Raphanus sativus* extract involves eNOS activation by the phosphorylation of Ser1177 and the dephosphorylation of Thr495, which are triggered by elevated concentrations of cytoplasmic Ca^{2+} resulting from the activation of Ca^{2+} channels in vascular endothelial cells. Several stimuli are known to activate eNOS through Akt-mediated phosphorylation of the enzyme. Hence, we evaluated the involvement of Akt in the phosphorylation and stimulation of eNOS by *Raphanus sativus*. Incubation with inhibitors of the MEK/ERK1/2 or p38MAPK pathways did not alter the *Raphanus sativus* vasorelaxation. Western blot analysis evidenced that *Raphanus sativus* induces phosphorylation of eNOS, PI3K and Akt in vascular endothelial cells. We identify PI3K/Akt pathways as critical mediators of the NO signaling activation by *Raphanus sativus*. These findings contribute to the notion that *Raphanus sativus* regulates arterial function and vascular dysfunction.

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P567

Cardiovascular risk in obese women with polycystic ovary syndrome using Framingham scoring system

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Objectives
Women with polycystic ovary syndrome (PCOS) are at increased risk for cardiovascular disease. Aim of our study was to determine the frequency of cardiovascular risk factors using Framingham Scoring system (FSS) in PCOS and controls.
Methods
FFS included age, value of cholesterol and HDL (mmol/L), smoking and systolic blood pressure (sysBP, mmHg). We also determined LDL (mmol/l), oxidized LDL (OxLDL, U/l) and triglycerides (mmol/l). We studied 22 obese women with PCOS (mean age: 27.55±5.89 yrs, mean BMI: 29.32±3.86 kg/m^2) diagnosed using Rotterdam 2003 Consensus criteria and respective obese controls.
Results
Between PCOS and controls we obtained: total cholesterol 5.62±1.55 vs. 4.75±0.62, $P>0.05$; HDL 1.21±0.24 vs. 1.41±0.36, $P>0.05$; LDL 91.20±36.71 vs. 56.31±22.98, $P>0.05$; OxLDL 91.2±36.71 vs. 56.31±22.98, $P<0.05$; triglycerides 1.87±1.01 vs. 1.193±0.83, $P>0.05$; sysBP 132.73±15.33 vs. 119.62±15.09, $P<0.05$. Age distribution for PCOS and controls was as following: 20 to 34 yrs in 86.4% and 92.3%, respectively; 35 to 39 yrs in 9.1 and 7.7%, respectively; 40 to 44 yrs in 4.5 and 0%, respectively. There were 45.5% smokers in PCOS and 61.5% in controls. Framingham Scoring showed 10 year risk of 2 to 10% in 13.6% of PCOS and 3.8% of controls, and 10 to 20% risk in 9.1% of PCOS and 3.8% of controls.

Conclusions
Significantly higher values of OxLDL were found in PCOS group. In spite of similar values of assessed lipid parameters between obese PCOS and controls, we found a higher 10 year risk for cardiovasular event in obese women with PCOS.

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P568

Association Kidney Neoplasm and recent diabetes: think about MODY 5

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Introduction
The association of kidney disease and diabetes mellitus is a classic feature evoking Maturity Onset Diabetes of the Young (MODY) 5 otherwise known as renal cysts and diabetes syndrome. Kidney Neoplasms are unusual feature of MODY 5. We report the case of a 45 year-old man diagnosed with kidney Neoplasm and Diabetes
Case report
A 45 year-old man with a history of Diabetes Mellitus treated with lifestyle management 8 months ago, presented to the Emergency Room with pain of the right flank and haematuria. He reported a similar episode of pain ten years prior, and the ultrasound showed no signs of kidney stone. On examination, the patient reported a progressive weight loss with polyphagia, polyuria, polydipsia and no anorexia. Initial blood and urine work-up showed diabetic ketosis with an elevate levels of Haemoglobin and haematocrit at 18.6 gram per decilitre and 56.8%, the patient was then admitted to the Endocrinology ward. He was initially put on intravenous Insulin and Saline perfusion, then on Insulin NPH twice a day. The Insulin dose was progressively decreased and then discontinued. Phlebotomy was prescribed twice a week. Kidney neoplasm was suspected because of the association of polycythaemia and haematuria Abdominal Ultra-sound showed a hypertrophy of the right kidney along with an ectopic pelvic left kidney. A CT-Urogram then showed a heterogeneous mass of the right kidney measuring 77*67*66 mm, with no vascular thrombosis. The patient underwent nephrectomy. Histo-pathological examination and genetic confirmation of MODY 5 are underway.
Discussion
Prevalence of MODY diabetes is unknown, but is estimated to be responsible of 1–5% of cases of diabetes mellitus. Mutation of the HNF1B gene is responsible of type 5, accounting for approximately 5% of MODY cases. Clinical features include renal abnormalities hypomagnesaemia, hyperuricaemia, pancreatic atrophy or partial agenesis, exocrine pancreatic dysfunction, liver test abnormalities, genital abnormalities. Some cases of chromohpobe renal cell carcinoma have been described.
Conclusion
The renal abnormalities, like kidney neoplasm, associated to Diabetes Mellitus, and low need of insulin, should make clinician suspect the diagnosis of MODY5. Screening for associated abnormalities and family screening should then be conducted.

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P569

Body composition (DXA) and hormonal picture in obese children

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Introduction
Obesity in children is rising worldwide with premature development which could involve greater risk of complications and comorbidities in adult life. Central adiposity is a well known feature of glucocorticoid excess and there are some speculations that cortisol biosynthesis is involved in pathogenesis of metabolic syndrome. However the circadian rhythm of cortisol axis or incrimination of cortisol excess in obese children is less known. Our aim is to investigate diurnal cortisol levels and other hormonal tests in relation to body composition in obese children.
Patients and method
Twenty three overweight and obese children (12 boys, 11 girls) were included in this study with ages 7–17 years. Height, weight and pubertal stage were recorded. Basal cortisol was taken at 8 a.m. as well as TSH, FT4, and ACTH. To determine skeletal maturation, hand radiography was performed. Body composition (BC) was measured using dual – energy x-ray absorptiometry (Hologic Delphi A: version 12.6.2). Whole body and regional body composition including fat mass and lean body mass were measured after an overnight fast, with participants in the supine position.
Results
Eighteen (78.2%) children were obese ($> 95^{th}$ percentile): 11 boys and 7 girls. Five (21.73%) children were overweight ($85–95^{th}$ percentile): 4 girls and 1 boy. Of overall participants, 18 children (10 girls and 8 boys) had DXA total body fat above 40%. TSH result was elevated ($>$ 5.5 uIU/mL) in 3 girls (13%) and moderate elevated ($>$4 uIU/mL) in 3 girls and 1 boy meaning 20% of participants. Diurnal cortisol was low ($<$5 μg/dL) in 2 boys and 1 girl (13%) and moderate low ($<$10 μg/dL) in 6 boys and 4 girls meaning 50% of children. Bone age exceeded chronological age by minimum 2 years in 6 of 9 children.
Conclusion
Overweight and obese children had low morning cortisol, this findings are in accordance with previous studies. One hypothesis is that obesity enhances cortisol clearance resulting low morning cortisol compensated by higher evening secretion. Also stress is suggested to play an important role in development of children obesity, so reducing direct emotional stress may be a critical prevention strategy. The mechanism of elevated TSH and obesity is not known, insulin resistance and leptin may be involved. Also, obesity is linked to advanced pubertal evolution that explains bone age maturation in our participants, most likely due to altered steroid hormones synthesis attributed to obesity.

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P570

Mineralocorticoid receptor and diabetes: in favour of other corticosteroids than aldosterone

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Background
Despite normal aldosterone levels, diabetics often profit from the treatment with mineralocorticoid receptor (MR) antagonists (MRAs). We therefore speculated if the expression of MR and 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) were changed in cells of glomerular origin under diabetic conditions and – if not - whether the synthesis of other corticosteroid hormones, that could act on MR, was increased in diabetics.
Methods
RNA transcripts and protein expression of MR and 11β-HSD2 were assessed in human mesangial (HRMC) and glomerular endothelial cells (HRGEC) under stimulation with high glucose and/or angiotensin 2. Urinary steroid hormone metabolites of 40 type 2 diabetics (20 females, 20 males) were analysed by gas chromatography–mass spectrometry and gender matched with 300 healthy controls (170 females, 130 males) from the Swiss Kidney Project on Genes in Hypertension (SKIPOGH) cohort.
Results
Expression of MR transcripts or protein was unaltered in HRMCs and HRGECs under normal and high glucose conditions with and without stimulation with angiotensin II. Both cell lines did not express 11β-HSD2 protein or RNA. Because this would leave the MR in glomerular cells accessible to glucocorticoid hormones, we looked also for these in the urinary steroid profile of diabetics. The excretion of mineralocorticoids were significantly increased in diabetic women for 18-OH-tetrahydrocorticosterone ($P<0.0001$) and for tetrahydroaldosterone in diabetic men ($P=0.0393$). Diabetic women excreted less tetrahydrocorticosterone ($P<0.0001$). Only cortisol excretion was significantly reduced in diabetic men ($P=0.0117$). For all other assessed glucocorticoids, there was an increased synthesis either in women, men or both. Diabetic women and men excreted more 11-deoxycortisol ($P=0.0013$ and $P=0.0081$, respectively) as well as well the cortisol metabolites 5α-tetrahydrocortisol ($P=0.0003$, $P=0.0007$), 5β-tetrahydrocortisol ($P<0.0001$, $P=0.0083$) and α-cortol ($P<0.0001$, $P=0.0079$). Excretions of cortisone and β-cortol did not differ in males, but were significantly increased in diabetic women ($P=0.0053$ for cortisone, $P<0.0001$ for β-cortol).
Conclusion
MR expression does not change in cell lines of glomerular origin upon diabetic conditions. 11β-HSD2 was not found in such cells leaving them freely accessible for glucocorticoids. In steroid profiles of diabetics the synthesis of mineralocorticoids was similar to controls. Mostly, the synthesis of mineralocorticoid active glucocorticoid metabolites was found to be increased in diabetics. By blocking the receptor from these metabolites, diabetics could profit from the treatment with MRAs.

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P571

Abstract Unavailable.

P572

Erythrocytes membrane plasmalogens level in Diabetes Mellitus depends from Arterial Hypertension and nephropathy

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Introduction
Metabolic disturbances at the Diabetes Mellitus (DM) leads to structural and functional abnormalities of the cell plasma membrane due to changes in the lipid content and composition, especially phospholipids. Plasmalogens are unique group of phospholipids with alcohol and ether bounds, presented in a few papers. We hypothesis their involvement into pathogenesis of DM.
Material and methods
We studied the content of Plasmalogens in blood plasma (PP) and erythrocytes membranes (PM) by nonorganic phosphorus in 81 DM patients and 14 healthy subjects (HS). In all groups plasma and membranes total phosphorus content, erythrocytes sialidase activity (ESA), glycemia, HbA1c level, arterial blood pressure (ABP) were measured.
Results
Were shown that PP and PM levels reduced at the DM in 4.89 (p'0.01) and in 5.85 ($P<0.01$) times respectively, compared to HS. These reduction were accompanied with the lower content of total phosphorus in plasma and erythrocytes membranes in 1.5 and 2.6 times, $P<0.01$ respectively. The glycemia level were increased in 2 times, $P<0.01$, HbA1c in 1.84 times, $P<0.05$, whereas ESA were in 9.68 times, $P<0.05$ higher in DM and suggest about serious metabolic disturbances. Interestingly, reducing of PM showed a linkage with ABP in both DM and HS, whereas reducing of PP and PM were depends from degree of diabetic nephropathy, suggest about involvement of plasmalogens into pathogenesis of DM and also arterial hypertension.
Conclusion
PP and PM content reduced in DM and had a linkage with degree of diabetic nephropathy, whereas reducing only PM depends from ABP in both DM and HS.

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P573

A hyperglycemic crisis as a first appearance of newly onset diabetes mellitus in a patient using dexamethasone: Blame the usual suspect or accuse a new one?

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We describe the case of a 60-year old woman admitted to the intensive care unit (ICU) for progressively diminishing consciousness and severe lethargy. The patient was recently diagnosed with small cell lung carcinoma with solitary cerebral metastasis. In order to shrink the metastasis-induced cerebral edema she was treated with dexamethasone. She was hospitalized four days before admission to the ICU to start carboplatin-etoposide based chemotherapy. The day of admission she had told her family to be very thirsty and consumed large quantities of soda. Her mental state regressed continuously which resulted in loss of consciousness and eventually the need for hospitalization. Her temperature at admission was 37°C, blood pressure was 107/63 mmHg with a pulse rate of 131 beats/min. Arterial blood gas showed lactic acidosis but could not measure glycemia, indicating the possibility of very high blood glucose. Laboratory analysis showed indeed a glycemia of 1717 mg/dl with concomitant hyperosmolarity and hypernatremia and acute renal disease due to extensive dehydration. Sodium corrected for glycemia was 167 mmol/l. There was no ketonuria. All put together, the patient suffered from severe hyperglycemic hyperosmolar syndrome. Measured HbA1c calculated 11.2% (99 mmol/mol), confirming a new diagnosis of diabetes mellitus. She was treated with very aggressive fluid resuscitation therapy (100 ml/kg/24u with 20 ml/kg the first hour), insulin therapy and potassium supplementation following hospital protocol with strict attention for glycemia and sodium correction not allowing the patient to decline in sodium levels too fast regarding cerebral edema. Furthermore, she was treated for pneumonia which could have co-attributed to the hyperglycemic crisis. Hereafter, we searched for the primary etiology of the hyperglycemic crisis and the diabetes mellitus. There was no history of disturbed glucose tolerance. She had a normal body mass index. She had a negative family history. The patient not only received 8 mg dexamethasone twice a day, she also used Trimbow two doses twice a day, which contains 87 µg beclometason per dose. Corticosteroid-induced diabetes mellitus was etiologically the logical choice. However, literature search showed a small but growing number of cases linking hyperglycemic crises and new onset diabetes mellitus to the use of platin-based chemotherapy. It is important to look beyond the usual suspect that is steroid-induced glycemic disturbance. Literature review suggests glycemic follow-up in patients treated with platin-based chemotherapy in order to pick up possible new-onset glucose intolerances.

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P574

Use of insulin therapy in the treatment of gestational diabetes

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Introduction
In most cases, the management of gestational diabetes is based on self-monitoring and dietary monitoring. The use of insulin therapy may be necessary if glycemic targets are not achieved. The aim of this work is to determine the factors involved in the use of insulin therapy during gestational diabetes.
Methods
It was a descriptive study performed in 150 diabetic pregnant women hospitalized in our department for monthly metabolic control. Each patient received a complete clinical examination and biological assessment.
Results
The average age of the patients was 33 years old. The average term of discovery for gestational diabetes was 28.6 ± 4.2 AS. A history of gestational diabetes was found in 25.1% of pregnant women. Pregnancy was programmed in 38% of cases, of which 84% had balanced diabetes during hospitalization (mean HBA1c 6.33%). Type 1 diabetes was found in 48% of patients. The average duration of diabetes progression was 9 years. Diet alone only achieved glycemic goals in 24% of our patients. The use of insulin therapy was necessary in 76%. A 3-injections pattern of rapid insulin was prescribed in 46% of gestants and a 2-injections pattern in 12%.The analytical study showed a positive association between the onset of gestational diabetes and the following factors: recurrence, the term early-onset (<24 AS), and age over 35 years.
Conclusion
Switching to early insulin therapy after failure of diet alone is increasingly necessary to prevent maternal-fetal complications.

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P575

The fasting of diabetic patients during Ramadan: a dilemma of religious conviction and medical prohibition

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Introduction
Ramadan is a holy month for Muslims where they have to fast from dawn until dark. It is a questionable issue in patients with chronic diseases who may experience or aggravate their metabolic complications, especially for diabetic patients. The purpose of this study is to assess diabetic patients, knowledge of fasting in a religious and medical point of view.

Materials and methods
This is a cross-sectional study conducted after the holy month of Ramadan, on 45 patients, whose clinical data (type, duration and complications of diabetes, an assessment of well-being during and after Ramadan in patients who fasted or not), and paraclinical data were collected.
Results and discussion
The mean age of patients was 53.62 years. 80% of patients had type 2 diabetes mellitus. Only 37% of patients have fasted during Ramadan for various reasons which were dominated by religious belief. For the 63% who did not fast: 64% out of them followed the advice of their doctors, and 21% of patient because they had comorbidities. 58% of the patients who fasted experienced complications, 50% of them had a diabetes ketoacidosis, a hypoglycemia for 40% of them, of whom 61% required hospitalization. Mean HbA1c in patients who did not fast decreased from 8.49% to 8.08%, while for fasting patients it increased from 7.96% to 8.08% after Ramadan.
Conclusion
Despite the therapeutic education, the majority of diabetic patients fast during the holy month of Ramadan, neglecting immediate complications, as well as long-term complications of fasting.

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P576

Myocardial infarction in diabetic patients and cardiovascular risk factors control

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Aim
Describe the control of cardiovascular risk factors (CVRF) in patients with diabetes and myocardial infarction (MI) as well as their treatment and control.
Patients and methods
Observational retrospective study of a cohort of patients with diabetes admitted to the cardiology department because of a MI between November 2015 and November 2016. Statistical analysis performed with SPSS 24th version.
Results
421 patients admitted because of a MI. 140 patients (33.4%) with diabetes (DM) prior to admission. 97.8% with type 2 DM. 8 patients (5.7%) diagnosed with DM during their stay. 65% of the diabetic patients received oral hypoglycemic agents (OHAs), 15.7% insulin and 15% OHAs + Insulin. 5 patients didn't receive pharmacological treatment. HbA1c test was ordered in 57.7% of these patients and 40.5% of them had a good glycemic control, with a HbA1c below 7%. Lipid panel was ordered in 70.5% of patients and 64.8% of them had LDL levels below 100 mg/dL. Smoking status was assessed in 51.7% of the patients: 42.9% were smokers and 31.2% were quitters. One year after the event 25.5% of patients had dead. Lipid panel was being followed in 79.2% of patients and 50.9% met their LDL target (below 70 mg/dL). There had been a statistically significant LDL reduction in these patients. Smoking status was asked in 51.9% of the patients and 60.9% of smokers had quitted, being the proportion of quitters statistically significant. In 81.13% patients HbA1c was being assessed and 36.8% of patients met their HbA1c target (below 7%). HbA1c was lower but the reduction was not statistically significant.
Conclusions
1. CVRF are assessed in most patients with diabetes admitted because of a MI being lipid panel the most ordered (70.5%) in comparison to HbA1c (57.7%) and smoking status (51.7%)
2. Most diabetic patients that suffer myocardial infarction do not meet their glycemic target (59.5%).
3. In our series there is a statistically significant reduction in LDL levels and in the proportion of smokers. HbA1c is also improved but the reduction is not statistically significant.

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P577

Comparison of effects of metformin used as a monotherapy or in combination with gliclazide MR on glycemic control and lipid profile in patients with type 2 diabetes mellitus

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Objective
To evaluate and compare the effects of metformin used as a single-agent therapy and in combination with gliclazide modified release (MR) on glycoregulation and lipid profile in patients with type 2 diabetes mellitus (T2DM).
Methodology
A multi-center observational epidemiological study was carried out in patients with T2DM, divided in two groups according to the current type of treatment: first group was on monotherapy with metformin in daily dose (DD) of 2.000 mg while second group was treated with metformin in same DD plus gliclazide MR 60 mg per day. Anthropometric measurements, fasting plasma glucose (FPG), hemoglobin A1c (HbA1c) and lipid profile (cholesterol, tryglicerides, HDL, LDL) were evaluated and statistically analyzied.
Results
A total of 105 patients were enrolled of whom 59 (56.2%) were treated with metformin (mean age 59.62 years, range of 40–78 years, SD 9.08; male: female = 27:32 patients) while 46 (43.8%) were on combined therapy with metformin plus gliclazide MR (mean age 60.24 years, range of 36–77 years, SD 10.13; male: female = 19:27 patients). No significant difference was observed between groups regarding age (t test, $P = 0.744$) and gender (Pearson chi square test, $P = 0.648$). Patients with metformin had higher body mass index (BMI), with mean BMI of 30.74 kg/m2 compared to 27.99 kg/m2 (t test, $P = 0.004$). No significant difference was registrated regarding FPG (t test, $P = 0.917$) and plasma lipids while patients with combined therapy had higher levels of HbA1c (t test, $P = 0.032$) and worse glycoregulation (Pearson chi square test, $P = 0.021$).
Conclusion
In patients with T2DM requiring combination therapy, a tight follow-up through various modalities in needed in order to achive and maintain an adequate glycaemic control.

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P578

Factors affecting effective gestational diabetes mellitus management: six-year experience from a single tertiary center

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Introduction
Effective gestational diabetes mellitus (GDM) management is pivotal for reducing delivery complications for both mother and offspring, since a linear and continuous association between blood glucose and unfavorable outcomes has been extensively reported. The aim of present study was to investigate possible factors affecting GDM treatment goals.
Methods
We retrospectively evaluated 136 consecutive patients with GDM, treated in our department from January 2013 to December 2018, with median(range) age 31.5(19–43) years, diagnosed at 27.5(6–37) week of gestation and mixed nationality (68 Greek, 44 other Europid, 19 Middle East, 5 Africans). Previous personal and family medical history was collected, while demographic, clinical and pregnancy outcomes for mother and offspring were also recorded.
Results
GDM diagnosis was made from fasting glucose in 4.5% and from OGTT with 75gr. glucose in 95.5% of patients. Body mass index (BMI) in overall sample was 30.3 (21–47). Non-Greek women had lower BMI values (Spearman's rho = −0.22, $P = 0.017$). Seventy-four (54.5%) were treated with diet only and 62 (45.5%) were treated with insulin plus diet. Previous GDM was reported in 21.82%. In overall sample median treated fasting glucose was 88 (69–130)mg/dl and median treated 1hour post-prandial glucose was 112 (87–180)mg/dl. Based

on universally accepted target mean fasting (<95 mg/dl) and mean 1hour post-prandial (<140 mg/dl) self-assessment glucose values, 83% of patients were characterized as adequately treated, whereas 17% were outside treatment goals and formed the two treatment groups. Number of monthly prenatal visits was strongly associated with adequate treatment (rho = 0.70, $P < 0.001$). No significant difference in offspring weight was found between groups [Mann-Whitney U-test 3127gr. vs 3377gr., $P = 0.38$, overall median(range) 3125(1550–4000)gr.]. No differences in complication rates were also recorded between groups. More patients outside treatment goals were recorded in insulin treated group (43.18% vs 72.2%, $P = 0.023$). Gravida status tended to be positively associated with adequate treatment (rho = 0.19, $P = 0.062$). Positive patient's mother family history for type 2 diabetes was strongly associated with outside treatment goals (rho = −0.26, $P = 0.008$) and also positively associated with higher BMI values (rho = 0.20, $P = 0.041$).

Conclusions

Regular, at least four, monthly prenatal visits are associated with optimal GDM management. Patient education is necessary and crucial from the first visit in order to maintain compliance. Positive patient's mother family history for type 2 diabetes is associated with higher BMI and higher fasting and post-prandial glucose values.

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P579

Oral glucose tolerance test is recommended for screening for new-onset glucose metabolism impairment during chronic low-dose glucocorticoid therapy

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Introduction

Patients with connective tissue diseases are susceptible to the occurrence of side-effects of long term treatment with low-dose glucocorticoids as these medications often cannot be withdrawn due to exacerbation of the underlying disease. The new-onset of glucose metabolism impairment is not considered common in patients treated with low-dose glucocorticoids and the risk factors are thought to be the same as in general population: increasing age, obesity or family history of diabetes. As glucocorticoids cause mainly postprandial hyperglycemia determining fasting plasma glucose to screen patients for diabetes (which is recommended by International Diabetes Federation and American Diabetes Association) can lead to false negative results. Since long-lasting hyperglycemia is a condition that can lead to higher cardiovascular risk it is important to properly diagnose and treat this condition.

Objectives

The aim of the study was to evaluate the prevalence and risk factors of steroid-induced glucose metabolism impairment in patients chronically treated with glucocorticoids.

Material and methods

Oral glucose tolerance test (OGTT) was performed in 107 patients diagnosed with connective tissue disease and treated with ≤ 7.5 mg of prednisone (or metyloprednisolone equivalent) for more than 3 months. All participants underwent clinical and biochemical evaluation: age, sex, time of treatment, current and cumulative dose of steroid, family history of diabetes, BMI, HbA1c, HOMA-IR, fasting insulin concentration. None of the patients had previous history of pre-diabetes/diabetes. Logistic regression analysis was used to evaluate the association between the presence of glucose metabolism impairment (dependent variable) and analyzed risk factors.

Results

Participants were divided into two groups based on results of OGTT. 75 patients had normal OGTT and 32 patients (29.9%) were diagnosed with glucocorticoid-induced glucose metabolism impairment. 18 patients (16.8%) had impaired glucose tolerance and 1 (0.9%) was diagnosed with diabetes without coincide impaired fasting glucose thus the disturbances would not be diagnosed without OGTT. No statistical significance was found for current or cumulative dose of glucocorticoids, time of treatment, waist circumference, family history of diabetes, BMI, HOMA-IR or fasting insulin concentration as the risk factors for developing new-onset glucocorticoid-induced glucose metabolism impairment. Only age (1 year increase) was found to be a significant risk factor (OR 1.05 95%CI1.01–1.08, p = 0.02).

Conclusions

17.7% of patients could be correctly diagnosed with pre-diabetes or diabetes based exclusively on OGTT. This test is the only standardized tool that is able to properly reveal the steroid-induced glucose metabolism impairment. It should be performed in every patients chronically treated with glucocorticoids even without other risk factors of diabetes.

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P580

Incidence of diabetes and its predictive factors in cancer patients treated with phosphatidylinositol 3 kinase inhibitors

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Background

Targeted therapy using phosphatidylinositol 3-kinase (PI3K) inhibitors has become widespread in the treatment of cancers. Although PI3K inhibitors raised concern about the alteration of glucose and lipid metabolism from animal studies, human clinical data have been rarely reported.

Aim

We investigated the clinical manifestations, incidence of diabetes and its predictive factors in cancer patients who treated with PI3K inhibitors.

Method

We analyzed 38 diabetes-free patients with advanced solid cancer who initiated PI3K inhibitor treatment at the university-affiliated hospital and followed up for average 239 days retrospectively. Cox regression analysis was performed to identify independent predictive parameters for the development of diabetes after initiation of PI3K inhibitors.

Results

Of 38 patients with PI3K inhibitors initiation (mean age 54.5 years, 23.7% female), 55.3% developed diabetes during the treatment within the mean period of 29 days. Of these, 28.6% presented the remission of diabetes, 72 mean days after the discontinuation of PI3K inhibitor use. Incident diabetes patients revealed higher proportions of use of hypertension medication, higher levels of HbA1c and fasting glucose at baseline, and longer duration of PI3K inhibitor use (Ps < 0.005). Presence of prior use of steroid and higher baseline HbA1c levels were associated with the development of diabetes (HR = 8.41,95%CI = 1.89–37.33; HR = 2.16,95%CI = 1.09–4.25, respectively). Patients showing remission of diabetes after discontinuing PI3K inhibitor use were younger ($P = 0.035$) and maintained lower fasting glucose levels during PI3K inhibitor use ($P = 0.001$) compared to patients with persistent diabetes.

Discussion

In conclusion, history of steroid use and higher HbA1c levels at baseline may be important predictors for developing diabetes in patients with cancers who treated with PI3K inhibitors. Close observation and careful intervention are needed when treating with PI3K inhibitors in these patients.

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P581

Flash glucose monitoring: repercussions in glycemic control

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Introduction

Flash glucose monitoring (FGM) allows non-invasive glucose level assessment. Studies have shown that patients using FGM test their glucose levels more often than those who use traditional blood glucose testing. Given that a higher rate of glucose testing has showed to improve glycemic control our objective was to describe the change in the glycemic control and time in euglycemic range in patients with FGM and the effect of the number of scans in this control.

Methods and patients

Observational longitudinal clinical study between June and December 2018 in patients with type 1 diabetes (DM1) in which FGM implementation was subsidized.

Results

69 patients included. Mean age: 16.59 ± 1.23 years, with a mean DM1 evolution time of 6.42 ± 4.79 years. 37.7% women. 47.8% had used FGM before it was

subsidized by the public system. After FGM implementation HbA1c levels were reduced from 7.07% to 7.02% although this reduction was not statistically significant. Time in range (between 70 and 140 mg/dL) didn't change after the implementation (56.61%) but time in hypoglycemia (below 70 mg/dL) was reduced from 9.74 to 8.66% ($P=0.394$). Among the patients we studied, the more glucose daily data was registered the lower was their HbA1c. Time in range was higher and time in hypoglycemia was reduced when daily scans increased. However, all these improvements didn't achieve statistical significance ($P>0.05$)

Conclusions

– In our series, FGM implementation reduced HbA1c levels and also the time patients spent in hypoglycemia, although these improvements were not statistically significant.
– The more scans patients performed and the more glucose daily data was registered, the lower was the HbA1c, the more time they spent in euglycemic range and the less time in hypoglycemia. However all these changes did not reach statistical significance.

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P582

The role of proper insulin injection technique to achieve optimal glycemic control

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Proper insulin injection technique is a prerequisite for achieving good diabetes control, reducing absorption variability, and getting the best effect from using the drug. At the same time, the rate of absorption of insulin depends on a number of technical features, which include the depth of needle insertion, the severity of blood flow and the presence of lipodystrophy in the injection zones. Compliance with a number of rules minimizes the variability of absorption of insulin and is a necessary condition for achieving their optimal therapeutic effect. However, a significant part of patients receiving insulin therapy, makes many serious mistakes that can lead to decompensation of diabetes and the formation of vascular complications. The aim of our study was to analyze the technical aspects of insulin therapy in patients with type 1 and type 2 diabetes, and to study the awareness of patients about the technique of insulin injections and identify the most common errors.The study involved 74 patients (30 men and 44 women) aged from 20 to 76 years. A special questionnaire consisting of 38 questions was used to assess patients' knowledge of technical issues of insulin therapy and to determine the most common errors encountered during insulin injections.According to the results obtained, the quality of insulin injection devices for 53 patients (72%) used pen-injectors, 21 (28%) used disposable syringes. The most widely used for injector – pens were needles with a length of 8 mm — 19 (36%) and 10 mm — 14 (26%) patients. The frequency of changing disposable needles was also analyzed, it turned out that 20 (38%) patients changed needles 1 time in 3 days, 21 (39%) - once a week, 9 (17%) - once every 2 weeks and 3 (6%) - 1 time per month. The questionnaire took into account data on the preferential use of 'favorite' zones for injections: 56 patients (76%) performed injections within one and two anatomical areas and only 6 (8%) used all the main anatomical areas. Analyzing the results, we concluded that patients with diabetes are not sufficiently informed about the technique of insulin injection and make a number of serious errors that can lead to a deterioration of carbohydrate metabolism. Proper insulin injection techniques are necessary for optimal control of diabetes mellitus, and therefore, injection techniques should be under the control of medical professionals and deserve special attention when educating patients at the School of Diabetes.

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P583

Metabolic effects of a novel myokine, Follistatin like protein 1 (FSTL1), in human primary adipocytes

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Object

FSTL1, an extracellular glycoprotein, is a novel myokine that is secreted by skeletal muscle. However, its functions in metabolism remain unclear, Adipose tissue is one of the important organs for maintaining energy homeostasis. FSTL1 is known to induce inflammatory response and inhibit insulin-mediated *Akt* signaling pathway, we aimed to investigate whether FSTL1 play metabolic roles in human adipose tissue. We hypothesized that FSTL1 increases lipolysis through its putative receptor DIP2A (Disco interacting protein 2 homolog A).

Methods

Human primary adipocytes were treated with recombinant FSTL1 in dose and time dependent manner. To determine its lipolytic activity, pHSL ser^{563,565,660}, perilipin, AMPK, PKA were determined by western blot and the rate of free fatty acid was assessed. Expression of DIP2A was determined by PCR and western blot. DIP2A was knocked-down to examine whether it mediates metabolic effects of FSTL1.

Results

FSTL1 did not affect catecholamine-induced lipolysis via PKA. FSTL1, however, increased lipolysis through AMPK activation and, *subsequently*, HSL ser^{565} phosphorylation in dose dependent manner. It was found that DIP2A expression did not change during differentiation of human primary adipocyte, suggesting that it is not involoved in adipocyte maturation.

Conclusion

FSTL1 increased basal lipolysis through AMPK activation. AMPK is well known sensor of the intracellular energy state and serves to regulate various signals. Its activation provides ATP by FA oxidation. Therefore, FSTL1 may play an important in the regulation of energy homeostasis. FSTL1 also has effect through DIP2A. These findings suggest that DIP2A plays important roles in FSTL1 mediated lipolysis.

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P584

Discordance between body-mass index and body adiposity index in classification of adiposity status in the elderly

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Introduction

The prevalence of obesity in elderly population increased. Obesity leads to increased morbidity and mortality as well as worsens quality of life in older individuals. Body-mass index (BMI) is the most widely used adiposity index. BMI correlates with body fatness but this index does not account for fat mass versus fat-free mass. Recently a new index of body adiposity the body adiposity index (BAI) was introduced. This novel index correlates well (in comparison to BMI) with body fat percentage.

Aim

We investigated the discordance between BMI and BAI in measuring adiposity status in patients hospitalized in the geriatric department.

Material and methods

The study group comprised 391 patients above 60 years, hospitalized in the geriatric department (age 76 ± 7 years, women 66%). In each patients we calculated BMI and BAI. Based on the BMI and WHO classification the patients were divided into three categories: normal weight, overweight and obesity. The value of BAI was classified too as normal weight, overweight and obesity. We calculated rates of misclassification to adiposity categories according BMI and BAI.

Results

Median BMI was 27.7 (24.8–31.3) kg/m^2 and median BAI was 33.9 (29.6–39.3) % We observed normal weight among 26.3% patients by BMI and 25.3% using BAI. Overweight was diagnosed among 40.7% using BMI and only 27.9% by BAI. However obesity was identified among 32.3% by BMI and as 46.8% using BAI index. There was a strong positive correlation between BMI and BAI index (Spearman $R=0.70$; $P<0.0001$). We observed a 54.7% rate of concordant assessment of adiposity status between BAI and BMI. In 28.6% of patients BMI underclassified patients and in 16.7% overclassified patients in compariconwith BAI. We observed a high rate of misclassification of adiposity status according to BMI and BAI index, especially in the normal weight and overweight subgroups. BMI tended to overclassify patients as normal weight and underclassify patients

as overweight and obese compared to BAI. Multivariate logistic regression identified independent predictors of underestimation od adiposity status by BMI: age (per 1 year increment) OR 0.96 95%CI: 0.94–0.99 $P=0.05$; male sex (female reference) OR 0.32 95%CI: 0.20–0.50 $P<0.0001$.

Conclusion

The accuracy of BMI in predicting adiposity status in elderly patients is insufficient as compared to BAI classification. BMI tended to overestimate the rate of normal weight and underestimate the rate of overweight and obesity.

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P585

The effect of Iranian propolis on glucose metabolism, lipid profile, insulin resistance, renal function and inflammatory biomarkers in patients with type 2 diabetes mellitus: a randomized double blind clinical trial

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Propolis is a natural product with many biological properties including hypoglycemic activity and modulating lipid profile. The present study was designed to evaluate the effect of Iranian propolis extract on glucose metabolism, Lipid profile, Insulin resistance, renal and liver function as well as inflammatory biomarkers in patients with type 2 diabetes mellitus (T2DM). A double-blind, placebo-controlled clinical trial was conducted. The duration of the study lasted 90 days. Patients with T2DM were recruited and randomly divided into an Iranian propolis group (1000 mg/day) ($n=50$) and a placebo group ($n=44$).There was a significant decrease in the serum levels of glycosylated hemoglobin (HbA1c), 2-hour post prandial (2hpp), insulin, homeostasis model assessment-insulin resistance (HOMA-IR), homeostasis model assessment of β-cell function (HOMA-β), High sensitive C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α). However, the serum HDL-C had significantly increased in the propolis group compared with the placebo group. There was also a significant decrease in serum liver transaminase (ALT and AST) and blood urea nitrogen (BUN) concentrations in the propolis group. Iranian propolis has beneficial effects on reducing post prandial blood glucose, serum insulin, insulin resistanc,e and inflammatory cytokines. It is also a useful treatment for preventing the liver and renal dysfunction, as well as, elevatating HDL-C concentrations in patients with T2DM.

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P586

Real-world experience of generalized and partial lipodystrophy patients enrolled in the metreleptin early access program

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Objective

To evaluate the real-world experience of patients with generalized (GL) and partial (PL) lipodystrophy initiating treatment with metreleptin as part of an early access program (EAP).

Methods

A retrospective data collection was conducted from four countries for patients enrolled in the EAP. A descriptive analysis was performed on selected patient characteristics, baseline organ impairments and complications, and response to metreleptin therapy, measured through changes in triglycerides (TG) and HbA1c.

Results

53 lipodystrophy patients (GL, PL: 28, 25) were identified in four countries (France: 19, Italy: 3, Spain: 11, UK: 20). Average age at metreleptin initiation for GL and PL patients was 17.4 (SD: 14.9) and 38.6 (SD: 12.6) respectively. Among patients treated in France, Italy, and UK, 100% presented with organ impairments at baseline, including liver impairment (GL, PL: 100%, 100%), cardiovascular damage (24%, 44%), kidney impairment (35%, 20%) and pancreatitis (12%, 16%). 93% of patients had diabetes. Prior to treatment, 95% of GL patients and 71% of PL patients had TG >200 mg/dl and 78% of GL patients and 68% of PL patients had HbA1c $>7\%$. Duration of patients' metreleptin exposure varied, with a maximum of 14.7 years (mean 5.4, s.d.: 3.5). Following treatment for GL patients, mean % TG change was a decrease of 53% ($P<0.001$) and mean HbA1c change was a 1.9 percentage point decrease ($P<0.001$) between baseline and 12 months. By month 12, 50% of GL patients (vs 5% at baseline) achieved TG ≤ 200 mg/dl and 57% of patients (vs 22% at baseline) achieved HbA1c $\leq 7\%$. For PL patients, mean % TG change was a decrease of 21.5% ($P<0.005$) and mean HbA1c change was a 0.5 percentage point decrease ($P<0.1$). By month 12, 52% of PL patients (vs 29% at baseline) achieved TG ≤ 200 mg/dl with no change in the 32% at baseline that achieved HbA1c $\leq 7\%$. No new safety signals emerged as EAP data were integrated with existing safety data. In the clinical trial, the most frequent adverse reactions reported included decreased weight (17%) and mild occurrences of hypoglycaemia (14%); other adverse reactions affected $<10\%$.

Conclusions

Response to metreleptin in real-world EAP patients was consistent with clinical trial experience for registration, which resulted in mean % TG decrease (GL, PL: 32.1, 37.4) and HbA1c percentage point decrease (GL, PL: 2.2, 0.9). Ongoing research is needed to further characterize the burden of lipodystrophy on patients and the impact of metreleptin.

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P587

Prevalence and characteristics of Nivolumab-induced diabetes: results from a monocentric observational study

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Introduction

Nivolumab is an anti-PD1 immunotherapy that restores the immune response against cancer cells, but can induce fulminant diabetes. The prevalence of such anti-PD1 induced diabetes is not clearly determined, but it has been recently estimated between 0.4% and 0.9% in recent studies. Here, we performed a monocentric epidemiological study in order to assess the prevalence and provide a description of Nivolumab-induced diabetes cases.

Material and method

We identified all Nivolumab deliveries by the pharmacy of Nantes University Hospital from its marketing authorization in October 2014 until July 2017. Nivolumab-induced diabetes (history of diabetes or biologically determined) were found by a file review.

Results

We identified a total of 5009 deliveries of Nivolumab for 377 patients (on average 13 cures per patient). We recorded 2 Nivolumab-induced decompensations of diabetes (including one case of pre-existing diabetes that required definitive use of insulin therapy), i.e. a prevalence of 0.5%. Since July 2017, we collected 10 other cases: 7 women and 5 men concerned with anti-PD1-induced diabetes, average age of 69.7 years, and average BMI of 22.6 kg/m^2. The time of onset of diabetes was between 3rd and 28th cures, with a median after the 5th cure. A fulminant pheotype with sudden onset of diabetes with frank hyperglycemia and ketoacidosis was noted in 7 patients. The average glycemia was 32.4 mmol/l, and the average HbA1c was 8.0% at diagnosis. All patients required insulin therapy and undetectable C peptide was found in 5 patients (5/9). Autoimmunity was mainly negative. Anti-GAD and anti-IA2 antibodies were absent in all patients tested (11/11 and 10/10 respectively). Anti-ZNT8 antibodies were positive in only 1 of the 6 patients tested. Increased lipase levels was found in 3 of the 6 patients tested. Unstable diabetes with glycemic variability and difficulty to achieve glycemic control was noted in 8 patients.

Discussion – conclusion

Our study found a prevalence of anti-PD1 induced diabetes of 0.5%. The clinical presentation was severe with a frequent occurrence of fulminant diabetes without markers of auto-immunity. We are currently analyzing the glycemic variability of these immunotherapy-induced diabetes, which seems to be difficult to manage for patients and clinicians. This new form of secondary diabetes requires close collaboration between oncologists and diabetologists.

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P588

Genetic diagnosis of maturity-onset diabetes of the young (MODY): experience of diabetology-endocrinology department of Oujda's Mohammed VI university hospital

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Introduction
Maturity Onset Diabetes of the Young (MODY) is a monogenic form of non-insulin-dependent diabetes that classically presents in a lean individual with non ketotic hyperglycaemia and an autosomal dominant inheritance pattern. The diagnosis remains a challenge and may be made by careful clinical evaluation, but exact sub-typing is possible only by genetic analysis.
Materials and methods
This is a prospective data analysis in the diabetology-endocrinology department of Oujda's Mohammed VI university hospital during a one year period as part of a research programm covering the Mediterranean region to detect monogenic diabetes among patients suspected to have atypical diabetes. A written informed consent was obtained from all the participants. 20 patients were recruited based on probant clinical evaluation with a positive predictive value ($>25\%$) on the MODY calculator. Saliva samples were used for genetic assays relying on targeted PCR-based enrichment and next generation sequencing.
Results
Almost full records were available for all the patients who were selected; but only 12 had the genetic testing. A MODY 3 and 2 were respectively identified in a 20 and 27 year old patients.
Conclusion
Identification of MODY by medical practitioners is important, as it has both genetic and therapeutic repercussions, which leads to lower diabetic complications and better quality of life.

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P589

Discrete choice and SF-36 estimates of patient quality of life and benefits of leptin replacement therapy (LRT) in generalized and partial lipodystrophy (GL, PL)

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We report new estimates of the disutility associated with GL and PL, and the quality of life (QoL) impact of leptin replacement therapy (LRT) based on two methods. The first approach estimates utility decrements associated with a range of impairments related to lipodystrophy through a discrete choice experiment (DCE) conducted with members of the general public; the second elicits QoL estimates from 8 PL patients using the SF-36 instrument. To characterize QoL consequences of specific impairments, a DCE was conducted with 1,000 members of the general population. Multinomial logit regression was used to estimate utility decrements associated with each impairment in quality-adjusted life-years (QALYs). While estimates of DCE-derived QALY decrements have been presented previously, the current analysis anchors the absolute value of these decrements to the UK's EQ-5D tariff. This mapping is achieved by scaling DCE values such that the absolute value of QoL for a patient with all measured lipodystrophy impairments equals the UK valuation of the worst EQ-5D health state (-0.594). Anchoring QALY values in this manner facilitates external comparison across studies. Scaled decrements were combined with previously reported data on the prevalence of impairments among lipodystrophy patients before, and 1 year after, initiating LRT to measure the impact of LRT on QoL. Overall, QALY gains associated with LRT were estimated at 0.313 across GL patients through the DCE (from 0.466 to 0.779). Changes in 'Inability to perform work/schoolwork' (-0.167 decrement, 45.6% point decrease in prevalence) accounted for 24.3% of the gain. Across PL patients, QALY gains associated with LRT were estimated at 0.224 through the DCE (from 0.624 to 0.848). Changes in 'Hyperphagia' (-0.071 decrement, 62.5% point decrease in prevalence) accounted for 20.6% of the gain. Additionally, SF-6D-R2 utility values were derived from surveys of 8 lipodystrophy patients diagnosed with PL using the SF-36 instrument (5 treated, 3 untreated). These results support a gain from treatment of 0.21 QALYs (0.67 for treated patients and 0.46 for untreated patients), very similar to the PL gain estimated through the DCE. The results of this study suggest that lipodystrophy is associated with a large QoL impairment and that the benefits of LRT are substantial in both PL and GL patients. Additional studies are needed to further characterize the burden of lipodystrophy and the impact of LRT on quality of life.

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P590

Are all hypoglycemic drugs similar for men with type 2 diabetes and testosterone deficiency?

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Background
To date, it has been established that appointment of testosterone replacement therapy (TRT) in men with type 2 diabetes mellitus (T2DM) and testosterone (T) deficiency improves control of carbohydrate metabolism. Although, studies of effectiveness of different hypoglycemic drugs in men with T2DM and T deficiency have not been conducted. The aim of this study was to compare the efficacy of various types of hypoglycemic therapy in patients with T2DM and late onset hypogonadism, as well as an assessment of its combination with TRT.
Materials and methods
We examined 90 men with T2DM and late onset hypogonadism, diagnosed by European Association of Urology criteria (2016). 40 patients, receiving TRT (Androgel 50 mg/day) for 9 months, were divided into 2 groups: 1 – 20 men, receiving sulfonylureas therapy and metformin, 2 – 20 patients treated with dipeptidyl peptidase type 4 (DPP-4) inhibitors and metformin. The control groups (patients with T deficiency without TRT) included 50 men: group 3 – 25 patients using sulfonylureas and metformin therapy, group 4 – 25 patients treated with DPP-4 inhibitors and metformin. All patients underwent clinical examination and assessment of carbohydrate metabolism. Statistical processing of data was carried out using Wilcoxon test (Statistics 11.0).
Results
The greatest dynamic of weight loss was found in group 2 – BMI reduced from 34.7 (30.6; 39.1) to 32.6 (29.6; 34.7) kg/m^2 ($P=0.008$), waist circumference (WC) – by 8.7 ± 0.3 cm ($P=0.01$), hip circumference (HC) – by 5.1 ± 0.4 cm ($P=0.03$). The assessment of anthropometric indices showed a decrease in body weight by 0.5 ± 0.2 kg and BMI by 0.1 ± 0.05 kg/m^2 in group 1, which weren't significant, while in the 3rd group there was a weight gain by 3.1 ± 0.3 kg ($P=0.04$). In group 4 significant changes did not occurred. The study of carbohydrate metabolism revealed a decrease in HbA1c by $0.3\pm0.1\%$, fasting glucose by 0.6 ± 0.2 mM/l ($P=0.08$) in the 1st group, but no significant changes in the 2nd and 4th groups, whereas there was a slight deterioration in the parameters of carbohydrate metabolism in group 3. The frequency of hypoglycemic events was higher in patients receiving sulfonylureas (groups 1 and 3), which reflects an increase in cardiovascular risks in these patients.
Conclusion
The administration of TRT in men with T2DM and late onset hypogonadism, improves metabolic control. The optimal treatment tactic for these patients is the DPP-4 inhibitors and metformin in combination with TRT.

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P591

A 5-years postoperative upper digestive endoscopy in obesity surgery

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Introduction
Postoperative upper digestive endoscopy seems to give conflicting results in literature after obesity surgery. Some stressed on the frequency of major digestive lesions such as esophagitis, cancer or endo brachy esophagus (EBO) especially after Sleeve Gastrectomy (SG). The incidence of EBO after SG was found in 1.2% to 15% at ten years of follow up. Accordingly to European Guidelines, it is mandatory to perform a routinely preoperative gastroscopy but not after surgery.
Methods
We conducted a prospective study. We mailed a prescription of gastroscopy by mail at each patient who had a bariatric surgery from April 1, 2010 to August 31, 2014. We collected results during their annual follow-up (January 2018), but also by mail or e-mail.

Results
57 out of 578 patients gave us the results of gastroscopy. The mean age was 51 ± 9.2 years, 92% were women, the average BMI before intervention was 44.14 ± 5.01 kg/m^2 and 48 had longitudinal sleeve gastrectomy, 9 had a revisional bariatric operation. The mean BMI loss was 14.24 kg/m^2 and the average follow-up 5 years. Only 28% presented gastroesophageal symptoms. The endoscopic results of these 57 patients were 17 normal, 21 gastritis, 10 oesophagitis, 13 hiatal hernia and 8 HP infections. There was no cancer and one EBO de novo with incomplete intestinal metaplasia. All patients with esophagitis underwent SG.
Conclusions
In our study the frequency of endoscopic abnormalities at mean follow-up of 5 years suggest the necessity of a systematic endoscopic follow-up, especially in asymptomatic patients. Strong recommendations about upper digestive endoscopic surveillance after bariatric surgery are needed especially in SG.

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P592

Occupational outcomes after bariatric surgery: relation to deprivation, satisfaction score

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Many studies but not all showed an increase in employment after bariatric surgery by 17–29%. We analyzed the relation of this increase of employment rate with weight loss, satisfaction and deprivation score. In an observational study, we evaluated the rate of employment (mean ± S.E.) 2.3 years ± 0.1 after bariatric surgery. We mailed to 791 patients a simple self-questionnaire to assess the employment status deprivation, satisfaction scale and Barros score. Patients had a bariatric surgery from September 1st, 2017 to August 2017. Questionnaires were collected during their follow-up (September 2018). One hundred thirty three patients answered to our request. The mean age of the patients was 45 years (range 19–67 years), with 88% women and a mean BMI of 42.7 kg/m^2 (range 33–74), 88% had sleeve gastrectomy. During the follow up, patients loss 12 ± 0.5 kg/m^2. The mean score of EPICES ($N < 30.17$), Barros and satisfaction scale (1 to 5) were 31.9, 1.3 and 4.27 respectively. Before surgery 58% had a job and 88% after (17 patients more). In univariate analysis, we compared patient who obtain a job with other (17 vs 115) for age, BMI, loss of BMI, scores. Only the social aspect of Barros score was significantly different and patient who obtain a job had less social relation (0.7 vs 0.3, $P = 0.0094$). Thus bariatric surgery aids to obtain a job. The employment of patient after bariatric surgery seems independent of BMI, weight loss, deprivation, or age.

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P593

Probiotic supplementation and β-cell function in type 2 diabetes: evidence from randomized clinical trial

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Background
Probiotics have beneficial effect on obesity, insulin resistance and associated metabolic disorders. However, effect of probiotics on β-cell function are inconsistent.
Aim
In a double-blind single center randomized placebo-controlled trials (RCT), effect of alive multistrain probiotic vs. placebo on β-cell function in type 2 diabetes patient were assessed.
Methods
A total of 54 patients met the criteria for inclusion. They were randomly assigned to receive multiprobiotic 'Symbiter' (concentrated biomass of 14 probiotic bacteria genera *Bifidobacterium, Lactobacillus, Lactococcus, Propionibacterium*) or placebo for 8-weeks administered as a sachet formulation in double-blind treatment. The primary main outcome was the assessment of β-cell function as change C-peptide and HOMA-β (homeostasis model assessment-estimated β-cell function) which calculated using HOMA2 calculator (Diabetes Trials Unit, University of Oxford). Secondary outcomes were the changes in glycemic control-related parameters, anthropomorphic variables and cytokines levels. ANCOVA was used to assess the difference between groups.
Results
Supplementation with alive multiprobiotic was associated with slight insignificant improvement of β-cell function (HOMA-β increased from 57.8 ± 4.5 to 65.56 ± 5.96 ($P = 0.249$), insulin sensitivity (S% - 51.75 ± 4.71 to 55.58 ± 4.09; $P = 0.523$) and reduction of insulin resistance (HOMA-2IR −2.44 ± 0.24 to 2.11 ± 0.15; $P = 0.260$) as compared to placebo. With respect to our secondary outcomes, HbA1c significant decreased by 0.45% ($P = 0.010$) only in probiotic responders (patient with increase in HOMA-β) as compared to non-responders was observed.
Conclusion
Probiotic therapies modestly improved β-cell function in patients with type 2 diabetes. Modulation of the gut microbiota represents a new treatment for diabetes and should be tested in larger studies.

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P594

Relationship between lipid profile and uricemia in diabetic type 2

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Introduction
Hyperuricemia is associated with an increase in cardiovascular risk and complications of type 2 diabetes (1). The aim of this study is to establish a possible link between lipid profile and hyperuricemia.
Method
A total of 321 patients with type 2 diabetes were included in our study. Clinical and par clinical data were collected from patients' medical records. The lipid profile includes low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG) and total cholesterol (TC).
Results and discussion
The mean age of the population was 58 ± 11.36. The mean body mass index (BMI) was 27.9 kg/m^2 ± 6.4. Data analysis showed: A positive and statistically significant correlation between TG and uric acid level ($P = 0.002$). HDL cholesterol was inversely correlated with uric acid levels ($P = 0.001$). however, there was no correlation between LDL and uric acid. The results of our study illustrate the strong association between uric acid increase and lipid disorder in diabetic type 2 suggesting a crucial role of uric acid in the regulation of dyslipidemia (2).
Conclusion
Previous studies have highlighted the intricacy of mechanisms of the pathogenesis of hyperuricemia and dyslipidemia. Thus, when establishing the diagnosis of hyperuricemia, coexisting dyslipidemia should be suspected. On the other hand, the management of hyperuricemia can help control dyslipidemia in patients with Type 2 diabetes (3).
Bibliography
1. Alderman, and all, J.S., 2004. Serum uric acid: a cardiovascular risk factor? *Ther. Umsch.*, **61**(9):547–552. [doi: 10.1024/0040-5930.61.9.547]. PubMed CrossRef Google Scholar.
2. Yili Xu and all, Published: October 24, 2013: Hyperuricemia as an Independent Predictor of Vascular Complications and Mortality in Type 2 Diabetes Patients: A Meta-Analysis https://doi.org/10.1371/journal.pone.0078206
3. Jiao Wang and all: Prevalence and Determinants of Hyperuricemia in Type 2 Diabetes Mellitus Patients with Central Obesity in Guangdong Province in China.Asia Pacific Journal of Clinical Nutrition 2013/11/05, P46–54.

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P595

Insulin resistance, systemic and regional inflammation in subcutaneous adipose tissue during weight loss in a population with obesity

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Background
Adipose tissue dysfunction, such as adipocyte hypertrophy and secretion of pro-inflammatory cytokines, develops in obese subjects and goes hand in hand with

obesity-related complications, especially insulin resistance (IR) and systemic inflammation. The exact mechanisms underlying adipose tissue dysfunction and consequently the obesity-related complications are not yet fully understood.
Aim
Investigate the association between systemic IR and inflammation, and markers of adipose tissue dysfunction during weight loss in a severely obese population.
Subjects and methods
Eighteen obese subjects (age 50 ± 11 years, BMI 43.7 ± 5.6 kg/m^2, 12 men) were recruited prior to adhering dedicated lifestyle changes ($n = 4$) or undergoing gastric bypass surgery ($n = 14$). Before start of weight loss, and six months and one year thereafter, subcutaneous abdominal adipose tissue (SAT) and fasting serum was collected. C-reactive protein (CRP), glucose and insulin were determined using standard laboratory assays. Homeostasis model assessment-estimated IR (HOMA-IR) was calculated. mRNA expression in SAT of glucose transporter 4 (GLUT4), bone morphogenetic protein 4 (BMP4), interleukin-6 (IL6), interleukin-10 (IL10), interleukin-33 (IL33) and tumor necrosis factor alpha (TNFα) were determined using qPCR.
Results
Before weight loss, median fasting glucose level was 5.5 (4.8–5.8) mmol/l and insulin level was 159.7 (76.4–208.4) pmol/l. At baseline, no correlations were found between BMI, CRP levels or HOMA-IR, and SAT expression of GLUT4, BMP4, IL6, IL10, IL33 and TNFα. During follow-up, BMI decreased to 32.6 kg/m^2 after six months and 29.7 kg/m^2 after one year ($P < 0.001$), as did CRP levels and HOMA-IR (all, $P < 0.005$). SAT expression of IL6 and TNFα significantly decreased ($F(2,13.853) = 10.191$, $P = 0.002$ and $F(2,16.636) = 4.009$, $P = 0.038$; respectively), while no changes in IL10 and IL33 mRNA levels were observed. mRNA levels of GLUT4 significantly increased after start of weight loss ($F(2,25.177) = 3.459$, $P = 0.047$), while for BMP4 no change was observed ($F(2,13.289) = 2.056$, $P = 0.167$). A positive trend between the change of CRP levels and change of HOMA-IR between baseline and six months was found ($r_s = 0.470$, $P = 0.077$) and also positive correlations between change in mRNA TNFα levels and change in HOMA-IR, CRP and BMI during follow-up (all, $P < 0.05$).
Discussion
Weight loss in a severely obese population leads to decreases in systemic inflammation and IR. In addition, expression of certain pro-inflammatory cytokines in SAT was lower, and expression of GLUT4 was higher six months after start of weight loss. Moreover, changes in SAT TNFα expression during weight loss are correlated with improvements in systemic inflammatory status and IR.

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P596

The effect of 3 months of daily consumption of sugar-sweetened beverages on liver, adipose tissue, and glucose metabolism in an animal study

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Background
Growing evidence suggests a link between sugar-sweetened beverages (SSBs) and metabolic disorders. We investigated the effect of SSBs that are commonly consumed by adolescents on glucose metabolism and fatty liver.
Methods
We treated 7-week old male C57BL/6 mice with water (control) or either of SSBs: carbonated soda (Coca-Cola®), sweetened milk coffee (Maxwell®), or chocolate-added cocoa (Choco-Latte®), for 13 weeks ($n = 10$ in each group). Half of the animals were allowed a regular chow diet and the other half was allowed a high-fat diet (40% fat). Body composition and biochemical variables were investigated at the end of the treatments. Histology of the liver and adipose tissue, and molecular signaling related to glucose and lipid metabolism were also evaluated.
Results
During the 13-week treatment, the mice treated with chocolate-added cocoa or sweetened milk coffee showed significantly greater increase in body weight compared with controls, especially when allowed a high-fat diet. Fasting glucose levels were higher in the three SSB-treated groups compared with the control group. The lipid droplets in the liver, fat cell size, and numbers of CD68-positive cells in adipose tissue were greater in the SSB-treated groups than in the control group. The SSB treatments increased gene expression related to inflammatory processes in the liver and adipose tissue. Phosphorylation of AKT and glycogen synthase kinase in muscle was significantly reduced in SSB-treated groups.
Conclusion
Daily consumption of SSBs over three months leads to metabolic impairment together with weight gain, and may contribute to the development of metabolic diseases.

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P597

A new neurocognitive phenotype in Alstrom sindrome

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Background
Alstrom syndrome (AS; OMIM#203800) is a rare (<1:100.000) autosomal recessive monogenic ciliopathy and it is caused by mutations in ALMS1 (chromosome 2p13), which function is still unknown. AS is characterized by multisystemic fibrosis, cone-rod retinal dystrophy leading to blindness, hearing loss, obesity, type 2 diabetes mellitus (T2DM), dilated cardiomyopathy, and progressive hepatic and renal failure. Most patients present neurological issue on developmental age and they had normal intelligence on adulthood with magnetic resonance study that showed brain atrophy, periventricular white matter abnormalities, lacune-like lesions, or supratentorial myelin abnormalities, lacune-like lesions, or supratentorial myelin abnormalities.
Aim
We aim to investigate cognitive functions in a group of pediatric and adult patients with AS.
Methods
We studied 19 AS patients (pts), 13 adults and 6 children (mean age 24.63 years; range 8–59, 8 males). All patients underwent neuropsychological tests: verbal comprehension index, digit span, phonemic and semantic verbal fluency, ideomotor and buccofacial apraxia, word and pseudo-word repetition, activities of daily living and instrumental activities of daily living. We also collected patients' clinical data.
Results
From a clinical point of view, we found 17/19 pts presented vision deficit, 16/19 pts had hearing deficit, 14/19 pts were overweight, 10/19 pts had dyslipidemia, 7/19 pts were diabetic, 3/19 pts had renal impairment, 11/19 pts had a liver dysfunction and 11/19 pts had cardiovascular comorbidities. At neuropsychological test the majority of the patients, 53%, showed difficulties in the auditory working memory test (pseudo-word repetition). The most important deficit, however, was observed in the apraxia tests. Both ideomotor and buccofacial apraxia were found in 74% of the sample. Correlational analyses showed that the performance on the ideomotor apraxia test negatively correlated with the onset of the visual deficit ($r = -0.48$; $P < 0.05$), whereas the performance on the buccofacial apraxia test negatively correlated with the onset of the auditory deficit ($r = -0.49$; $P < 0.05$).
Conclusions
We found that patients with AS showed difficulties in the auditory working memory with a buccofacial and ideomotor apraxia. These new findings may be related with sensory deficit onset but further tests are needed to explain this relationship.

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P598

Physical activity counteracts metabolic syndrome-induced hypogonadotropic hypogonadism and erectile dysfunction in the rabbit

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Metabolic syndrome (MetS) clusters cardiovascular and metabolic risk factors, along with hypogonadism (HG) and erectile dysfunction (ED). Lifestyle modifications, including physical exercise (PhyEx), are well-known treatments for this condition. We previously established a non-genomic, high-fat diet

(HFD)-induced rabbit model of MetS that recapitulates the human phenotype, including HG and ED. We now report studies on the effect of PhyEx on hypothalamus-pituitary-testis (HPT) axis and penile relaxation (readout of erectile dysfunction). Rabbits fed a regular diet were used as controls (RD). RD and HFD rabbits were exercise-trained to run on a treadmill for 12 weeks (RD + PhyEx and HFD + PhyEx). HFD rabbits showed typical MetS features, hypogonadotropic HG (reduced testosterone, T, and LH) and a reduction of androgen-dependent tissue weights. GnRH immunostaining was reduced in the HFD hypothalamic preoptic area, and genes related to inflammation (COX2, IL6, CD68), glucose metabolism (GLUT1, GLUT4, IRS1), estrogen action (ERβ, GPR30) and GnRH inhibitory factors (NPY and PDYN) were increased in the HFD hypothalami. PhyEx completely restored T and LH plasma levels, prostate weight and GnRH immunostaining, doubling its gene expression. The HFD-induced increases in inflammation, estrogen signaling and glucose metabolism-related genes in the hypothalamus were all significantly reduced in HFD + PhyEx, along with a decrease in MCP-1 and its receptor (CCR2), TNFR and GLUT3. PhyEx increased Kiss1 and decreased orexigenic and GnRH-inhibiting factors (PDYN and its receptors OPRD1 and OPRK1), whereas increased anorexigenic ones (POMC). Kiss1 receptor immunostaining, decreased by HFD, was restored by PhyEx. In the testis, genes related to T formation (17βHSD3) and metabolism (5α-reductase) were increased by PhyEx. Accordingly, PhyEx increased the ratio of androstenedione to T concentration within the testis, which resulted downregulated by HFD, as demonstrated by mass-spectrometry analysis of testicular steroids. Corpora cavernosa (CC) strips from HFD rabbits showed hypo-responsiveness to acetylcholine and electrical field (EF) stimulation. In addition, sildenafil action on EF- or sodium nitroprusside-induced relaxation were also impaired. PhyEx reverted these alterations. In CC extracts, genes related to NO formation (DDAH1) and signaling (GCSA1, GCSB1, PDE5, PKG), smooth muscle differentiation (SM22, αSMA) and androgen action (AR, STAMP2) were upregulated by PhyEx. In conclusion, our results show that PhyEx may rescue erectile function, exert anti-inflammatory effects on hypothalamus and testis, and increase LH levels and T production, thus supporting a primary role for lifestyle modification to combat MetS-associated HG and ED.

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P599

Testosterone restores metabolic syndrome-induced impairement in physical activity by ameliorating skeletal muscle fiber metabolism

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Background
Metabolic syndrome (MetS) is a clustering of metabolic and cardiovascular risk factors, with insulin resistance being one of the main components. In male, MetS is also associated to hypogonadotropic hypogonadism. Lifestyle modifications (e.g. physical activity) could prevent or considerably reduce MetS progression, however the ability to perform physical activity is often impaired in MetS subjects.
Aim
Considering the known trophic role of T in the increase of muscle mass, this study was aimed at evaluating, in an animal model of MetS, the effects of T treatment on the skeletal muscle composition and function, both in presence or absence of physical exercise.
Methods
Animal model of MetS was obtained by feeding male rabbits, for 12 weeks, with a high fat diet (HFD), with or without T supplementation (30 mg/kg/week), and compared to regular diet animals (control). A subgroup of control, HFD and HFD + T animals was subjected to a treadmill running protocol for 12 weeks.
Results
Gene expression analysis on quadriceps femoris demonstrated a significant reduction of type I muscle fibers markers (oxidative) and an increase of type II muscle fiber markers (glycolytic) in HFD respect to control group. T reverted this effect restoring type I fiber markers and also inducing the expression of mitochondrial respiration chain enzymes and normalizing HFD-induced mitochondrial cristae reduction. Moreover, T treatment increased myogenic and muscle differentiation markers, reduced the atrophy marker Atrogin-1, and restored the HFD-reduced fiber diameter almost to the control level. T ameliorated the expression of genes related to muscle metabolism (insulin-dependent signaling/glucose metabolism), along with insulin resistance, as measured by oral glucose tolerance test (OGTT). At the end of the physical activity protocol, when compared to control rabbits, HFD rabbits showed a significant reduction of physical performance (running distance and running time), while T was able to counteract the HFD-related reduced exercise endurance, also decreasing the lactate production (plateau at T physiological dose, 10.4 nM). Moreover, muscle histology evidenced a further reduction of type-I fibers in HFD as compared to RD and a positive effect of T in maintaining oxidative metabolism and in restoring the mitochondrial cristae arrangement.
Conclusions
Our results indicate that MetS determines a reduced proportion of fatigue-resistant type I fibers in response to physical exercise, while T promotes slow oxidative muscle metabolism thus improving exercise performance. Hence T administration can improve the ability of MetS subjects to perform regular physical activity.

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P600

Compliance with gestational weight gain in women with gestational diabetes mellitus

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Introduction
The present study aimed to investigate whether women who developed gestational diabetes mellitus (GDM) comply with the guidelines for gestational weight gain (GWG) according to their pre-pregnancy Body Mass Index (BMI).
Methods
A retrospective study was conducted involving 195 pregnant women with GDM, aged 25–45 years, attending an academic hospital outpatient clinic. These women were divided into three groups according to pre-pregnancy BMI (underweight, optimal, overweight).
Results
The mean GWG was 9.9 ± 6.3 kg; in 28% of cases, GWG was higher than suggested by the Institute of Medicine (IOM) guidelines. The three groups differed in GWG (underweight: 5.5 ± 5.1 vs optimal: 10.9 ± 2.7 vs overweight: 16 ± 5.4 kg, $P < 0.001$), with those being underweight gaining less, and those being overweight gaining more than suggested by IOM. Fetal weight in the optimal and overweight groups was higher compared with the low weight group (underweight: 2990 ± 456 vs optimal: 3146 ± 467 vs overweight 3201 ± 650 g, $P = 0.089$).
Conclusion
GWG in women with GDM depends on the pre-pregnancy weight. A better compliance of women to the guidelines is advisable, to avoid pregnancy complications.

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P601

Clinical and ultrasonographic characteristics of women with co-existing gestational diabetes mellitus and thyroid disease

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Introduction
Gestational Diabetes Mellitus (GDM) is a disorder of glucose tolerance which is diagnosed for the first time during pregnancy. Thyroid disease is common in

women of reproductive age and during gestation; both diseases have an adverse impact on pregnancy outcomes. The aim of this study was to assess the clinical and ultrasonographic characteristics in women with co-existing GDM and thyroid disease.
Material and methods
In total, 112 pregnant women were included in the study, diagnosed as having GDM ($n=42$), thyroid disease ($n=40$) or both GDM and thyroid disease ($n=30$). All women attended an academic hospital outpatient clinic. They were assessed through personal, obstetric and family history, clinical examination, and fetal ultrasonography in the 32nd gestational week.
Results
Women with co-existing GDM and thyroid disease were older than those with GDM or thyroid disease alone (36.3 ± 5.0 vs 34.7 ± 3.7 vs 33.6 ± 4.2 years, respectively, $P=0.03$). Gestational weight gain (GWG) at birth was higher in women with thyroid disease alone in comparison to the other groups (13.9 ± 5.7 vs 11.0 ± 5.6 vs 9.4 ± 8.9 kg, respectively, $P=0.025$). Fetal ultrasound characteristics (estimated fetal weight, head circumference, bilateral diameter, abdominal circumference, femoral length) did not differ among the three groups. Pregnancy outcomes (gestational week at birth, birthweight) did not also differ among the three groups.
Conclusion
Co-existence of GDM and thyroid disease do not modify ultrasound characteristics and pregnancy outcomes compared with either disease alone. These results, though need to be confirmed by larger studies, may reflect the optimal clinical management of these patients.

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P602

Platelet reactivity in patients with type 2 diabetes mellitus after treatment intensification with DPP-4i, SGLT-2i and GLP-1RA

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Introduction
Patients with type 2 diabetes mellitus (T2DM) exert a higher risk for thrombotic events. Platelet reactivity may be used to assess prothrombotic state in such patients. The aim of this study was to investigate whether the administration of novel antidiabetic agents could influence the platelet reactivity in T2DM patients.
Patients and methods
We enrolled 99 consecutive patients (males = 63.3%), 64.92 ± 8.3 years old, receiving metformin for T2DM who did not achieve therapeutic targets. Subjects were assigned to 1:1:1 age and sex matched groups ($n=33$ per group) to receive an additional antidiabetic agent; dipeptidyl peptidase-4 inhibitor (DPP-4i), sodium/glucose cotransporter-2 inhibitor (SGLT-2i) or glucagon like peptide-1 receptor agonist (GLP1-RA). Platelet reactivity was measured with PFA-100 assay; collagen/epinephrine (CEPI) and collagen/ADP closure time (CADP) were calculated in seconds. Glycosylated hemoglobin (HbA1c) was assessed at baseline and 3 months later.
Results
There was no difference for gender ($P=0.10$) or age ($P=0.27$) between the 3 study groups. All groups achieved better glycemic control in terms of HbA1c values between baseline and follow-up (7.78% vs 6.92% for DPP-4i, 7.52% vs 6.73% for SGL-2i and 8.19% vs 6.85% for GLP-1RA, $P<0.001$ for all). Platelet reactivity did not differ significantly at baseline between study groups ($P=0.71$ for CEPI and $P=0.6$ for CADP). Additionally, CEPI ($P=0.54$) or CADP ($P=0.43$) did not change significantly at follow-up time in all groups.
Conclusions
These preliminary data provided evidence that treatment intensification with DPP-4i, GLP-1RA, SGLT-2i and GLP-1RA in patients with T2DM receiving metformin does not affect their platelet reactivity. Further enrollment of patients and detailed subgroups analyses will elucidate the topic.

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P603

Renoprotective effects of weekly dulaglutide in type 2 diabetes patients: A routine clinical practice study

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Introduction
Data from several clinical trials have shown positive effects of GLP1 analogue drugs on renal function in patients with type 2 diabetes (T2DM). However, there are very few reported results on its potential renoprotective effect in routine clinical practice. Our aim is to evaluate the effects of the addition of weekly dulaglutide (a GLP-1 analogue) to the normoglycemic treatment of patients with T2DM on renal function in a real-world cohort of patients.
Methods/design
Observational, retrospective study carried out in poorly controlled patients with T2DM in routine clinical practice conditions whom dulaglutide was added-on to their previous treatment. Renal fuction was evaluated by changes in estimated glomerular filtration rate (eGFR), creatinine serum levels and urine albumin/creatinine ratio (UACR) after dulaglutide add-on. Continuous variables are presented as mean and standard deviation or as median and interquartile range based on data distribution. Categorical variables are presented as frequencies. A multivariate analysis was performed to identify potential predictors for renal effects.
Results
Data from 46 patients (75% women; age: 60.5 ± 9.2 years; HbA1c: 9.1 [8.4–9.7] %; duration of T2DM: 10 [6 – 16.5] years) were collected. Macroalbuminuria was present in 8.7%. After dulaglutide add-on (time for re-evaluation: 16 [12–24] weeks), a rise for eGFR was observed in 47.9% of the patients. Significant differences weren't observed nor eGFR (83.7 ± 18.1 vs 83.1 ± 19.1 mL/min/1.73 m^2, $P=0.36$), or serum levels of creatinine (0.81 ± 0.2 vs 0.83 ± 0.2 mg/dl, $P=0.26$) after dulaglutide addition. A significant reduction in UACR was detected after intensification with the GLP-1 analogue (15 [7.4–71] vs 8.9 [4.6–22.1] mg/g, $P<0.001$). There was any reduction of AUCR in 76% of the cohort. Reduction in UACR was independently observed in a multivariate analysis model including diabetes duration, weigth loss, HbA1c reduction, use of ACE inhibitors and previous antidiabetic treatment
Conclusions
Addition of weekly dulaglutide in pooly controlled patients with T2DM led to improvement in renal function profile in routine clinical practice conditions. This effect was independently observed of any epidemiological or clinical variable.

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P604

The effects of testosterone treatment on fat tissue dysfunction and nonalcoholic fatty liver disease in obese men undergoing bariatric surgery

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Objective
Substitution treatment of hypogonadism in clinical and experimental models has shown beneficial effects on insulin sensitivity and accumulation of visceral and liver fat. Aim of the study was to analyze the effects of testosterone replacement therapy on benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS) clinical parameters, adipose tissue dysfunction and nonalcoholic fatty liver disease (NAFLD) in obese patients candidates for bariatric surgery.
Material and methods
Patients were divided into three groups: eugonadal, untreated hypogonadal and symptomatic hypogonadal treated for 6–8 months with testosterone. BPH/LUTS parameters were assessed by IPSS (International Prostate Symptom Score) and prostate ultrasound. Preadipocyte cells (hPADs) isolated from adipose tissue biopsies were used to evaluate insulin sensitivity, adipogenic potential and mitochondrial function. NAFLD was evaluated by triglycerides (TG) assay and histological examination of liver biopsies.

Results
Clinically, notwithstanding a prostate volume increase, testosterone treatment improved the IPSS score and hyperemia. Liver TG levels correlated positively with both steatosis and NAS scores, and resulted significantly higher in hypogonadal patients when compared to eugonadal patients, with testosterone treatment significantly reducing TG levels. In the liver, testosterone treatment induced an increased mRNA expression of lipid metabolism markers, whereas in visceral adipose tissue it induced an increased mRNA expression of lipid catabolism and mitochondrial biofunctionality markers. In hPADs testosterone treatment induced an increased mRNA expression of brown adipogenesis and mitochondrial biofunctionality markers. Testosterone treatment normalized hPADs ability to respond to increasing concentrations of insulin. Accordingly, glucose uptake AUCs showed a positive correlation with testosterone levels. Hypogonadal hPADs mitochondria displayed a lower average length and a superoxide generation increase, compared to eugonadal, with testosterone treatment normalizing both parameters.
Conclusions
Our data suggest that testosterone treatment improves LUTS and induces a metabolically healthier phenotype in hPADs in obese hypogonadal male patients, also displaying a potentially protective role on the progression of NAFLD.

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P605

Parabens and their relationship to obesity

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Introduction
Parabens are a group of chemicals used as preservatives in the food, cosmetic and pharmaceutical industries. They are known to possess estrogenic effects, and therefore have been classified as endocrine disruptors. In addition to the classical endocrine organs, other tissues have endocrine activity, including adipose tissue. Several chemicals are known to cause obesogenic effects, and parabens are currently being studied in this context. The aim of this study was to investigate the possible connections of paraben exposure and obesity.
Methods
Our study included 27 healthy women with regular menstrual cycle. Basal anthropometric measures, levels of parabens (methylparaben, ethylparaben and propylparaben), adipokines (adiponectin, adipsin, leptin, resistin and visfatin) and hormones affecting energy balance and metabolic health (c-peptide, ghreline, GIP, GLP-1, glucagon, insulin, PAI-1) were measured.
Results
A Kolmogorov-Smirnov test showed higher methylparaben and propylparaben levels in women with BMI 25–34.9 compared to those with 18.5–24.9. Plasma levels of methylparaben as well as the sum of parabens were positively associated with the plasma adipsin levels. Negative associations for methylparaben were found for glucagon, leptin and PAI-1.
Conclusion
In accordance with other experimental studies we observed important associations of methylparaben and hormones affecting energy balance and metabolic health, indicating its obesogenic potential. This study highlights that the usage of parabens in varios food, cosmetic and pharmaceutic products may be connected not only with hormone dependent health problems but also with diseases of civilization like obesity.

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P606

Complex use of noninvasive methods for estimating microcirculation of the blood and oxidative metabolism on the big sting finger in patients with diabetes, such as permeable diagnostic diagnostics diagnostics, patients with diable diagnosis

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Purpose of the study
Assess the criteria for early diagnosis of the risk of developing diabetic foot syndrome as a microvasculature using laser Doppler flowmetry and tissue metabolism using fluorescence spectroscopy in diabetic patients.

Materials and methods
The studies are carried out with the help of the Laser Diagnostic LASMA ST Apparatus '(OOO NPP' LAZMA', Moscow) on the plantar surface of the big toe in three stages: resting state - 8 minutes; with cooling 10°C - 1 minute; when heated to 35°C - 4 minutes. Inclusion criteria: HbA1c 6.5-11.0%. Criteria for non-inclusion: the presence of violations of the main blood flow of the vessels of the lower extremities; severe somatic diseases; pregnancy. Control group: 40 people without diabetes mellitus, main blood flow of the vessels of the lower extremities, severe somatic diseases. Patients assessed HbA1c levels and the duration of diabetes mellitus.
Results
94 patients with diabetes aged 19 to 70 years were examined: 70 women and 24 men. Values of microblood flow (Mk), reserve (metabolic reserve), IU (recycling index) in the control group depending on age: 25–40 years old: MK 15.0–18.0; Reserve 62.0–78.0; PS-1.5–2.6; 40–60 years: MK 5.0–8.0; Reserve 164–235; PS 2.9–7.7. More than 60 years: MK 8.0–12.0; Reserve 134.0–170.0; PS 2.8–4.0; Patients were divided into the following groups: Subcompensated violations: microcirculation is active, a decrease in OM is detected: Mk - no more than 20% increased, the Reserve and IU reduced no more than 20%; microcirculation is not active, OM decrease: Mk increased by more than 20%, the Reserve and IU are reduced by no more than 20%; microcirculation is active, pronounced decrease in OM: Mk - increased by no more than 20%, the Reserve and IU are reduced by more than 20%; Persistent decompensated disorders: microcirculation is not active, pronounced decrease in OM: Mk increased by more than 20%, the Reserve and IU are reduced more than 3 times. Signs of the risk of developing diabetic foot: Mk decreased by more than 60%. Reserve and IS reduced by more than 3 times.
Findings
Comprehensive use of LDF and LPS methods allows non-invasive, safe to determine the risk of developing diabetic foot syndrome in patients with diabetes mellitus and reserve indicators of energy metabolism by assessing the dynamics of coenzymes of energy metabolism and microcirculation during functional tests (cold test 10°C and thermal test 35°C).

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P607

Liver fibrosis and steatosis severity evaluation in patients with chronic hepatitis C and type 2 diabetes mellitus

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Background
Non-alcoholic fatty liver disease and chronic hepatitis C (CHC) are systemic diseases with a broad spectrum of coexisting disorders, but their common features are insulin resistance and higher frequency of concomitant type 2 diabetes mellitus (DM). According to recent studies, a higher frequency of CHC in patients with DM is not associated with this cohort exposure to multiple medical interventions, but with CHC being a possible risk factor for developing DM. CHC may accelerate the development of DM nearly for 10 years compared to the general population.
Aim
To evaluate the part of severe liver disease in CHC patients with type 2 DM taking into account body mass index (BMI).
Materials and methods
Transient fibroelastometry (TF) with the use of «Fibroscan FS-502» and additional Controlled Attenuation Parameter (CAP^{TM}) function for liver steatosis (LS) quantitative evaluation was performed in 47 patients with CHC and type 2 DM and no history of antiviral treatment. Several groups were formed: with LS (group 1, $n=37$), without LS (group 2, $n=10$). Female/male ratio and mean age were 41%/59%, 52 ± 1.7 (39–76 years old), and 40%/60%, 59.1 ± 3.4 (31–71 years old), respectively.
Results
In the study group, LS was diagnosed in 79% (37/47) of cases: no LS – 21% (10/47), LS stage 1 – 4/9%, LS stage 2 – 9/19%, LS stage 3 – 24/51%. Severity of LS in group 1: stage 1 – 4/11%, stage 2 – 9/24%, stage 3 – 24/65%. Obesity of different stages was diagnosed in 73% (27/37) in group 1, 79% out of which with LS stage 2–3. In group 2, obesity was diagnosed in 30% (3/10). Normal BMI was in 6% (3/47) of patients. Mean BMI in group 1 was 34.4 ± 1.0 (in stage 1 LS – 28.8 ± 1.4, stage 2-3 LS – in 35.1 ± 1.1). Mean BMI in group 2 – 27.5 ± 3.2. BMI in LS group varied from 26.2 to 48.3, BMI in the group with no LS – from 20.7 to 38.5. The fibrosis stage patients distribution in group 1 with LS comprised:

F0 – 4/11%, F1 – 4/11%, F2 – 7/19%, F3 – 9/24%, F4 – 13/35%. In group 2, severe fibrosis F3 was diagnosed in 70% (7/10).
Conclusion
In the group CHC and type 2 DM, there is a higher percentage of overt LS with concomitant obesity, and severe fibrosis and liver cirrhosis regardless of LS presence. That confirms the priority of the cohort for immediate antiviral treatment irrespectively to diagnosed fibrosis stage on primary examination.

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P608

Determinant factors for prescription of antidiabetic drugs with beneficial effects on weight

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Introduction
Sodium glucose cotransporter 2 inhibitors (SGT2-i) and glucagon-like peptide-1 receptor agonists (GLP-1-ra) conform two families of drugs with beneficial effects on weight and glycemia. Our aim is to identify epidemiological and clinical characteristics of patients, candidates to receive one of these classes of drugs, that can influence on physician's decisions.
Methods/design
Retrospective observational research. Data from patients with type 2 diabetes mellitus (T2DM) attended in a Cardiovascular Risk Factors Unit between January 2016 and December 2017, whom a SGT2-i or a GLP-1-ra was prescribed, were collected. Patients who were already taking one drug of the other class, were excluded from analysis. Univariate and multivariate analysis were performed to identify potential predictors associated with the prescription of each type of drug.
Results
Data from 150 patients were analyzed (SGT2-i and GLP-1-ra was prescribed for each 50% of the sample). Patients who received GLP1-ra for intensification, were more likely to be women (74.7% vs 30.7%, $P<0.001$) and younger (mean age: 55.6 ± 10.9 vs 59.4 ± 10.9 years, $P=0.021$). Also, higher body mass index (BMI) was observed among those who received GLP-1-ra (40.1 ± 7.8 vs 33.7 ± 6 Kg/m^2, $P<0.001$). SGT2-i was the preferred choice among patients with any documented macrovascular complication (63.4% vs 36.6%, $P=0.04$). In multivariant analysis, age (younger) (OR: 6.8 [95% IC: 3.1–15.4], $P<0.001$), higher BMI (OR: 3 [95% CI: 1.4–15.4], $P=0.006$), and gender (female) (OR: 1.04 [95% CI: 1–1.1], $P=0.039$), were associated with GLP-1-ra prescription.
Conclusions
Female gender, younger age and higher BMI are clinical determinants that influence clinical decisions to prescibe antidiabetic drugs with beneficial effects on weight.

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P609

Gut microbiota pattern in relation to diet, physical activity and malnutrition in patients with inflammatory bowel disease: cases-control study

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Introduction
Modifications of gut microbiota have been described in relation to inflammatory bowel disease (IBD), dietary habits and nutritional status.
Objective
To relate gut microbial pattern of patients with IBD compared to healthy individuals; and link gut microbial pattern with activity of the disease, nutritional status and dietary habit.
Material and methods
Observational study of 56 subjects (44 with IBD and 12 controls). We collected clinical and analytical data (nutritional and inflammatory profile), anthropometric, dietary habits (record of 3 days) and microbial study (grouped by a dendrogram for Lactobacillus and the clusters were amplified by PCR).
Results
Mean age 44.7 ± 2.07 years (54.5% males). The disease ratio Crohn's disease (CD)/ulcerative colitis (UC) was 23/21. 38.6% presented remission of the disease and the rest had mild (27.3%), moderate (27.3%), severe activity (11.4%). 37% with activity had malnutrition and 76.9% had moderate or severe vitamin D deficiency ($P=0.025$, 11.61 ± 5.42 vs 21.99 ± 1.81). In the analysis of gut microbiota we found greater similarity between controls and those patient in remission (M1 pattern). The other microbial pattern (M2) showed lower bacterial diversity (patients with higher use of corticosteroid therapy). However, M1 had a higher vitamin D deficiency (75% vs 52.4%) and malnutrition (37.5% vs 22.7%). M2 was associated with the highest protein and carbohydrate intake: meat ($P=0.003$, 60.63 ± 32.55 vs. 128.73 ± 10.26); dairy products ($P=0.040$, 137.13 ± 64.43 vs 285.36 ± 34.28) and pasta ($P=0.049$, 15.88 ± 8.62 vs 40.82 ± 8.23). However, malnourished patients took more vegetables ($P=0.024$, 161.25 ± 43.1) and less fat products ($P=0.032$, 74.84 ± 6.34 vs 92.93 ± 4.24).
Conclusions
Gut microbiota pattern changes according to diet. M2 (more Firmicutes and Proteobacteria and less Bacteroidetes); Active IBD (M2) is associated with a Western diet. The dietary influence on gut microbiota is greater than inflammatory pattern.

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P610

Description of a novel AGPAT2 gene mutation (R159C) responsible for congenital generalized lipoatrophy type 1 (Berardinelli-Seip Syndrome)

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Berardinelli-Seip congenital lipoatrophy type 1 (BSCL1) is a rare autosomal recessive disease caused by mutations in the AGPAT2 gene. This syndrome is characterized by near total absence of adipose tissue since birth, associated with the progressive development of metabolic complications. The AGPAT2 gene encodes for 1-acylglycerol-3phosphate-O-acyltransferase highly expressed in white adipocytes that catalyzes the acylation of lysophosphatidic acid to form phosphatidic acid, a key intermediate in the biosynthesis of triacylglycerol and glycerophospholipids. Close to 95% of patients affected by BSCL have identified mutations. Most of the homozygous or compound heterozygous mutations reported in BSCL patients cause frame-shifts, insertions, deletions or alter the splicing determining a nonfunctional enzyme, fewer cause amino acid substitutions. We describe the case of a 53 years old woman referred to our Center for a suspicion of BSCL. She was born from consanguineous parents (second-degree cousins) and diagnosed at 10 years with lipoatrophic diabetes and hypertriglyceridemia. Over the years, diabetes control was poor and she developed bilateral proliferative retinopathy and diabetic-hypertensive nephropathy. At the time we first visited her, she had striking acromegaloid features, diffuse lipoatrophy, muscolar pseudo-hypertrophy and a small umbilical hernia. BSCL1 syndrome was confirmed after the detection of a double homozygote gene mutation leading to the substitution of the residue Serine at position 61 with an Arginine (S61R) and substitution of the Arginine residue at position 159 with a Cysteine (R159C). The intriguing combination of two different homozygotes missense mutations never described previously, raised the question on which of the two mutations was likely to be causing the disease. The mutation Ser61Arg results in an aminoacid change at evolutionary non-conserved sites. The mutation was also present as homozygote in the unaffected brother. The mutation Arg159Cys affects a conserved aminoacid site and resides in a highly conserved region among mammalian species. This substitution was present in the heterozygote state in the unaffected brother. In this case the homozygote mutation segregated with the disease and the in silico score was predictive of disruption, making its pathogenic role likely. In conclusion we describe a novel missense AGPAT2 mutation (R159C) which is responsible for BSCL1.

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P611

Prenatal metformin treatment in obese rats: Evaluation of liver norepinephrine and lipogenic enzymes in offspring

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Maternal obesity during pregnancy is associated with several metabolic impairments in offspring, some of them evidenced from early infancy. Some reports have demonstrated that offspring of obese rats, whose obesity was induced by high fat diet consumption, have an increase sympathetic tone and increased norepinephrine (NE) content in kidney, liver and ovary. We recently reported that maternal administration of metformin prevents the increase in ovarian NE in offspring when they are adult. Since norepinephrine signaling is like glucagon in liver, we aimed to evaluate whether hepatic gene expression of lipogenic enzymes is altered in adult offspring of obese rats and if it is associated with norepinephrine levels. Also, we evaluated whether metformin (250 mg/Kg) during pregnancy prevented the liver alterations observed in offspring of obese mothers. To achieve this, we measure norepinephrine b..y HPLC coupled to electrochemical detection, Tyrosine hydroxylase by Western blot, and acetyl CoA carboxylase (ACC) and fatty acid synthase (FAS) by qPCR in the liver. Our results showed an increase in FAS and ACC expression in offspring of obese mothers, along with a tendency to increase in liver norepinephrine. Metformin prevented the increase in FAS and ACC expression in offspring of obese mothers but, intriguingly, it increased TH expression and norepinephrine levels both in offspring of obese and offspring of control rats. In conclusion, metformin prevented the alterations in the expression of lipogenic enzymes induced by maternal obesity during pregnancy but altered the sympathetic control of the liver.

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P612

Profile of celiac disease in diabetic children

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Introduction
Celiac disease (CD) is a common condition in children with type 1 diabetes (T1D). This condition is often asymptomatic and predisposes to severe complications of diabetes. The aim of this work was to study the clinical, biological, and evolutionary features of CD in diabetic children compared to a control group of non-celiac diabetic children.
Patients and methods
Retrospective study of a cohort of 10 T1D children with CD compared to a control group of 20 non-celiac diabetic children collected in the Pediatric Department of Tahar Sfar University Hospital of Mahdia over 30 years.
Results
The prevalence of CD in children with diabetes was 2.7%. Diabetes was revealed in celiac children by ketoacidosis in 70% of cases versus 40% in controls. The mean duration of diabetes progression was 8.6 ± 1.8 years in celiac patients versus 10.2 ± 2.1 years in controls. The mean age of discovery of CD was 7.8 ± 3.1 years, 3.6 years in mean after the discovery of diabetes with a sex ratio of 1.5. At the time of diagnosis of CD, 50% of children were asymptomotic, 40% had growth delay, 14% had abdominal pain, 14% recurrent hypoglycaemia, 7% chronic diarrhea, 60% anemia, and 70% CD positive antibodies. Jejunal biopsies showed total villous atrophy in 40% of cases, subtotal villous atrophy in 30% of cases and partial villous atrophy in 30% of cases. Gastric biopsy revealed associated Helicobacter pylori gastritis in 50% of cases. After initiating a gluten-free diet, 60% of celiac children had poor diet adherence because of their low socioeconomic status. Short stature was observed in 50% of celiac patients versus 15% of controls. Hypoglycemia was a cause of re-hospitalization twice as common in celiac children than in the control group. Mean HbA1C in celiac patients was 10.4% versus 9.1% in controls.
Conclusion
This study confirms the high prevalence of CD in children with T1D who are prone to severe comorbidities and who are generally poorly adherent to the gluten-free diet. Serologic screening for CD allows early diagnosis and management to improve the balance in diabetes and avoid complications.

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P613

A common but forgotten cause of electrolyte disturbances in patients with cachexia

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Fluid and electrolyte disturbances are a challenging problem of inpatients, especially in those subpopulations, in whom the electrolyte imbalance is involved in the pathogenesis of the primary disease. Here we present the case of a 58 year old woman, with ongoing alcohol abuse on a daily basis, who was admitted with progressive fatigue and dysphagia. At the admission BMI was 17.8 kg/m^2, and the patient presented deficiency of vitamins A, B, and D. The diagnostic procedures did not reveal the cause of dysphagia, which was therefore considered to be a functional disorder. We started parenteral nutrition to provide sufficient calories and intravenous substitution of vitamins. Despite clinical improvement we were confronted with a gradual decompensation of electrolytes, i.e. marked hypokalemia, hypocalcemia, hypomagnesemia, and hypophosphatemia. The electrolyte deficiencies were refractory to intermittent intravenous substitution and required continuous administration via perfusor with very rapid relapse after discontinuation. Acute or chronic kidney injury could not be proven. Hyperaldosteronism and hypercortisolemia were also excluded. The existence of a genetic disorder affecting the electrolyte balance was considered unlikely because of the absence of similar findings at younger age and no affected family members. Taken together we considered the electrolyte decompensation to be caused by refeeding syndrome. Refeeding syndrome is a well described but often underestimated condition that reflects hormonal and metabolic changes in a malnourished patient after initiation of iso- or hypercaloric nutrition and reflects the adaptation of intracellular electrolytes in the anabolic state. Given that many electrolyte disturbances can be asymptomatic, refeeding syndrome needs close monitoring of fluid and electrolyte fluctuations, especially in at-risk patients. Under rigorous monitoring, we could stepwise reduce the continuous substitution of potassium and phosphate and the need for magnesium. At the time of discharge, the patient achieved a BMI of 18.5 kg/m^2, reported substantial improvement of the dysphagia and no need for oral intake of electrolyte supplements.

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P614

Vitamin D status and bone metabolism in adult patients with Type 1 diabetes mellitus

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Introduction
Vitamin D is essential for calcium metabolism and is involved in bone turnover. The purpose of this study was to examine vitamin D status and its relation with bone metabolism in adult patients with T1DM.
Methods/Design
We studied 118 patients with T1DM (Group-D) (mean age: $35.4 + 10.3$ years) and 94 healthy controls (Group-C) matched for age, sex and body mass index (BMI). In both groups HbA1c, 25(OH)Vitamin D (Vit-D), serum calcium (Ca), phosphorus (Ph), magnesium (Mg), alkaline phosphatase (ALP), albumin (alb), parathyroid hormone levels (PTH), β-crosslaps, type 1 procollagen total N-terminal propeptide (TP1NP) were measured. Vit-D levels 30–50 ng/ml were defined as optimal concentration (OC), 20–30 ng/ml as suboptimal concentration (SC), 10–20 ng/ml as deficiency (DE) and 0–10 ng/ml as insufficiency (IN).
Results
In Group-D, mean duration of DM was $16.2 + 9.5$ years and mean HbA1c was $7.8 + 1.4$%. In Group-D, Vit-D OC occurred in 20%, SC occurred in 27.1%, DE occurred in 34.3%, with the remaining 18.6% having a Vit-D level below 10 ng/m(IN). In Group-C, Vit-D OC occurred in 23.4%, SC occurred in 31.6%, DE occurred in 28.4%, with the remaining 16.6% having a Vit-D level below 10 ng/ml (IN). The overall mean Vit-D levels were not significantly different between groups (D: $20.4 + 11.0$ vs C: $21.2 + 8.4$, $P = 0.743$). Also, Ca, Ph, Mg, ALP and PTH levels were comparable in both groups. B-crosslaps were significant lower in Group-D compared to control (D: $325.7 + 198.9$ vs C:

442.8 + 220.6, $P = 0.002$) but TP1NP were lower in Group-D but not statistical significant (D: 50.34 + 30.97 vs C: 53.12 + 24.43, $P = 0.594$). In T1DM patients, no correlation was found between Vit-D and HbA1c ($r = 0.032$, $P = 0.794$), Vit-D and β-crosslaps ($r = -0.004$, $P = 0.976$) and Vit-D and TP1NP ($r = 0.009$, $P = 0.944$).

Conclusion

These data suggest that Vit-D and calcium metabolism in patients with T1DM were comparable with the controls and were not correlated with glycemic control and bone metabolism.

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P615

The effect of antidiabetic drugs on serum 25-hydroxyvitamin D level: A preliminary report

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Objective

This study aimed to assess the early results of the effect of antidiabetic drugs on serum 25-hydroxyvitamin D (25(OH)D) level in patients with type 2 diabetes mellitus (T2DM).

Methods

Thirty-five patients with T2DM having vitamin D deficiency (< 20 ng/ml) or insufficiency (< 30 ng/ml) were included. They were divided into 5 groups according to the drug therapy (metformin alone ($n = 9$), metformin in combination with insulin ($n = 6$), or sulphonylurea ($n = 4$), or DPP-4 inhibitor ($n = 7$), or SGLT-2 inhibitor ($n = 9$)). All participants were given daily supplementation of 2000 IU vitamin D3. Serum levels of phosphate, ionized calcium, parathyroid hormone (PTH), 25-hydroxyvitamin D (25(OH)D), HbA1c were measured at baseline and 12 weeks after the aforementioned supplementation, for comparison purpose. Serum level of 25(OH)D was measured by mass spectrometry method using Cobas e411. Statistical analysis included descriptive statistics (percentage, mean and median) and multiple comparisons by non-parametric tests.

Results

The mean age of the patients was 48.32 ± 19.83 (37–75) years. There were 17 men and 18 women. The median 25(OH)D level in serum (mean ± s.d. 14.7 ± 7.28 (3.0–29.8) ng/ml) was low in all participants. When compared the 5 groups according to therapy, there was no significant difference in the levels of serum phosphate, ionized calcium, PTH, 25(OH)D and HbA1c. However, in the dapagliflosin group the level of phosphorus (1.65 ± 0.06 mmol/l) was significantly higher than the metformin alone group (1.19 mmol/l ± 0.06) ($P = 0.002$); the serum 25(OH)D levels were similar (15.12 ± 7.13 ng/ml and 14.8 ± 7.14 ng/ml respectively) ($P > 0.05$).

Conclusions

Preliminary results show that patients on dapagliflozin therapy have higher serum phosphate levels compared to patients on metformin therapy.There is no meaningful association between 25(OH)D level and type of T2DM therapy. However, due to the limited number of participants and short duration of the study potential effects on clinical outcomes still remain to be answered. These should be assessed in future studies with larger sample sizes and longer follow-up.

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P616

Serum total and bioactive fibroblast growth factor 21 levels are similar in patients with gestational diabetes mellitus and healthy pregnant controls

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Aim

Fibroblast growth factor (FGF) 21 is a hormone which plays an important role in metabolic diseases such as diabetes, obesity and dyslipidemia. In this study; we aimed to investigate the serum total and bioactive FGF21 levels in patients with gestational diabetes mellitus (GDM) and compared with healthy pregnant controls.

Material and Methods

A two-step screening method and Carpenter and Coustan criteria were used in the diagnosis of GDM. Forty patients with GDM and 39 healthy pregnant controls were included in the study. Serum samples of patients and controls were taken in the morning following 8–10 hours fasting period between $24^{th} - 28^{th}$ gestational weeks to measure serum biochemical variables and FGF21 levels. Total and bioactive FGF21 levels were determined by enzyme-linked immunosorbent assay (ELISA).

Results

The mean age and body mass index were higher in patients with GDM compared with healthy pregnant controls (33.1 ± 5.0 vs 28.4 ± 6.2 years, $P < 0.001$ and 30.4 ± 5.2 vs 24.8 ± 2.8 kg/m^2, $P < 0.001$; respectively). Serum glucose levels were also higher in patients with GDM (97.0 ± 18.3 vs 87.0 ± 10.8 mg/dl, $P = 0.012$) while serum insulin levels of the two groups were not statistically different (13.8 ± 7.6 vs 12.9 ± 4.1 mU/l, $P = 0.65$). When the patients with GDM were compared with healthy pregnant controls, there was no statistically significant difference in serum total and bioactive FGF21 levels between the two groups (197.8 ± 107.5 vs 222.4 ± 108.9 pg/ml, $P = 0.054$ and 148.3 ± 80 vs 165.3 ± 81.2 pg/ml, $P = 0.067$; respectively). Serum total and bioactive FGF21 levels were positively correlated with serum insulin levels ($P = 0.007$, $r = 0.300$ and $P = 0.007$, $r = 0.301$) while negatively correlated with the age ($P = 0.037$, $r = -0.235$ and $P = 0.044$, $r = -0.228$).

Conclusions

We found that serum total and bioactive FGF21 levels were similar in patients with GDM and healthy pregnant controls and positively correlated with serum insulin levels. These results suggest that serum total and bioactive FGF21 levels were associated with serum insulin levels rather than the presence of GDM.

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P617

Liraglutide restores the hyperglycemic oxidative imbalance and induces the expression of CRH, UCN1, UCN2 AND UCN3 neuropeptides in macroendothelial cells

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Introduction

Liraglutide treatment reduces cardiovascular complications in patients with diabetes mellitus (DM), which may imply a favorable impact on the endothelial function. The aim of the present study was to investigate *in vitro* the effect of liraglutide on endothelial redox balance and the parallel expression of CRH, UCN1, 2 and 3 neuropeptides, under normoglycemic and hyperglycemic conditions.

Methods

Macroendothelial cell line EAhy926 was incubated for two hours in the presence of hypeglycemic (25 mM) and normoglycemic (5 mM) conditions in the presence of liraglutide (40 nM). Intracellular H_2O_2 levels, eNOS (endothelial nitic oxide synthase) and produced NOx, SOD (superoxide dismutase), catalase and GPx (glutathione peroxidase) activities were determined in cells lysates and culture media, and CRH, UCN1, 2 and 3 gene expression was assessed in total RNA extracts.

Results

Hyperglycemia was accompanied with significant increase of intracellular H_2O_2 and decrease of the studied antioxidant response enzymes ($P < 0.005$). Liraglutide restored the endothelial oxidative balance while it also reduced the activity of the antioxidant enzymes ($P < 0.005$). CRH and UCNs' expression were further increased ($P < 0.05$) in the presence of liraglutide. Liraglutide did not affect eNOS and SOD activity in normoglycemic conditions, but decreased significantly catalase and GPx activity ($P < 0.005$). CRH and UCNs expression was upregulated in both normoglycemic and hyperglycaemic conditions ($P < 0.005$).

Conclusions

Liraglutide restores the endothelial redox balance of macroendothelial cells which are exposed to high glucose levels and triggers the expression of CRH and UCNs suggesting that part of the antioxidant response is mediated by the CRH family neuropeptides' expression.

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P618

The effects of hyperinsulinemia on cochlear functions

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Purpose
Hyperinsulinemia is the metabolic change, which is related to the cochleo-vestibular diseases the most. It is thought that undiagnosed deafness is highly probable in individuals with prediabetic hyperinsulinemia. We aimed at investigating the results of hearing function test in hyperinsulinemic individuals.
Material and Method
164 patients were included in the study, which was designed as a prospective research, 76 of which were in case group and 88 of which were in the control group. 76 patients who were between 18 and 64 years of age and with insulin resistance (HOMA-IR $\geq$ 2.5) comprised the case group of the study and 88 patients with HOMA-IR values $<$2.5 comprised the control group. All patients were administered the 75 gr OGTT chemical analysis (lidip panel, creatinine, fasting serum glucose and fasting serum insulin level), hormonal analysis (TSH and sT4), audiological assessment, electrocochleography (EcochG) and transient evoked otoacoustic emissions (TEOAE) test.
Findings
The pure sound audiometry threshold values at the 500, 1000, 2000 and 4000 Hz for both ears were found higher in the patients in the case group than the patients in the control group ($P<0.01$). A positive correlation was found between HbA1c and right ear 500, 1000, 4000 and 8000 Hz threshold values and left ear 2000, 4000, 6000 and 8000 Hz threshold values ($P<0.05$). A negative correlation was found between HbA1c and speech recognition ($P<0.01$). The right ear 1.00 and 2.83 kHz TEOAE measurements in the individuals with normal glucose tolerance (NGT) were found higher than the patients with impaired glucose tolerance (IGT); and the 1.42 kHz TEOAE measurements and reproducibility were found higher than the patients with impaired fasting glucose (IFG) ($P=0.013$, $P=0.035$, $P=0.031$). The left ear 1.00 kHz and the 1.42 kHz TEOAE measurements of the IGT patients were found lower than the IFG and NGT patients ($P=0.004$, $P=0.006$).
Conclusion
In our study, it was shown that hearing loss developed in hyperinsulinemic cases and prediabetic conditions (IFG/IGT) were related with hearing function impairment. Based on the data of our study, pure sound audiometry and speech recognition scores are recommended in metabolism related hearing loss studies, as electrocochleography does not make an additional contribution, although they are not practical.

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P619

Trial-in-progress: ZEPHYR, a pivotal phase 2b/3 randomized, placebo-controlled study of livoletide, a novel unacylated ghrelin analog, for the treatment of hyperphagia and food-related behaviors in patients with Prader-Willi syndrome

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Background
Prader-Willi syndrome (PWS) is a rare disease characterized by hyperphagia and abnormal food-related behaviors that contribute to severe morbidity and early mortality and to a significant burden on patients and caregivers. There is no approved treatment for hyperphagia in PWS. Patients with PWS have increased circulating levels of the orexigenic hormone acylated ghrelin (AG) with a relative deficit of unacylated ghrelin (UAG). Livoletide (AZP-531) is a first-in-class UAG analog that was previously shown in a Phase 2 randomized, double-blind, placebo-controlled study of 47 PWS patients to significantly improve hyperphagia, food-related behaviors, and metabolic parameters, and to be well-tolerated. [Allas S *et al*. (2018) PLoS ONE 13(1): e0190849].
Objective
ZEPHYR (EudraCT 2018-003062-13; NCT03790865) is a pivotal Phase 2b/3 study that is designed to evaluate the long-term safety and efficacy of livoletide in patients with PWS.
Methods
The ZEPHYR study is currently being conducted in North America and Europe. In its Phase 2b portion, approximately 150 patients with PWS will be randomized to receive livoletide ~60 ug/kg, livoletide ~120 ug/kg, or placebo, once daily by subcutaneous injection for a 3-month core period. Patients will then enter a 9-month extension period. The Phase 3 portion will be initiated following results of the Phase 2b core period with patients randomized to livoletide at a dose based on Phase 2b core data or to placebo. After 6 months of treatment in the Phase 3 core period, patients will enter the 6-month Phase 3 extension period. Main entry criteria for ZEPHYR include genetic diagnosis of PWS, age 8–65 years, single primary caregiver available for the duration of the study, and BMI $\leq$65 kg/m^2 for adult patients. Patients with type 2 diabetes with HbA1c $\leq$10% may be enrolled. Use of human growth hormone will be allowed if dosage is stable. The primary outcome measure is the Hyperphagia Questionnaire-Clinical Trials (HQ-CT) score. The HQ-CT has been validated and is considered by regulatory authorities to be a valid primary endpoint. Secondary outcome measures include metabolic and body composition parameters such as fat mass as assessed by DEXA, BMI, and body weight in overweight/obese patients.
Results
The study is ongoing: enrollment began in early 2019 and updates will be reported.
Conclusion
ZEPHYR is a pivotal study that will provide data on the long-term safety and efficacy of the novel UAG analog livoletide on the treatment of hyperphagia and food-related behaviors in patients with PWS.

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P620

Next generation sequencing reveals ABCC8 (MODY 12) variants in two families with diabetes mellitus (DM)

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Introduction
Maturity Onset Diabetes of the Young (MODY) constitutes a genetically and clinically heterogeneous type of Monogenic Diabetes (MD). It is characterized by autosomal dominant inheritance, early onset diabetes, defect in the β-cell insulin secretion, positive family history, absence of diabetic ketoacidosis, auto-antibodies and insulin resistance. To date, 14 different MODY subtypes have been reported each one with distinct genetic etiology, however MODY patients are frequently misdiagnosed as DT 1 or 2. *ABCC8* gene variants are associated with neonatal diabetes, hyperinsulinism and MODY.
Aim
To identify the molecular defect of two families suspected for MODY employing a Next Generation Sequencing (NGS) Targeted Gene Panel for 7 MODY genes (*GCK, HNF1A, HNF4A, HNF1B, INS, ABCC8,KCNJ11*).
Methods-Results
Family A: A 24 year old man (BMI=23) presented at the emergency department with hyperglycaemia (glucose=365 mg/dl, HbA1c=11.9%), without ketoacidosis and negative anti GAD/ICA antibodies. He was treated with insulin and metformin. Insulin was decreased and discontinued within a month. While on metformin and appropriate diet his HbA1c was 5.5%, but later increased at 7.7%. *Father:* DM on tablets since the age of 48. *Mother:* impaired glucose tolerance (IGT). *Maternal grandfather:* insulin-treated DM since the age of 45. Genetic analysis of patient's DNA revealed that the patient and his mother were heterozygotes for the p.Glu1206Lys variant of the *ABCC8* gene. After switching him to gliclazide and adding metformin, his HbA1c was 5.6% with stable glucose levels.
Family B: *Son 1(49 years old):* DM at 32 with glucose>300 mg/dl, HbA1c=10.6% and BMI=29. His was treated with metformin±pioglitazone±sitagliptin with 5.5% *Son 2 (39 years old): DM at 25 with HbA1c=7.9% and BMI of 24. He was treated with metformin±saxagliptin and 9 years later basal insulin was added. His HbA1c is 5.6% and BMI=27. Both sons had no diabetic complications, anti GAD/ICA antibodies nor ketoacidosis. Father: DM at 46, on metformin±sulfonylurea±sitagliptin, BMI=26.5, HbA1c=6.3%. Mother: IGT. Genetic analysis of the family revealed that the two sons and their father were heterozygotes for the p.Ser1386Phe variant of the ABCC8 gene.*
Conclusions
ABCC8 (MODY 12) patients exhibit genetic heterogeneity, even within the same family, ranging from impaired glucose tolerance to insulin treated diabetes. Genetic testing for the recognition of MODY subtype is of outmost importance for diagnosis, prognosis, treatment and family counseling.

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P621

Nonclinical development of livoletide (AZP-531), a peptide analog of unacylated ghrelin for the treatment of hyperphagia in Prader-Willi syndrome

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Prader-Willi syndrome (PWS) is a rare complex endocrine disease characterized by hyperphagia and abnormal food-related behaviors that contribute to severe morbidity and early mortality and to a significant burden on patients and caregivers. There are no approved treatments for hyperphagia in PWS. Patients with PWS have increased circulating levels of the orexigenic hormone acylated ghrelin (AG) with a relative deficit of unacylated ghrelin (UAG). These abnormalities in AG and UAG levels may be involved in the underlying mechanisms of hyperphagia. UAG is a 28-amino-acid peptide that does not bind the growth hormone secretagogue receptor (GHSR), unlike AG. UAG has intrinsic central and peripheral effects that counteract the effects of AG and are exerted through a GHSR-independent mechanism. Livoletide is a cyclic 8-amino-acid analog of UAG with improved plasma stability and pharmacokinetics. The objective of this nonclinical development program was to support the clinical development of livoletide, which includes a pivotal Phase 2b/3 clinical trial in patients with PWS initiated in early 2019. The program was designed to define the safety pharmacology and the chronic toxicologic and toxicokinetic profile of livoletide and to identify parameters for clinical monitoring of potential adverse effects. Genotoxicity, safety pharmacology, reproductive toxicity, and repeat-dose 13-week toxicology studies were all completed. In the *in vivo* studies, livoletide was administered subcutaneously consistent with the clinical route of delivery. Livoletide was not found cytotoxic or genotoxic. Safety pharmacology studies indicated no treatment-related effects on major physiological systems. Results from preliminary embryo-fetal developmental toxicity studies in rat and rabbit indicated that livoletide at high multiples of the anticipated human exposure was not associated with adverse maternal toxicity, embryo-fetal toxicity or teratogenic potential when administered throughout the period of organogenesis. Repeat-dose toxicity studies of up to 26 and 39 weeks' duration in rats and dogs demonstrated that livoletide was very well tolerated, with no evidence of systemic toxicity. Cumulative data indicated that livoletide has a wide safety margin relative to planned clinical exposures. The highest chronic doses tested were 45 mg/kg in rat and 30 mg/kg in dog; these were considered to be the NOAELs. These dose levels provided AUC values of $\geq$50-fold the intended clinical systemic exposure ($\sim$1200 ng·h/ml). No anti-livoletide antibodies were detected in any of the toxicology studies. These results confirm the favorable long-term safety profile of livoletide and support the subcutaneous administration of the highest anticipated human clinical dose in the Phase 2b/3 study.

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P622

Assessment of materno-fetal complications in pregnant women with type 1 diabetes exposed to insulin degludec

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Introduction
Pregnancy in women with type 1 diabetes mellitus (T1DM) is associated with an increased risk of adverse outcomes, so pregnancy planning in order to achieve an optimal glycemic control is essential. This control has been made possible, in part, by the widespread use of insulin analogues, especially the long-acting ones, glargine and detemir. Insulin degludec, an ultra-long-acting insulin is not currently approved for pregnant women due to the lack of randomized controlled studies in this special population, although its use during pregnancy could be helpful to improve glycemic control.
Objectives
To describe obstetric and perinatal outcomes in a cohort of patients with T1DM who became pregnant while taking insulin degludec.
Material and methods
Retrospective observational study of perinatal and obstetrical data from patients who used insulin degludec in the periconceptional period and had follow-up consultations between 2016 and 2019.
Results
Data were analyzed from 12 women with T1DM (27.5 $\pm$ 8 years old), 14.9 $\pm$ 7.4 years of diabetes duration, a pre-pregnancy weight of 84.8 $\pm$ 12 Kg and periconceptional HbA1c 7.8 $\pm$ 1.5%. The insulin degludec dose at the time of conception was 0.42 UI $\pm$ 0.16 IU/kg and was suspended at 9.5 $\pm$ 4.8 weeks of pregnancy. It was changed to insulin glargine in six patients, to insulin detemir in five patients and to NPH insulin in one patient. One of them was also treated with statins and angiotensin-converting enzyme inhibitors (also suspended). Two abortions occurred in the sixth and seventh week of gestation, respectively.
Up to now, 6 births (3 term and 3 pre-term) have taken place, all of them by caesarean section, with a newborn weight of 3438 $\pm$ 690 grams. As complications, 3 patients presented pre-eclampsia and we had 3 cases of neonatal hypoglycemia. None presented neonatal jaundice, respiratory distress, congenital malformations or required admission to the neonatal intensive care unit.
Conclusions
- Causality between observed complications and insulin degludec cannot be established since insufficient perinatal metabolic control itself constitutes a risk factor of developing these complications, as well as the small sample size.
- Controlled clinical trials are needed to confirm the efficacy and safety of insulin degludec in pregnancy.

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P623

Myeloproliferative disorder: a rare cause of insulin auto-immune syndrome leading to recurrent severe hypoglycaemia

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Insulin autoimmune syndrome (IAS; Hirata syndrome) is a rare cause of hypoglycemia. It seems to be related to specific HLA class II alleles. Rarely, monoclonal antibody acts as an insulin-binding autoantibody: until now 10 cases have been described in association with a myeloproliferative disorder. In June 2015, a 60-year-old patient presented in a local hospital in Mayotte with confusion, sweating and severe hypoglycemia (blood glucose as low as 20 mg/dl). He was suffering of chronic obstructive pulmonary disease and had no history of diabetes neither use of any drug or hypoglycaemic agent. His physical examination revealed obesity: IMC 34 kg/m^2. Laboratory evaluation showed anemia (Hb 9.2 g/dl). Liver, renal, thyroid and adrenal functions were all normal. Fasting blood sugar was 28 mg/dl with total plasma insulin level of 788 mU/l. He was thus referred to our center in La Reunion, for further investigations: magnetic resonance of the abdomen and ultrasound failed to detect lesions or suspicious masses suggesting insulinoma. A plasma-protein electrophoresis revealed a restricted gammaglobulin band of 1 g/l. Immunoelectrophoresis revealed a monoclonal IgG kappa. But the bone marrow biopsy didn't show excess of plasma cells ($<$2%). At 72-h observed fast, there was no hypoglycemia. A 75-gram oral glucose tolerance test caused a severe hypoglycemia after 4 hours (25 mg/dl) with total insulinemia level of 247 (T0) reaching 1722 mU/l (3 h). Concurrently, free insulin level was 10.3 (T0) and reached 63.5 mU/l (3 h) and C-peptide level: 1.12 (T0) and 6.18 µg/l (3 h). These results led to consider an insulin auto-immune syndrome (IAS). Indeed, the dosage of antihuman insulin antibodies (IAA) showed a high level $>$ 50 u/ml. Infectious serologic testing and autoimmune marker were all negative. The serologic typing of HLA alleles was not in favour of HLA DR4. He went back to Mayotte. Despite 2 years treatment (Rituximab-Prednisolone every 2 months), hypoglycaemic events persisted and he was again referred in 2018. High level of insulin antibodies was still found and the IgG level increased to 3.1 g/l (plasma cells $<$ 10% in the marrow). His treatment regimen was changed to bortezomib and high dose of dexamethasone with subsequent remission of hypoglycemia, decrease of IgG level (0.8 g/l) and antihuman insulin antibodies after 8 cycles. In conclusion, the search for paraproteinemia should be undertaken in Hirata syndrome or IAS particularly in case of relapse to immunosuppressive drug.

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P624

Augmented Mitophagy and Inflammasome Activation with Metformin therapy in patients with T2DM

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Background
Impaired mitophagy (mitochondrial autophagy) and NLRP3 inflammasome activation have been implicated in the etiopathogenesis of insulin resistance and T2DM. Metformin beside being an insulin-sensitizer, also induces autophagy. However, further research is warranted in elucidating its effect on mitophagy and NLRP3 activation in patients with T2DM.
Methods
45 drug-naïve, newly diagnosed T2DM patients, with HbA_{1C} 53–75 mmol/mol (7–9%) were randomly assigned to receive either metformin or voglibose (active comparator) or placebo for 3 months, along with lifestyle intervention ($n=15$ each). Mitochondrial oxidative stress (MOS) parameters, quantitative real-time PCR and immunoblotting of mitophagy-related markers (PINK1, PARKIN, MFN2, NIX, LC3-II, LAMP-2), p-AMPKα (T172) and NLRP3 proteins, as well as transmission electron microscopy (TEM) for assessing mitochondrial morphology, were performed in the study subjects.
Results
Both metformin and voglibose showed a similar efficacy towards the reduction in FPG and HbA_{1c} levels, and MOS indices. However, a significant upregulation in mitophagy and NLRP3 expression was observed with metformin monotherapy. Further, multivariate ANCOVA anaylsis revealed that mRNA and protein expression of mitophagy markers, NLRP3, and p-AMPKα (T172), increased significantly only with metformin, as compared to voglibose and placebo. TEM studies further confirmed reduced distortions in mitochondrial morphology, in the metformin group. Moreover, PINK1 expression showed a significant positive association with HOMA-β indices.
Conclusions
Our observations underscore the beneficial effects of metformin on mitochondrial morphology and function via promoting mitophagy. Hence, pharmacological modulation of mitophagy may represent a novel therapeutic approach to prevent or contain the worsening of β-cell function in subjects with T2DM by restoring mitochondrial health.

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P625

Features of IL-17 expression in focus of inflammation modulating in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease

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According to recent views, underlying cause and characteristic of type 2 diabetes mellitus (DM2), complicated by non-alcoholic fatty liver disease (NAFLD) is chronic systemic low-gradient inflammation, in which the leading role in liver damage and DM2 decompensation is given to the cytokine production. The purpose of this study was to compare the levels of interleukin 17 (IL-17) expression in patients with DM2 and NAFLD, as well as to assess the relationship between IL-17 and anthropometric (BMI), laboratory characteristics (HOMA-IR, IL-1β, INF-γ, CD-95) in these patients. Methods. We observed 118 patients, including 64 patients with DM2 and NAFLD, 26 patients with DM2 and 28 patients with NAFLD. The control group consisted of 25 apparently healthy individuals. Results. Significant increase in content of IL-17 cytokine in 3–4 times was established in patients with NAFLD only ($P<0.05$) and in combination of DM2 and NAFLD ($P<0.05$), which confirms the presence of progressive inflammatory response in these patients. In addition, IL-17 also contributes to the development of insulin resistance, as it leads to disorder of insulin -mediated glucose transport and suppresses the expression of genes involved in lipid metabolism. Our results also showed that there is a significant positive correlation between IL-17 and BMI ($r=0.62$, $P<0.05$), HOMA-IR ($r=0.43$, $P<0.05$), and INF- γ ($r=0.59$, $P<0.05$).
In the combination of DM2 and NAFLD, the content of INF-γ is increased in 6 times compared to control and in 2 times compared DM2 alone ($P<0.05$). Such changes lead to a disturbance in insulin signaling in adipocytes, a link that binds mechanisms of T-cell mediated inflammatory process with insulin resistance. IL-17 stimulates macrophages to increased production of IL-1β, which in turn has a cytotoxic effect on beta cells. The excretion of IL-1β in main group was the highest and was 6.85 pg/ml comparing to control of 1.6 pg/ml ($P<0.05$). The established moderate correlation ($r=0.32$, $P<0.05$) between the level of IL-1β and the content of CD-95+ in main group is evidence of inflammatory reactions and apoptotic processes in the liver with further fibrogenesis. Conclusions. The combination of DM2 with NAFLD is accompanied by an elevated IL-17 expression level in all studied groups of patients, its positive correlations with BMI, HOMA-IR, expression of INF-γ, IL-1β and CD-95+. All this, as the mightful inflammatory background, promotes the activation of hepatocyte apoptosis and is an important basis for liver fibrosis progression.

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Interdisciplinary Endocrinology 1

P626

Autoimmune thyroiditis (AIT) and diet – the patients' and medical professionals' view

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An increasing interest in improving the quality of life of patients with autoimmune thyroid disorders has been noted during recent years. Although there is little scientific evidence, many patient-oriented publications, websites and support groups recommend changes in diet as well as nutritional supplement use as a cure for thyroid disease and the mean for ailments reduction. The presented survey aimed to explore the patients' and medical professionals' approach to nutritional treatments of AIT.
Material and methods
(1) Medical professionals: 30 physicians, 32 nutritionists, 35 medical students and 27 dietetics students responded to an internet questionnaire on the recommendations for a nutritional approach in AIT (gluten-free and lactose-free diet, selenium, vitamin D, and iodine supplementation). (2) AIT patients: 150 subjects aged 18 to 70 years (146 females, 4 males) responded to an internet questionnaire on the nutritional approach in their disease. Questions concerned: gluten-free and lactose-free diet, as well as vitamins and microelements use, the source of the patients' knowledge, and the recommending body behind their decision on changes in nutrition.
Results
(1) Medical professionals. 54% of the surveyed subjects recommended their patients the use of selenium supplements (9.7% in Graves' ophthalmopathy), 41.3% - iodine supplements, 92.3% -vitamin D supplements. 6.4% of responders advised a gluten-free diet regardless of the coexistence of gluten-related disorders, and 4.8% - a lactose-free diet even in the absence of lactose intolerance. There were discrepancies in recommendations between professionals: physicians advised iodine and selenium least often. (2) AIT patients. 44.3% of responders were on a lactose-free, and 37.3% - on a gluten-free diet. Only 2% of responders were diagnosed with celiac disease. 38% of responders who had modified their diet, have decided to do so following the recommendation of a medical professional, the remaining 62% - without any advice. 36.7% of responders were using selenium supplements (27.3% following a physician's recommendation), 8% - iodine supplements (all advised by a physician), 74.7% - vitamin D supplements (48.7% of them have obtained recommendations). Websites (80.7%) and patients-oriented publications (50.7%) were the main sources of AIT patients' knowledge and opinions on the role of nutrition in AIT management.
Conclusions
AIT patients commonly decide to implement a nutrition-based approach to their disease, even without any professional advice. Although the results of the survey are biased by internet methodology, it is worrying that many medical professionals advise introduction of diets and supplements against guidelines of medical societies.

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P627

Abstract Unavailable.

P628

Diabetes and dementia in the geriatric population – The icing on the cake

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Background
The association between diabetes and dementia has been well documented (1, 2, 3) and with Australia's aging population, the already significant disease burden of both pathologies will inevitably progress over time. Despite both being progressive pathologies which escalate over time, there have not been any studies pertaining to degree of glycaemic control and the extent to which this relates to prevalence of dementia.
Aims
To determine association between diabetic control and prevalence of dementia. Secondary aims are 1) Assessment of the role of having stringent control to reduce prevalence of dementia and 2) Juxtaposition of risks relating to tight control in terms of rates of hypoglycaemia.
Methods
Retrospective study of 128 admissions between 1st January to 31st December 2016 were studied. 25 variables were analyzed. Partition modelling was used to identify variables which could affect outcomes, and hence, measure impact of variables upon incidence of dementia and macro/microvascular complications. Chi square analysis was utilized to determine statistical significance.
Results
128 admissions met inclusion criteria (mean age 84, SD =5.6, male =39%). Mean length of stay was 30 days. Dementia was associated with suboptimal glycemic control, while tightly controlled BSL's (blood sugar level) had minimal impact upon rates of hypoglycaemia, until post prandial BSL's dropped below 7. We found that a range of 7–10 mmol/L, reflecting the current gold standard of <11.1 mmol/L (4) would result in reductions in dementia prevalence, length of stay and readmission rates by 41%, 6.43 days and 0.58 admissions per year respectively.
Conclusions
Our recommendation is that single agent regimens in elderly diabetic patients with targets between 7–10 mmol/L, which resulted in hospital budget benefit of $2,438,696.96 per annum in the context of a 30 bed Acute Geriatric Unit.
References
1) Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of Vascular Risk Factors and Risk of Incident Alzheimer's Disease. *Neurology*. 2005;65(4):545–551.
2) Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function. Arch Neurol. 2004;61:661–666.
3) Borenstein AR, Wu Y, Mortimer JA, Schellenberg GD, McCormick WC, Bowen JD, *et al*. Developmental and vascular risk factors for Alzheimer's disease. Neurobiol Aging. 2005;26:325–334.
4) Cho NH, Colagiuri S, Distiller L, Dong B, Dunning T, Gadsby R *et al*. Managing Older people with Type 2 Diabetes. *International Diabetes Federation.* 2013.

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P629

Gender affirming therapy in Female to Male individuals – lipid profile alterations

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Background
Individuals with gender incongruence receive gender affirming therapy which is fundamental to sex reassignment. Cross sex hormone treatment both improves and impairs several surrogate markers of cardiovascular risk. In the aging population of transsexual persons, we are called to address clinical endpoints of the long-term gender affirming hormone therapy.
Aim
Aim was to assess changes in the fasting serum lipid profile during gender affirming hormone therapy in Female to Male individuals in a long-term follow-up.
Methods
Retrospective longitudinal study included 10 individuals with Female to Male gender incongruence in the Clinic for Endocrinology, Clinical Center of Serbia, Belgrade, from 1990 to 2017. Diagnosis of transsexualism was confirmed at 26.2+4.3 years of age, based on principles of World Professionals Association for Transgender health. None of the patients has been taking any medication at the initiation of the therapy. Mean body mass index was: 24.1+2.1 kg/m^2. Median duration of therapy before the assessment was 17.1+1.9 years. Testosterone administered intramusculary was the mainstay of therapy. Socio-demographical, anthropometric and laboratory data were collected. Outcomes of interest included body mass index, total cholesterol, LDL, HDL and triglycerides. Not any patient was lost during a follow up. Data are shown as mean ($\pm$ standard deviation). Comparisons between means were done by *Sign test* for paired items. $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS Statistics 17.0 software (SPSS Inc., Chicago, IL).
Results
In Female to Male individuals, analysis showed no significant difference in total cholesterol, LDL and HDL. TRG levels improved over time (2.0+1.3 to 1.8+0.3 mmol/l), in a statistically significant manner. There was a highly significant difference in body mass index (24.1+2.1 to 26.8+2.5 kg/m^2, P=0.04).
Conclusion
During long term gender affirming therapy in Female to Male individuals, there was no significant deleterious effect in lipid profile, in spite of gaining weight, which could not be attributed to induction of androgen milieu. Lifestyle management was further advised. Gender affirming therapy administration to transsexual individuals is acceptably safe in the short and medium term. The data of surrogate markers of cardiovascular disease leave room for a cautious optimism. Prioritizing long term follow up studies could lead us to, urgently needed, true insight how surrogate cardiovascular risk markers translate into clinical endpoints.

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P630

Therapeutic education specifically dedicated to patients being followed for stunting with somatotropin

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Introduction
Therapeutic education is one of the cornerstones in the management of various chronic diseases in children and adults. Several models of therapeutic education have been well developed (obesity, type 1 diabetes…); nevertheless, it remains less common and less developed in certain endocrine diseases. The purpose of this work is to present the therapeutic approach designed for children requiring treatment with growth hormone.
Materials and method
It is an interactive educational educational approach focused on patients requiring growth hormone therapy (intrauterine growth retardation, growth hormone deficiency, Turner and Prader-Willi syndrome, certain bone diseases, and children with chronic renal failure), performed at the level of the therapeutic education unit of the Department of Endocrinology, Diabetes and Metabolic Diseases at Arrazi Hospital - CHU Med VI of Marrakech -. This unit has 3 rooms of two beds each, a room of therapeutic education which presents a site of exchange between the child, his family and the attending physician. The program being 2 days including the reception of the patient, the presentation of the program, various thematic workshops and educational topos (definition of the pathology, technique and sites of injection and conservation…) aiming at the acquisition of the skills of know that to know how to act technical regarding the management of the disease and its treatment.
Results
The sessions (workshops, modules) of therapeutic education include the collection of needs and expectations with respect to growth, the definition of the pathology and therapeutic options, the demonstration of the different types of pens by the doctor, the phase of initiation of treatment with assessment of technical skills (pen manipulation). A phase of clinico-biologico-radiological monitoring of the treatment, carried out using a specially elaborated grid (3, 6 months..), with a synthesis interview on the clinical results of the treatment on the growth (speed of growth expressed in cm/yr, compliance with treatment with IGF-1, with the analysis of growth-specific quality of life questionnaires).

Conclusion
The doctor's role is no longer limited to the treatment of the patient alone, but rather to his autonomy from his chronic illness; this by learning the technical skills of handling the pen to the child and his family to promote better compliance and subsequently a quality of life of the child.

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P631

Mobile technologies for nutritional support and exercise for improving life of a patient with HIV: Case report

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Introduction
There are a lot of conditions associated with human immunodeficiency viri such as lipodystrophy, fat atrophy, insulin resistance, low levels of high-density lipoprotein cholesterol, and hypertriglyceridemia. A diet program combined with exercises can help to treat patients with HIV.
Methods
We used an online system for patient education based on video lessons, full of humor, pictures, and cartoons to convey the necessary information on good nutrition and exercises.
Results
A 42-year-old white man received the diagnosis of HIV infection in 2014 and was treated with a combination of stavudine, lamivudine, and nevirapine beginning in 2017. In January 2014, his blood HIV RNA level was 2583 copies/mL and subsequently, from January 2014 through the most recent test on June 2018, was $<$400 copies/mL; The CD4 count was 434 cells/mm^3 in January 2014, and 560 cells/mm^3 in June 2018. From January 2014 through September 2016, he gained 12 kg and was diagnosed with lipodystrophy. Watching the short movies, the patients formed the habits of good nutrition during the first month already, which includes a moderate-fat, low-glycemic-index, high-fiber diet with an exercise program for home and fitness center and push-notifications through the special online system. At 6 months he decreases his body weight by 6.5 kg. His maximal dynamic strength increased by 58%. His dietary intake of protein increased from 12% to 21% of total calories, and his intake of saturated fat decreased from 20% to 10% of total calories. His intake of dietary fiber more than doubled.
Discussion
So online systems could improve the quality and duration of life of our patients to make motivation and remind about treatment, diet, and exercises. So, we need to improve the quality of information material, including using online technologies to improve the quality and duration of life of our patients.

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P632

Alleviation of Autoimmune phenomena in Hashimoto's thyroiditis after Thyroidectomy: Is this an additional surgical indication?

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Introduction
Hashimoto's thyroiditis (HT) is one of the commonest endocrine disorder. Often, HT is associated with a plethora of autoimmune co-morbidities (AIC) such as vitiligo, arthitides, pernicious anaemia, skin allergy, thrombocytopenia, addison's disease, type 1 diabetes, celiac disease, eosinophilia etc., The etiology of these AIC in HT is enigmatically idiopathic and hypothesized to be autoimmune in origin. Many studies suggests that thyroid specific antibodies have shared epitopes of antigens in other organ systems such as skin, connective tissue, skeletal, visceral systems making them potential targets of AIC in HT. The treatment is symptomatic and supportive with euthyroidism, but no curative option. There are meagre anecdotal reports of thyroidectomy role for cure in HT. In this context, we report our experience on impact of total thyroidectomy on AIC in HT.
Material & Methods
This is a retrospective study conducted in Endocrine Surgery department of tertiary care Hospital. In all, 25 patients with HT and various AIC combinations are included in this study. All the clinico-investigative and operative data are scrutinized and analysed. All of them underwent total thyroidectomy. Informed consent obtained. The surgical indications were large goiter/painful thyroiditis/cosmetic/pressure symptoms and not AIC. Mean follow-up after surgery was 1.6$\pm$0.8 years (1.3–2.9).
Results
F:M ratio was 3:1 and mean age was 44.5$\pm$4.4 (24–52). There was no hypoparathyroidism or recurrent laryngeal nerve palsy in any case. None had associated hypertension, migraine, diabetes or any other neurological illnesses. All of them had Preoperative serum anti-thyroperoxidase antibody (Anti-TPO Ab) above the upper reference limit of 60 IU/L and was 434$\pm$103.2 IU/L (244–608) and post operative level was 52.75$\pm$25 IU/L(22-101). 19/25 (76%) had resolution or significant alleviation of AIC manifestations. The major improvement in AIC were skin allergy (9/12), eosinophilia (14/15), arthritides (5/14), vitiligo (3/8), celiac disease symptomatic episodes (1/4); but type 1 diabetes and addison's disease showed static response.
Conclusions
Retrospectively, Surgical thyroidectomy appears to have beneficial role in alleviation of AIC making it a potential additional surgical indication in HT. Anti-TPO Ab related autoimmunity appears to play a role in AIC. Long term impact and multi-institutional results are required to validate the curative role of surgery for HT associated AIC.

Keywords: Thyroidectomy, Hashimoto's thyroiditis, hypocalcemia, thyroid peroxidase antibody, autoimmune disease

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Is Hashimoto's encephalopathy Reversible with Surgical Thyroidectomy: A South Indian experience

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Introduction
Hashimoto's thyroiditis (HT) is one of the frequent endocrine disorder. Clinical picture in Hashimoto's thyroiditis is predominantly due to associated hypothyroidism and/or goiter related neck complaints. Rarely, HT can be associated with recurrent encephalopathy characterized by seizures, amnesia and comatose episodes. The etiology of this Hashimoto's encephalopathy (HE) is enigmatically idiopathic and hypothesized to be autoimmune in origin. The treatment is symptomatic and supportive with no curative option. There are meagre anecdotal reports of thyroidectomy role for cure. In this context, we report our experience on impact of total thyroidectomy on HE.
Material & Methods
This is a retrospective study conducted in Endocrine Surgery department of tertiary care Hospital. In all, 5 patients with HT with HE are included in this study. All the clinico-investigative and operative data are scrutinized and analysed. All of them underwent uneventful total thyroidectomy. Informed consent obtained. Mean follow-up after surgery was 2.5$\pm$0.9 years (1.7–3.2).
Results
F:M ratio was 4:1 and mean age was 45.6$\pm$3.4 (35–55). None had associated hypertension, migraine, diabetes or any other neurological illnesses. All of them had Preoperative serum anti-thyroperoxidase antibody (Anti-TPO Ab) above the upper reference limit of 60 IU/L and was 445$\pm$106.2 IU/L (370–650) and post operative level was 61.75$\pm$14 IU/L (32–94). In three patients, there were no episodes of HE in follow-up period and in one patient with Anti-TPO Ab of 650, the frequency and severity of HE episodes have decreased from 3 monthly to more than 1 year.
Conclusions
Total thyroidectomy appears to be a viable curative option for Hashimoto's encephalopathy. Anti-TPO Ab related autoimmunity appears to play a role in HE etiologic cascade. Long term impact and multi-institutional results are required to validate the curative role of surgery for HE.

Keywords: Thyroidectomy, Hashimoto's thyroiditis, hypocalcemia, thyroid peroxidase antibody, encephalopathy

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P634

Abstract Unavailable.

P635

Hypothyroidism and Down syndrome

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Background and Aims
Individuals with Down syndrome have an increased risk of developing hypothyroidism, autoimmune etiology. Prevalence of hypothyroidism in Down syndrome people is from 15% to 65%. Congenital hypothyroidism is about 25 times more common among newborns and infants with Down syndrome in comparison with the general population with incidence of 0.7% permanent cases and 0.3% transient congenital hypothyroidism cases, detected by newborn screening. Beyond the newborn period, the incidence of elevated TSH values in DS increases and has been reported to be as high as 85% of infants under the age of 12 months.
Goal
To estimate hypothyroidism during twelve years period (2007–2018.) in people with DS in Institute for Children and Youth Health Care of Vojvodina, Novi Sad, Serbia.
Results
During period 2007–2018. at Institute for Children and Youth Health Care of Vojvodina, there were 60 children who suffering from DS. Twelve people with Down syndrome develop hypothyroidism (20%), two cases were detected by newborn screening as congenital hypothyroidism.
Conclusion
Down syndrome people have mild to moderate mental retardation, and untreated hypothyroidism cause deeper mental retardation. Hypothyroidism is a treatable cause of mental retardation. Clinical signs of DS and hypothyroidism overlapping and it is necessary to know that DS people more common have hypothyroidism, and check regularly thyroid hormone two times per year during a first year of life, and later during childhood one time per year. Early detection and treatment are essential to maximize cognitive abilities in this already impaired population. Regular follow a thyroid hormone fT3, fT4 and TSH in people who suffer from Down syndrome.

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P636

Helicobacter pylori infection in patients with celiac disease

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Introduction
Different studies indicated the possible association between celiac disease and Helicobacter pylori (HP) infection, although this evidence is not consistently accepted. The aim of our study was to determine whether HP infection and celiac disease were associated among patients undergoing upper gastrointestinal endoscopy.
Methods
Between January 2017 and June 2018, patients undergoing upper gastrointestinal endoscopy with both gastric and duodenal biopsies were included for analysis. The diagnosis of celiac disease was based on positive serology and the presence of villous atrophy at duodenal biopsy. Antrofundic biopsies were performed looking for HP infection.
Results
Overall, 140 patients divides in 85 women and 55 men were enrolled. The median age was 28.7 years. Seventy of them (50%) had a celiac disease. The prevalence of HP infection among celiac disease patients was 14.5%, compared to 50% in non-celiac patients ($P=0.03$). In patients with celiac disease and HP infection, total flattening of duodenal fold in upper gastrointestinal endoscopy was found in 45% of patients, compared to 55% of patients without HP infection ($P=0.8$). Total villous atrophy was observed in 23% of patients with HP infection compared to 28% of patients without HP infection ($P=0.7$).
Conclusion
Our study revealed that HP infection was less frequent in celiac disease. Amon gpatients with celiac disease, endoscopic markers of villous atrophy and histological damage severity were similar between patients with and without HP infection.

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Polyphenol health effects on cardiovascular and neurodegenerative disorders: a meta-analysis

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Background
Polyphenols are proposed as protective factors against the occurrence of degenerative diseases affecting several systems, such as cardiovascular and neurocognitive ones. The beneficial effect of polyphenol-enriched diets is assumed to be multifactorial, including direct antioxidant and anti-inflammatory properties, as well as the polyphenol-related capability to modulate lipid metabolism and gut microbiota function. However, the prediction of polyphenols' impact on human health remains uncertain, since available long-term studies provide controversial results.
Aim of the study
This meta-analysis was designed to assess the effect of polyphenols as food supplement or isolated compound on cardiovascular and neurocognitive parameters, to clarify their beneficial properties on human health.
Methods
Two literature searches were conducted to identify double-blind, randomized, controlled clinical trials published in English language until November 2018 and evaluating chronic polyphenols administration with a treatment period over 2 weeks on both cardiovascular health (search 1) and neurocognitive function (search 2). All available polyphenol-enriched compounds were considered eligible.
Results
High heterogeneity has been found in both literature searches, in terms of treatment formulation, dose, source and compounds evaluated. Thirty-four studies were included in the first analysis, evaluating cardiovascular health parameters. Polyphenols administration reduced both systolic (-1.01 mmHg, 95%CI: -2.04;0.02, $P=0.005$) and diastolic (-1.32 mmHg, 95%CI: -2.37; -0.27, $P=0.001$) pressure, as well as low-density-lipoprotein cholesterol levels (-4.39 mg/dl, 95%CI:-7.66; -1.11, $P=0.009$). On the contrary, the polyphenols assumption significantly increased high-density lipoprotein cholesterol serum levels (2.68 mg/dl, 95%CI: 2.43;2.92, $P<0.001$) and brachial artery flow mediated dilation (0.89%, 95%CI:0.40;1.38, $P<0.001$). Twenty-one trials were analysed in the search 2, with a great heterogeneity in neurocognitive outcomes, mostly measured with questionnaires. Although few specific neurocognitive domains, such as visual attention, immediate memory and learning, seemed to benefit from the polyphenols administration, global cognitive functions resulted not significantly improved.
Conclusion
The overall analysis revealed a significant effect of polyphenols in modulating positively the cardiovascular health parameters. Although definitive recommendations for the use of these compounds in the prevention of cardiovascular disease and cognitive decline are currently not applicable, a potential role of polyphenol compounds for diseases prevention is clearly evident, at least in the cardiovascular setting.

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Causes and outcomes of hyponatraemia at Mater Dei Hospital, Malta

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Context
Hyponatraemia is the most common electrolyte balance disorder in clinical practice, amounting to 15–20% of casualty visits. While there is general agreement that associated mortality rates are high, most studies are uncontrolled.
Objective
To determine the characteristics, causes and outcome of severe hyponatraemia (<125 mmol/l) in hospitalised patients and to indentify mortality predictors.
Design
This is a retrospective case-controlled study of all medical admissions in the months of February, June and November, who at any point during the index admission developed a serum sodium <125 mmol/l. For each case, an age- and gender-matched control was identified.
Results
A total of 5195 medical admissions were reviewed. Of these, 193 patients had a sodium level <125 mmol/. 26 patients were excluded from the case group leaving a total of 167 cases and 193 controls. Length of hospital stay was more prolonged in the case group (12 vs 8 days, $P<0.001$). There was a highly significant excess mortality, both during the index admission (25% in cases vs 7% in controls ($P < 0.001$)) as well as till the end of the follow-up period (52% in cases vs 22% in controls ($P<0.001$)). Mortality was unrelated to severity of hyponatraemia. Patients who developed the lowest serum sodium later on during their admission (ie sodium levels continued falling during the admission or fell *de novo*), had a higher rate of mortality than patients whose lowest serum sodium was on the day of admission (64.3% vs 45%, P 0.019). A cox regression analysis showed that hyponatraemia ($P<0.001$), male gender (P 0.033), age (P 0.021), and serum creatinine level (P 0.008) were independent risk factors for mortality. There was no statistically significant difference between the rates of ITU admission at different levels of hyponatraemia <125 mmol/l ($P=0.497$). Thus, serum sodium levels of <125 mmol/l should be used to identify patients who need more intensive monitoring and therapy irrespective of the degree of hyponatraemia. Only 41% of cases developed neurological symptoms, of these, confusion and altered level of consciousness were the more prevalent at 12% each, followed by falls (9%), unsteady gait (4%) and seizures (4%). The cause for hyponatraemia was frequently poorly evaluated and in 23% of cases no definite diagnosis was made.
Conclusion
Data on assessment, investigation and management of hyponatraemia illustrates variability and shortcomings in clinical practice. The question remains whether the relationship between hyponatraemia and increased mortality is causal or associative.

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Constitutive activity of human RXFP2

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Introduction
The relaxin family peptide receptor 2 (RXFP2) is the receptor for Insulin-like peptide-3 (INSL3). The INSL3/RXFP2 signaling is necessary in the first stage of testis descent. Besides, it is proposed that RXFP2 has a role in bone metabolism or in development of cancers (thyroid, prostate). RXFP2 is a rhodopsin-like G protein-coupled receptors (GPCR). Recently, it has been demonstrated that Drosophila RXFP2 had constitutive activity, i.e., a ligand-independent signaling. In addition, RXFP2 exhibits strong structural homology with RXFP1, a constitutively active receptor. In this context, we sought to characterize the constitutive activity of human RXFP2 (hRXFP2).
Methods
HEK293 cells were transiently transfected with hRXFP2 or with the empty vector pcDNA3.1Zeo. Receptor activity was analyzed by measuring intracellular cAMP production under different conditions.
Results
In cells transiently transfected with hRXFP2, we showed that in absence of INSL3 the basal cAMP level was about 13.5 ± 1.2 fold higher than in control cells, after incubation with IBMX, a phosphodiesterase inhibitor. This agonist-independent activity accounted for $60 \pm 1.8\%$ of the maximal response to INSL3. We also demonstrated in cDNA-dosing experiments that cAMP production increased linearly with increasing amounts of hRXFP2. Finally, we confirmed the constitutive activity of hRXFP2 showing that hRXFP2 not only increased the basal level of cAMP, but also potentiated forskolin-induced cAMP production. By RT-PCR, we ruled out a local production of INSL3 that can skew the results of a ligand-independent activation. All these results were also confirmed in another cellular model: the COS-7 cell line. Currently, we are validating the constitutive activity of RXFP2 in a cellular model with endogenous expression.
Conclusion
For the first time, we showed that expression of hRXFP2 results in strong agonist-independent increase in intracellular cAMP. Moreover, hRXFP2 stimulates forskolin-induced cAMP production, a feature of constitutively active Gs protein-coupled receptors. The fact that hRXFP2 is highly constitutively active raises a series of questions concerning the physiological importance of this activity which remains to be defined.

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Different regulation of erythropoietin and VEGF in clear renal cell carcinoma

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Clear renal cell carcinoma (ccRCC) is a highly vascularized and proliferative tumor. ccRCC can be sporadic or familiar, usually associated with von Hippel-Lindau (VHL) gene mutations. VHL protein is part of the E3 ubiquitin ligase complex that regulates hypoxia-inducible factor (HIF). When a defective and inactive VHL protein is produced, HIF is not degraded, resulting in over-expression of hypoxia related genes including erythropoietin (EPO) and vascular endothelial growth factor (VEGF), thus promoting angiogenesis, proliferation and tumorogenesis. We analyzed tumor and surrounding healthy tissue from radical nephrectomy of 43 ccRCC patients. Direct sequencing and multiplex ligation-dependent probe amplification (MLPA) of the VHL gene in tumors and surrounding healthy tissues revealed somatic mutations in 27/43 (62.8%) of ccRCC samples. By testing genetic alteration or loss of heterozygosity (LOH), we detected 23 biallelic and 4 monoallelic *VHL* inactivations among 27 samples with genetic alteration in *VHL* gene. We also detected an increase in VEGF mRNA expression in ccRCC by 30 fold compared to healthy tissue. To assess how HIF-1 affects VEGF mRNA, tumors were divided in HIF-1 negative and HIF-1 positive samples. Increased VEGF mRNA expression was observed in both groups with the most prominent induction in HIF-1 positive tumor cells in comparison to normal renal tissue. We observed a significant induction of VEGF mRNA expression in wild type tumor samples compared to normal renal tissue, and a progressive increase in monoallelic and biallelic inactivation of VHL. Western blotting confirmed higher expression of VEGF protein in ccRCC. Beyond VEGF, EPO is also a HIF-responsive gene. Western blots revealed that EPO protein expression was significantly decreased in tumors without HIF-1 expression, while HIF-1 presence in tumor indicated a strong upregulation compared to HIF-1 negative tumors. Alterations in VHL gene did not change the expression of EPO protein. EPO acts by binding to its receptor-EPOR. Alike EPO, the expression of EPOR was decreased in tumors with the lack of HIF-1 protein, while HIF-1 presence induced EPOR expression. Alterations in VHL gene influenced the expression of EPOR protein. The expression of EPOR protein was very similar among control healthy tissue, tumors without mutations and tumors with biallelic inactivation of VHL gene expression. The only change was observed in tumor with monoallelic inactivation of VHL as a downregulation of EPOR protein expression compared to other groups. We demonstrated increased VEGF level in ccRCC supported by HIF-1, while EPO/EPOR expression were decreased in ccRCC reverted by HIF-1 presence.

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Digital epidemiology of hypothyroidism: pilot study

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Introduction
Digital epidemiology uses digital data which was not generated with the primary goal of serving epidemiological research (Life Sci Soc Pol 2018; 14:1). Recently, time and geographical correlation was noted between Google Trends findings and the prevalence of coronary artery disease (JACC, 2018, 71:98). Furthermore, using Google Trends, we have noted that the search terms 'fatigue/weakness' were correlated with the terms 'hypothyroidism/thyroiditis' worldwide (Cureus 2019; 11: e3965).
Aim
To use Google Trends search results on hypothyroidism versus published epidemiological data.
Methods
We used Google Trends for searches on 'hypothyroidism' worldwide for the years 2004–2018. We noted the – relative - popularity of this search term by country and compared it with available published data on the prevalence of hypothyroidism for ten countries (USA, Australia, UK, India, Thailand, Netherlands, Germany, Spain, Italy and Japan; Nat Rev Endocrinol 2018; 14: 301-316) using Pearson's correlation.
Results
The Google Trends popularity for 'hypothyroidism' was highest in the USA at 97% and lowest in Italy and Japan with 1%. The reported prevalence of hypothyroidism ranged from 7.99% (India) to 0.20% (Spain and Italy). Pearson's R was $+0.51$ ($P=0.10$).
Discussion
In this coarse pilot study we noted that internet search data showed some degree of correlation with the prevalence of hypothyroidism. Thus this approach provided information - albeit indirectly - on a disease's pattern, supporting the use of Google Trends for epidemiology (PLoS One 2014; 9:109583). We have though to acknowledge that this approach has shortcomings, such as the use only of the search term in English. Furthermore, it is limited to internet-literate persons and that internet searches are often prone to be influenced by media reports on diseases and patients. A more robust analysis using disease incidence data would be the next step in the evaluation of this approach.

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To what extend biotin interferes with hormones immunoassays?

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Introduction
Biotin (vitamin B8) is a coenzyme of carboxylases involved in many metabolic pathways and also used in therapeutics as a dietary supplement (diffuse alopecia) (<30 mg/day), in the treatment of rare congenital enzymatic deficiencies (5–40 mg/day) or more recently in the treatment of progressive multiple sclerosis at higher doses (300 mg/day). At such high doses, interferences with thyroid hormones assays using biotin-streptavidin amplification system were reported, leading to an apparent biological hyperthyroidism (low T4L, high TSH).
Materials and methods
The impact of biotin concentrations ranging from 5 to 400 ng/ml, thus covering the range of serum levels reached in therapeutics, was evaluated on a wide panel of serum hormones (TSH, T4L, T3L, Tg, FSH, LH, SHBG, Prolactin, estradiol, progesterone, and cortisol), assayed on the automated analyzer (Cobas®, Roche).
Results
We confirmed that TSH, T4L and T3L were the most sensitive parameters to biotin interference, being significantly affected from a biotin concentration of 30 mg/l (induced variation superior to the accepted inacurrancy of these assays, i.e. 5–10%). Thyroid parameters were followed by steroids (estradiol, progesterone, and cortisol) and FSH which were affected from a biotin concentration of 40 mg/l, and finally by the other protein hormones (LH, SHBG, Prolactin, and Tg) affected from a biotin concentration of 80 mg/l. Interestingly, biotin interference depended particularly on the ratio between the volumes of patient serum and of biotin-streptavidin reagent required for the dosage.
Conclusion
Below a biotin concentration of 30 mg/l, only thyroid parameters seem to be affected. Therefore, in patients treated by high doses of biotin for multiple sclerosis, hormones should be either dosed on an analyzer, not using biotin-streptavidin amplification system or assayed after specific pre-treatment of blood samples. For other biotin-based treatments at lower dose, the respect of a minimal delay after biotin ingestion before blood sampling should prevent from any significant interference (8h for 10 mg, 3h for 5 mg).

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Unexpected manifestation of autoimmune thyroid disease in a lipoid proteinosis patient

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Extracellular matrix protein 1 (ECM1) is an 85 kDa glycoprotein that plays an important role in skin physiology, angiogenesis, tumor progression and malignancies. However, the function of ECM-1 in regulation of the immune responses has not been identified. Recent studies showed ECM-1 deficiency lowers the capacity of T helper 2 (Th2) cells to emigrate from draining lymph nodes to an inflamatory site. Lipoid proteinosis (LiP) and Licken Sclerosus (LS) are immunogenetic counterparts; both target ECM-1 and sharing similar skin pathology. LiP is associated with loss of function mutations in the ECM-1 gene which located on 1q21. Mutation leads to abnormal degradation of glycolipids or sphingolipids, increased production of basal membrane collagens and decreased production of fibrous collagens. It is characterized by hyaline like material deposition in the skin, oral cavity; causing hoarseness, chicken-pox like scars, eyelid papules. Nevetheless, LS is caused by the development of humoral autoimmunity to ECM-1 which is characterized by small papules and pruritus. Attributed to the underlying pathogenic mechanism, LS were reported to have an increased incidence of autoimmune diseases especially Graves' disease (GD). Hyperthyroidism; most common feature of the GD, is caused by autoantibodies to the thyrotropin receptor (TSH-R). The derangement of immune function leading to pathalogic autoantibody production is complicated. Disturbing the T cell response, in particular disrupting the anti inflamatory regulatory T cells can result hyperthyroidism by increasing production of Trab, demonstrating GD is primarily a Th2 type autoimmune disease. Our case, a 20-year-old female presented with palpitation, fatigue and a slowly-enlarging mass in her front neck. Her weight was 53 kg, height was 155 cm. Thyroid function tests were consistent with hyperthyroidism. Thyroid Peroxidase Antibody (TPOAb) was negative. We could not measure Tyroglobulin Antibody (TgAb) due to economic issues. Her thyroid ultrasound and sintigraphy was compatible with GD and methimazole treatment was started. In her medical history, she had undergone a epiglottis biopsy because of hoarseness which had revealed lipoid proteinosis, 2 years ago. She had acneiform scars and eyelid papules which is charesteristic for the disease. She was on retinoic acide treatment for skin lessions. Unlike the current literature, our case demonstrated an Th2 type autoimmune thyroid disease with an underlying lipoid proteinosis disorder which is supposed to have decreased capability of Th2 response in the ECM-I deficiency. As it is a rare condition, further studies is needed to understand the immunregulatory role of ECM-1 and also immune mechanism of the GD.

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Dominance of ovarian follicles is determined by follicle-stimulating hormone receptor (FSHR) and G protein-coupled estrogen receptor (GPER) heteromers

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Mechanisms regulating the selection of antral ovarian follicles are poorly understood and supposed to rely on low estrogen levels, decline of follicle-stimulating hormone (FSH) levels and receptor (FSHR) expression on the surface of granulosa cells. These concepts are challenged *in-vitro*, where apoptosis of human granulosa cells (hGLC) and transfected cell lines is induced by high doses of FSH or FSHR overexpression, while estrogens induce anti-apoptotic signals via nuclear and a G protein-coupled estrogen-receptor (GPER). Therefore, *in-vitro* data suggest that antral follicle selection may be driven by under-estimated, FSH-FSHR-dependent apoptotic signals due to transiently maximized FSHR expression and overload of cAMP signalling, prevailing on estrogen-dependent signals. In this study, we demonstrate how estrogens can rescue the dominant follicle from FSHR-mediated death.

Experiments

10 nM FSH induces high intracelular levels of cAMP (FSH $160\times10^{-3}\pm26\times10^{-3}$ vs basal $5\times10^{-3}\pm9\times10^{-3}$ bioluminescence resonance energy transfer (BRET)-changes; Mann-Whitney's *U*-test; $P<0.05$; $n=5$; mean ± S.D.) and apoptosis in cultured hGLC under conditions where GPER levels are depleted by siRNA. This result was confirmed in transfected HEK293 cells overexpressing FSHR. Using BRET and photo-activated localization microscopy (PALM), we also demonstrate that FSHR forms heteromers with GPER at the cell surface. The role of FSHR-GPER heteromers may be relevant to inhibit FSH-induced death signals, since increasing GPER expression levels in HEK293 cells coexpressing FSHR results in displacement of the Gαs-protein to FSHR ($IC_{50}=0.221\pm0.002$; $r^2=0.546$; nonlinear regression; $n=3$; mean ± S.D.), blockade of FSH-induced cAMP production (FSH $0-10^{-3}\pm6-10^{-3}$ vs basal $1-10^{-3}\pm9-10^{-3}$ BRET-changes; Mann-Whitney's *U*-test; $P<0.05$; $n=5$; mean ± S.D.) and inhibition of apoptosis. Interestingly, in HEK293 cells coexpressing GPER/FSHR, FSH-induced activation of the anti-apoptotic AKT-pathway via a Gβγ-dependent mechanism, as demonstrated by Western blotting in cells treated using the inhibitor gallein. Critically, inhibition of both FSH-induced cAMP production (FSH $152\times24^{-3}\pm24\times10^{-3}$ vs basal $5-10^{-3}\pm9-10^{-3}$ BRET changes; Mann-Whitney's *U*-test; $P<0.05$; $n=4$; mean ± S.D.) and apoptosis was lost when FSHR is coexpressed together with a mutant GPER, unable to heteromerize with FSHR ($r^2=0.7\times10^{-3}$; $P=0.86$; linear regression). GPER-FSHR coexpression is confirmed in secondary follicles from paraffin-embedded tissues of human ovary by immunohistochemistry, suggesting that FSHR-GPER heterodimers could be physiologically relevant *in-vivo* for inhibiting cAMP-linked apoptosis. We demonstrate that death signals in atretic follicles are delivered through overexpressed FSHR and inhibited by FSHR-GPER heteromerization, activating anti-apoptotic pathways. This finding unveils a novel working model of the physiology of dominant follicle selection and the relationship between FSH and estrogens.

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Demonstration of follicle-stimulating hormone receptor (FSHR) and G protein-coupled estrogen receptor (GPER) heterodimerization by bioluminescence resonance energy transfer (BRET)

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During the menstrual cycle, selection of the dominant follicle is characterized by changes of gonadotropin and steroid hormone receptor expression. We aim to evaluate whether co-existing follicle-stimulating hormone receptor (FSHR) and G protein-coupled estrogen receptor (GPER) form heterodimers, suggesting their role in ovarian follicle selection. FSHR-GPER dimerization was evaluated in transfected HEK293 cells *in vitro* by bioluminescence resonance energy transfer (BRET). To this purpose, a 3D model of FSHR-GPER heterodimer was predicted by structural bioinformatics tools, which identified the sixth and seventh transmembrane segments (T6, T7) of both receptors as carriers of contact residues. Seven T6 and eight T7 amino acid residues from GPER were identified as putative interaction interfaces with FSHR and mutated to alanine (mutGPER). WT *GPER, FSHR (wtGPER; wt FSHR)* and *mutGPER* were C-terminally tagged with either the BRET donor Rluc8 or acceptor yFP. Increasing amount of yFP-tagged FSHR or GPER were expressed in HEK293 cells, together with a fixed amount of Rluc8-tagged GPER or FSHR and protein-protein interaction was evaluated by BRET technique, in the presence of the luciferase substrate coelenterazine H. Data were represented as donor:acceptor emission ratio (net BRET) and plotted against the ratio of the donor:acceptor concentration. Heterodimer formation was evaluated after data interpolation using non-linear regression. In transfected HEK293 cells, expressing the wtGPER-yFP and wtFSHR-Rluc8, heterodimer formation was demonstrated, revealing a BRET max (donor:acceptor proximity) and BRET50 (interaction affinity) of 0.71 ± 0.04 and 0.05 ± 0.02 ng yFP:Rluc8 cDNA/well respectively; $P<0.0001$; mean ± S.E.M.). In contrast, HEK293 cells transfected with mutGPER, exhibited no specific BRET interaction indicating an inability of heterodimerization between wtFSHR and mutGPER. Experiments assessing heterodimerization in cells expressing exogenous receptors fused with exchanged biosensors, i.e. wtFSHR-yFP and wt/mutGPER-Rluc8, did not reveal any saturation in BRET signal. Since heterodimers were demonstrated by wtFSHR-Rluc8 and wtGPER-yFP, receptor with exchanged BRET tags are functional but not suitable for evaluating dimerization, likely due to unproper molecular conformation not allowing biosensor-biosensor contact and energy exchange. We demonstrated for the first time FSHR-GPER physical interaction *in vitro*, and identified a molecular interface mediating this interaction, which could be exploited to understand the role this heterodimer may play in granulosa cell physiology.

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Spingosine-1-phosphate induces cAMP/PKA-independent pCREB activation, but not steroidogenesis, in human granulosa cells

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Sphingosine-1 phosphate (S1P) is a lysosphingolipid present in the ovarian follicular fluid at the nanomolar concentration. The physiological functions of S1P are mediated through five specific G protein-coupled receptors (GPCRs), known as S1PR1-5. S1PR1 and S1PR3 are expressed in human primary granulosa lutein cells (hGLC), as well as in the immortalized human primary granulosa cell line hGL5. S1PRs are activated at nanomolar concentrations inducing specific activation or inhibition of different signaling pathways. This *in vitro* study aims to characterize the role of S1P in the ovarian follicle. hGLC and hGL5 cells were cultured and treated by a fixed dose (100 nM) of S1P, or by S1PR1 and S1PR3 specific antagonists SEW2871 and CYM5541, after dose-finding experiments. cAMP production, ERK1/2, AKT and cAMP-responsive element binding protein (CREB) phosphorylation, intracellular Ca^{2+} increase, gene expression, cell viability and progesterone synthesis were evaluated by ELISA, Western blotting, bioluminescence resonance energy transfer (BRET), real-time PCR, MTT-assay and immunoassay, respectively. Specific inhibitor/antagonists were also used. In granulosa cells, S1P and, to a lesser extent, SEW2871 and CYM5541 induce cAMP/PKA-independent activation of pCREB via a PLC/PI3K-dependent mechanism. Indeed, no cAMP production was detected (unstimulated $=2.6\pm0.2$; agonists 2.5–1.9 ± 0.8 range pmol/ml; means ± S.D. two-way ANOVA; $P\geq0.05$; $n=2$) and pCREB activation occurred even in the presence of the PKA

inhibitor H-89 ($n=3$). This is relevant because both cAMP and PKA activation are known to precede the phosphorylation of CREB, inducing steroidogenesis. Moreover, S1P-dependent CREB phosphorylation is dampened by preventing pERK1/2 activation using the inhibitor U0126 and by the L-type Ca^{2+}-channel blocker verapamil. The complete inhibition of CREB phosphorylation occurred by antagonizing either S1PR2 or S1PR3 by the receptor-specific compound JTE-013 and TY52156, or under PLC/PI3K depletion, detected by Western blotting ($n=3$). CREB phosphorylation is not linked to expression of genes encoding steroidogenic enzymes and pro/anti-apoptotic molecules in granulosa cells, while induces *FOXO1* and the EGF-like epiregulin-encoding gene (EREG) expression (two-way ANOVA; $P<0.05$; $n=4$). However, cell viability and proliferation is not modulated upon treatment by S1P or agonists. Most importantly, we demonstrated that S1P-dependent CREB phosphorylation does not induce steroidogenic signals (basal progesterone $=30.3\pm3.8$; agonist-induced progesterone $=28.7$-26.1 ± 3.2 ng/ml range; means $\pm$SD; two-way ANOVA; $P\geq0.05$; $n=4$). We demonstrated a novel cAMP/PKA-independent activation of pCREB not inducing intracellular steroidogenic signals and progesterone synthesis in granulosa cells. However, S1P-induced *FOXO1* and *EREG* gene expression suggest that lysosphingolipids may act synergistically with gonadotropins in modulating follicle development.

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5-Beta-reductase (AKR1D1) deletion leads to increased insulin sensitivity in mature male mice

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Bile acids (BA) are potent steroid hormones that mediate a variety of metabolic effects. They play a pivotal role in cholesterol catabolism, intestine nutrient absorption, and regulate lipid, glucose and energy metabolism. 5-Beta-Reductase (AKR1D1) is a key enzyme in the BA synthesis pathway, required for cholesterol metabolism into bile acids. We generated a novel global AKR1D1 knockout (KO) mouse which, as expected, has decreased total serum and hepatic BAs and altered BA composition. Here we demonstrate that AKR1D1 deletion leads to increased insulin sensitivity in mature male mice. Male WT and AKR1D1 KO mice were maintained on a control diet with metabolic assessments undertaken at 30-weeks of age. AKR1D1 KO mice presented with enhanced insulin sensitivity as measured by intraperitoneal insulin tolerance test compared to WT littermates (WT 793; KO 647 mMol/min). At a molecular level, qPCR analysis of skeletal muscle insulin signalling pathway genes showed increased mRNA expression of insulin receptor substrate 1 (IRS-1) in AKR1D1 KO mice compared to WT (WT 0.46 ± 0.03; KO 0.71 ± 0.07 relative expression $n=12$ $P<0.05$) but no changes in phosphoinositide 3-kinases (PI3Ks), protein kinase B (total-AKT) or insulin receptor subunit β (INSRβ). Despite the unchanged mRNA levels, western blotting revealed increased protein levels of skeletal muscle INSRβ (WT 1.82 ± 0.13 $n=9$; KO 1.24 ± 0.21 protein/total protein $n=9$ $P<0.05$), total-AKT (WT 1.83 ± 0.21 $n=9$; KO 0.9864 ± 0.2504 protein/total protein $n=9$ $P<0.05$) and mTOR (WT 1.86 ± 0.05 $n=3$; KO 1.13 ± 0.11 protein/total protein $n=3$ $P<0.05$). Muscle glycogen levels were also elevated suggesting increased anabolic metabolism in the KO animals. QPCR analysis of the hepatic IRS-1, PI3Ks, total-AKT and INRβ showed no differences in mRNA expression levels. Western blotting detected elevated hepatic total-AKT protein levels (WT 1.05 ± 0.09 $n=9$; KO 0.60 ± 0.07 protein/total protein $n=9$ $P<0.05$) although INRβ, mTOR, and glycogen levels were unchanged. Despite the increased insulin sensitivity, there was no change in intraperitoneal glucose tolerance. However, in the fed state, circulating insulin levels were significantly reduced in AKR1D1 KO mice (WT 1.31 ± 0.22 $n=9$; KO 0.57 ± 0.01 ng/ml $n=6$, $P<0.05$) with normal blood glucose levels (WT 14.36 ± 0.7 $n=14$; KO 14.21 ± 0.52 mMol/l $n=12$ $P<0.05$). Taken together, our results suggest that AKR1D1 plays an important role in glucose homeostasis by mediating insulin sensitivity in liver and skeletal muscle. Further studies are required to define the underpinning mechanisms.

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Ghrelin expression in breast carcinomas

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Introduction
Breast cancer is, by far, the most frequent cancer among women. Local and systemic factors have been shown to drive growth in breast cancer cells. There is increasing evidence that hormone ghrelin, known for the growth hormone releasing effect and food intake modulator, may also influence cancer growth. Ghrelin has been shown to be produced by some tumor cells, including breast cancer cells.
Objective
To analyze ghrelin expression in correlation with current imunohistochemical prognostic factors in breast carcinomas.
Patients and methods
Tissue samples from 30 patients with invasive breast cancer which underwent breast surgery between 2015 and 2016, were selected in the Department of Pathology. Patient characteristics including age at surgery, tumor size, grade, expression of hormone receptors, HER2 and Ki67-index were collected. For immunohistochemical staining anti-ghrelin antibodies (Bioss Antibodies, MA, USA) were used. Samples were examined by two independent observers and graded as non-immunoreactive, weak, moderate and strong. Normal human gastric mucosa was used as positive control.
Results
Mean age at surgery was 62.7 ± 14 years (between 36 and 83 years). Ghrelin intensity score was evaluated negative in 2 cases (6.7%), weak in 11 cases (36.7%), moderate in 14 cases (46.7%), and strong in 3 cases (10%). Ghrelin negatively correlated with Ki67-index ($r=-0.553$, $P=0.002$) and with the Elston-Ellis score ($r=-0.469$, $P=0.009$), especially with the tubular differentiation ($r=-0.493$, $P=0.006$). Expression of estrogen receptors ($r=0.481$, $P=0.008$) and progesterone receptors ($r=0.525$, $P=0.003$) was positively correlated with ghrelin expression.
Conclusion
The negative correlation to Ki67 and Elston-Ellis score indicate that ghrelin may be a marker for less aggressive tumors and possibly for a better prognosis. Obesity is associated with a poorer prognosis in breast cancer. Since ghrelin is an appetite stimulating peptide, and is almost always decreased in obesity, further studies regarding the possible relationship between ghrelin, obesity and breast cancer would be of interest.

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Polydispia can reveal underlying non-osmotic arginine-vasopressin secretion

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Inroduction
Polydipsia -excessive oral intake of liquids, with/without thirst- can induce euvolemic hyponatremia. Adequate inhibition of AVP secretion induced by low plasma osmolality (POsm) is reflected in a urinary osmolality (UOsm) ≤100 mOsm/kg. However, increased fluid intake can also reveal underlying non-osmotic AVP secretion, induced by pain, nausea, and/or SIADH, with UOsm >100. Iatrogenic polydipsia is characterized by increased liquid intake without thirst, following the recommendations of health professionals. Polydipsia can also be secondary to increased fluid intake to correct dryness of the mouth. Primary care in Madrid recommends a minimum water intake of 2–3 liters daily for adults during summer months, to avoid dehydration - characterized by hypernatremia. We describe cases in which patients presented marked hyponatremia induced by increased fluid intake.

Methods
Retrospective analysis of 22 adult patients presenting euvolemic hyponatremia associated with elevated fluid intake, attended in Endocrinology of a general hospital in Madrid over 12 months. Initial Nadir serum sodium (SNa)-associated POsm was available in 20/22, initial urinary electrolytes and urine osmolality in 9/22, Creatinine in 22/22, GFR/MDRD-4 in 20/22. All presented normal cortisol and thyroid hormone levels. Sodium in mmol/L, Osm in mOsm/kg. SPSS 25.
Results
12/22 were women. Age: 74.5(IQR:73) Median fluid intake: 3250 ml(IQR:4400). 12/22 episodes were during the summer. In 7/22 increased fluid intake was induced by specific recommendations of health care professionals, another 7 by health campaigns, 3 by dryness of the mouth. Two patients presenting UOsm$\leq$100 were diagnosed with primary polydipsia. 19/21 presented UOsm$>$ 100: 6/19 with nausea/pain, 13/19 SIADH. 3 patients required initial 3% hypertonic saline therapy. Four SIADH patients required tolvaptan treatment to normalize SNa. The rest responded to 'fluid hygiene': drinking/swallowing only when thirsty. 21/21 patients with prior SNa available had presented previous hyponatremic episodes: SNa 130(IQR:1). In one patient UOsm was unavailable, making diagnosis impossible.

Table 1

	SNa	Urinary Na	POsm	UOsm	Serum creatinine	GFR/MDRD-4
Associated with nadir SNa	125 (IQR:30)	54 (IQR:97)	271 (IQR:103)	300 (IQR:425)	0.69 (IQR: 0.71)	110 (IQR:128)
At diagnosis	132 (IQR:23)	59 (IQR:145)	274 (IQR:39)	400 (IQR:652)	0.67 (IQR:0,78)	103 (IQR:96)

Conclusions
Polydipsia can induce marked hyponatremia, is often iatrogenic, and can reveal underlying SIADH. In this series, all patients with available SNa records had presented prior episodes of hyponatremia. Physicians must be cautious when recommending drinking without thirst to patients with a prior history of hyponatremia, even in hot, dry climates.

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P650

Helicobacter pylori infection in patients with celiac disease

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Different studies indicated the possible association between lymphocytic gastritis and both celiac disease and *Helicobacter pylori* infection, although this evidence is not consistently accepted.
Objective
We aimed to determine whether *Helicobacter pylori* infection and celiac disease were associated among patients undergoing upper gastrointestinal endoscopy.
Methods
Between January 2016 and June 2017, patients over 18 years old undergoing upper endoscopy who required both gastric and duodenal biopsies were included for analysis. Enrolled subjects were divided in two groups: those with a diagnosis of celiac disease and those without a celiac disease diagnosis. *Helicobacter pylori* infection prevalence was compared between groups. Among celiac patients, endoscopic markers of villous atrophy as well as histological damage severity were compared between those with and without *Helicobacter pylori* infection.
Results
Overall, 140 patients were enrolled. Seventy of them had a diagnosis of celiac disease. *Helicobacter pylori* infection prevalence among celiac disease patients was 14.5%, compared to 50% in non-celiac patients [OR$=$0.33 (0.15–0.71)]. There was not a significant difference in terms of the severity of villous atrophy in patients with Helicobacter pylori infection compared to those without it. There was a slight increase in the prevalence of endoscopic markers in those *Helicobacter pylori*-negative celiac subjects.
Conclusion
Helicobacter pylori infection seems to be less frequent in celiac patients; among those celiac subjects with concomitant *Helicobacter pylori* infection, histological damage degree and presence of endoscopic markers suggesting villous atrophy seem to be similar to those without *Helicobacter pylori* infection.

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Biguanides exert antitumoral actions in pituitary tumor cells through AMPK-dependent and -independent mechanisms

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Background
Pituitary adenomas represent a commonly underestimated pathology in terms of incidence and associated morbimortality. Additionally, some patients poorly respond or develop resistance to current medical treatments [i.e. somatostatin analogues (SSAs) and dopamine agonists]. In this context, it is necessary to develop novel and/or optimize currently available medical therapies. Biguanides (metformin, buformin and phenformin) are antidiabetic drugs that have been described to exert anti-proliferative effects in several tumor types. However, their pharmacological effects on different pituitary tumor cells are poorly known.
Aims
We aimed to explore the direct effects of biguanides on key functional parameters(cell viability, hormone release, apoptosis, and signaling pathways) in primary cell cultures from human functioning (GH-, PRL- and ACTH-secreting cells) and non-functioning pituitary tumors (NFPTs). Additionally, we evaluated the effect of the combination therapy of metformin with SSAs on cell viability and hormone secretion.
Patients and methods
The role of the pre-surgery treatment with metformin was evaluated in 62 NFPTs, 42 ACTH-secreting and 28 GH-secreting pituitary tumors that underwent surgery. Additionally, primary cell cultures from 13 corticotropinomas, 13 somatotropinomas, 13 NFPTsand 3 prolactinomas were used. Cell viability, hormone release, apoptosis and signaling pathways were evaluated using validated methods.
Results
Pre-surgery treatment with metformin was not associated with tumor size, extrasellar growth, hormone secretion or clinical evolution. In human primary cell cultures, biguanides reduced cell viability in all types of pituitary tumorsand increased apoptosis in GH-secreting tumors. Phenformin was the most effective antiproliferative drug. Buformin and phenformin, but not metformin, reduced hormone secretion in a cell type specific manner. Finally, the combination therapy of metformin with SSAs did not increase the effectiveness of SSAs as monotherapy in corticotropinomas or somatotropinomas, butcombination therapy of metforminwith octreotide and pasireotide in NFPTs seemed to produce a higher decrease on cell viability as compared to the different treatments alone. These effects of biguanides on pituitary tumors may be explained by the modulation of AMPK-dependent (intracellular calcium, PI3K/Akt pathways) and/or -independent (ERK pathway) mechanisms.
Conclusion
In conclusion, our study provides primary evidence that biguanides exert important anti-proliferative and anti-secretory effects in different pituitary tumor cell types and pave the way to consider these compounds as a potential new therapeutic optio n in the treatment of these severe pathologies.

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Restoring the sleep disruption by blue light emitting screen use in adolescents: a randomized controlled trial

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Introduction
Adolescents spend much time using blue-light emitting screen devices such as smartphones, tablets and computers. Blue light affects the central circadian clock in the suprachiasmatic nucleus (SCN) as well as melatonin secretion by the pineal gland. Screen use in adolescents strongly associates with reduced sleep quality and sleep duration. However, there is a lack of intervention studies that reduce blue light exposure due to screen use in adolescents.
Methods
We identified frequent screen users (use $\geq$ 4 hr per day, $n=25$) and infrequent screen users (use $\leq$1 hr per day, $n=30$) among Dutch adolescents aged 12–17 yr. In a 5-week randomized controlled crossover trial, the frequent screen users were assessed for 3 evening interventions of 1 week each, with 1-week washout periods: 1) during habitual screen use; 2) while wearing blue-light-blocking glasses; 3) while completely refraining from screen use. In a case-control sub-study, infrequent screen users were assessed for 1 week. In every measurement week, sleep was assessed using sleep diaries and actigraphy, and melatonin onset was assessed using at home 30-minute saliva sampling on the final evening of each intervention week. The trials were registered as NTR6712 (RCT) and NTR6722 (case-control).
Results
In frequent screen users, blue-light-blocking glasses as well as refraining from screen use induced an earlier mid-point of sleep compared to habitual screen use. Both interventions restored sleep times of frequent users to around those of infrequent users. In many subjects it was difficult to identify a clear-cut melatonin onset, but blue-light-blocking glasses reduced absolute melatonin levels compared to habitual screen use.
Conclusion
This is the first randomized controlled study in a real life setting showing that, among frequent screen using adolescents, blue-light-blocking glasses as well as abstinence of screen use restores their late sleep towards the earlier timing seen in infrequent screen users. These effects may be partly mediated via reduced melatonin suppression by blue light.

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Dietary glycemic index and dietary glycemic load is associated with apelin gene expression from visceral and subcutaneous adipose tissues of adults

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Background and aim
Apelin, as an adipokine, is encoded by the APLN gene. It is a key regulator in glucose and lipid metabolism and plays an important role in the pathogenesis of insulin resistance and type 2 diabetes. It seems that habitual dietary intake of carbohydrates including quality and quantity by chronic manipulating insulin concentration might have a distinguishing role in the prediction of apelin gene expression in adipose tissue, but there is no evidence in this regards. Thus, this study aimed to determine whether dietary quality and quantity of carbohydrates were associated with gene expression of apelin in subcutaneous and visceral adipose tissue.
Methods
In this cross-sectional study, 102 participants, aged more than 20-year-old, who underwent minor abdominal surgery with minimal impact on dietary intakes, were selected. Before the surgery, a reliable and validated semi-quantitative FFQ was completed to assess habitual dietary intake of total carbohydrate intake, glycemic index (GI) and glycemic load (GL). Then, the food items were also categorized based on their glycemic index and load into three different groups including high ($\geq$70), medium (56-69) and low ($\leq$55) glycemic index and high ($\geq$20), medium (11–19) and low ($\leq$10) glycemic load foods. To control the effect of energy intake, the residual method was used for all dietary exposures. The mRNA expressions of APLN were measured by SYBER-Green qPCR. Multivariable linear regression was performed, standardized β (STZβ) was reported, and age, body mass index (BMI), and sex were adjusted.
Results
Participants characterized by a mean age of 41.7 ± 14.6 years, mean BMI of 35.2 ± 10.7 kg/m^2. Among participants, 16.3% presented insulin resistance. The association between dietary GI and APLN expression was significant in visceral (STZβ$=0.402$, $P<0.001$) and subcutaneous (STZβ$=0.477$, $P<0.001$) adipose tissue after controlling for potential confounders. Furthermore, there was a significant association between dietary GL and apelin mRNA levels in both visceral (STZβ$=0.224$, $P=0.029$) and subcutaneous (STZβ$=0.350$, $P=0.001$) adipose tissue. APLN expression in visceral (STZβ$=0.253$, $P=0.013$) and subcutaneous (STZβ$=0.255$, $P=0.014$) adipose tissue was associated with intake of foods with higher GI index.
Conclusion
Higher dietary intake of GL, GI, high GI foods were positively associated with APLN gene expression of adipose tissues. It seems that when considering the effect of dietary carbohydrate intake on adipose tissue metabolism, the carbohydrate quality is more important than carbohydrate quantity.

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P654

Habitual physical activity are associated with fat mass and obesity-associated gene (FTO) gene expression in visceral and subcutaneous adipose tissues among non-diabetic people

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Introduction
Human fat mass and obesity-associated gene (FTO) gene expression are associated with body mass index and type 2 diabetes. It is unknown whether lifestyle factors, such as physical activity, can attenuate weight gain and obesity by contribution to the FTO gene regulation. The objective of the present study was to investigate the association between habitual physical activity and the FTO gene expression among morbid obese and non-obese subjects.
Materials and methods
Visceral and subcutaneous adipose tissues were gathered from 87 ($n=37$ non-obese and $n=50$ obese) non-diabetic participants aged $\geq$20, who had undergone elective abdominal surgery. Physical activity was collected using a valid and reliable International Physical Activity Questionnaire (IPAQ)-long form, and the metabolic equivalent of task (MET) was calculated. Respondents were asked to report time spent in the physical activity performed across leisure time, work, domestic activities, and transport at each of 3 intensities: walking, moderate, and vigorous. The mRNA expressions of the FTO gene in visceral and subcutaneous adipose tissues were analyzed by Real-Time PCR.
Findings
The mean age of participants (22.7% male) were 41.7 years. BMI for morbidly obese and non-obese participants was 43.3 and 24.6 kg/m^2, respectively. There was no significant difference between FTO gene expression in subcutaneous and visceral adipose tissues between non-obese (BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2) participants. After controlling for total energy intake, BMI, and insulin level, FTO gene expression in visceral adipose tissue among obese participants was inversely associated with total MET ($r=-0.625$, $P<0.001$); however FTO gene expression in subcutaneous fatty tissue was not significantly associated with total MET. Among non-obese individuals, visceral adipose tissue FTO gene expression was related to total MET (β$=-0.417$, $P=0.012$). Furthermore, among obese participants, MET related home ($r=-0.316$, $P=0.035$) and leisure time ($r=-0.341$, $P=0.027$) were inversely associated with FTO mRNA expression in visceral adipose tissue.
Conclusions
Decreased FTO gene expression in visceral adipose tissue is linked to total MET in obese participants, suggesting an essential role of physical activity pathways in the causal relationship between consequences of higher physical activity and the development of obesity.

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Meningiomas and hormone therapy: a multicenter, epidemiological, retrospective, uncontrolled study

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Meningiomas are the most common intracranial tumors accounting for 20 to 30% of central nervous system tumors. Currently, only two risk factors have been highlighted: the history of exposure (therapeutic or accidental) to ionizing radiation, and some genetic predispositions syndromes in particular Neurofibromatosis type 2. Given the feminine predominance and the presence of progesterone receptors expression in meningiomas, authors began to focus on hormonal factors as a risk factor of meningioma especially drugs like cyproterone acetate. Cyproterone acetate (CPA) is an antiandrogen drug with a relative oral progestational activity of 1200. In France, CPA has market authorization for idiopathic hirsutism, polycystic ovary syndrome, for palliative treatment of prostatic carcinoma or sexual disorder. Knowing this background, we explored the potential relation between CPA exposure and meningiomas in a retrospective, multicentric cohort of meningiomas treated by surgery or/and radiotherapy. The aim of this study was to determine the prevalence of the use of cyproterone acetate among patients treated for meningiomas and we investigated the association between intracranial meningioma and sex hormone exposure. Eligible patients included all patients who went through neurosurgery with anatomopathological confirmed intracranial meningioma in the Nantes University Hospital Central and all patients who went through radiotherapy treatment for an intracranial meningioma in the René Gauducheau ICO Cancer Center (diagnostic was accepted based on the imaging) from January 1, 2014 to December 31, 2017. We excluded patients with NF2 mutation, previous radiotherapy exposure and extracranial meningiomas. Clinical data were retrospectively collected from medical records: age at diagnostic, sex, BMI, if the discovery was incidental or symptomatic, size of the tumor, localization, Simpson grade, anatomopathological characteristics of resected meningiomas (WHO grade, presence of hormonal receptors). We also collected the history of polycystic ovarian disease, breast cancer, prostatic cancer, number of pregnancies and children, the actual or past use of cyproterone acetate, tamoxifen, oral contraceptive, clomiphene or androgenic therapy. 388 patients (292 F, 96 M) were enrolled in the study, 277 treated by surgery and 111 treated by radiotherapy. 74 patients (69 F, 5M) (19%) had history of hormonal treatment, there was 15 (3.9%) patient with actual or past use of cyproterone acetate. More complete data will be available for the congress.

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Epidemiological characteristics of transsexual people referred to a single-center during its first fifteen years in Catania (Italy)

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Gender Dysphoria (GD) is defined as incongruence between gender identity and physical phenotype. This condition exists in different psychological typologies: male-to-female (MtF) and female-to-male (FtM) transsexualism. In most cases the first manifestations can occur even during childhood. The transition project is a long and difficult path that involves a multidisciplinary team including endocrinologists, psychologist and plastic surgeons. Our study aims to describe socio-demographic characteristics in a population of transsexuals referred to Endocrinology Dept. in Catania during the last 15 years. A total of 117 patients were enrolled at the Garibaldi-Nesima Andrology Clinic in Catania from 2003 to 2018. During the years and especially during the last 5 years the number of patients who required hormone conversion therapy (HCT) has been increasing both between MtFs and FtMs. Patients who have come to our observation in recent years have started HCT earlier than patients who came to our Center in the early 2000s. The average age of FtM patients at the first observation is 27.7 years (SD 9.9 years), among them 3 minors (including the youngest of 14.2 years) and 4 over 40. Among our MtFs, the vast majority live in a situation of social hardship with weak family support. Among FtMs after HCT the final phenotype is significantly adherent to the virile image desired by these patients, although among the MtFs this is sometimes not entirely satisfactory. The surgical conversion of MtFs was performed preferably in centers in northern Italy and abroad, the interventions performed by FtMs mainly concern mastectomy and hysterectomy with ovariectomy performed in Sicilian centers. In our City there is still no reception center for transsexual people. Over the years, especially for the 'word of mouth' the number of subjects has increased, even though the drop-out level remains high, especially among the MtFs. Like has been observed elsewhere, at our center the MtFs are more represented than the FtMs. It has been observed also a younger patients' age asking for the first endocrine consultation. In conclusion even if the overall prevalence of transsexualism reported in the literature is increasing, it is still very low and is mainly based on individuals attending clinical services and so does not provide an overall picture of prevalence in the general population.

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Endocrinological management of male-to-female (MtF) transgender persons: a single center experience during the last decade

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In MtFs therapy with oestrogens and antiandrogens, actually considered the best strategy, requires a careful baseline and follow-up hormonal evaluation. We conducted a retrospective analysis to define the most frequent hormonal treatment prescribed and the relationship between the dosage and patients' hormonal changes. Among 85 pts referring to us between March 2003 and June 2018 with a mean age of 28.4 years we have selected 42 treated with Oestradiol Valerate (OV) and Cyproterone Acetate (CPA). We both analyzed baseline and post-therapy serum testosterone (TE), LH, FSH and prolactin (PRL) levels. 11/42 Pts were treated with the same dose from the beginning, while 31/42 needed to increase the dose at least one time. A total of 2 patients were treated with OV 2 mg/die plus CPA 50 mg/die (2 + 50 mg), 14 with 4 + 50 mg, 14 with 6 + 50 mg, 4 with 8 + 50 mg, 3 with 8 + 100 mg and 5 with 4 + 25 mg. Patients usually started hormonal treatment with 6 + 50 mg, while further adjustments were made on the basis of clinical and laboratory findings; the lowest posology (4 + 25 mg) was prescribed only after a previous treatment with higher doses. Mean serum hormones levels were calculated for each OV and CPA dosage. When adequately tailored for each patient according to clinical and previous laboratory results, each dose showed itself to be able to suppress hypothalamic–pituitary–gonadal axis without major adverse events. Lowest TE, LH and FSH were observed, as expected, with OV + CPA 8 + 100 mg. The 5 patients switched to the lowest dose (4 + 25 mg) showed slightly increased mean testosterone levels if compared to other groups, although still within the normal female reference range. Serum PRL values were similar between different groups and no linear relationship between serum PRL and OV + CPA dose was found. None of the patients was taking other medications. Over the past decade, we have seen an increasing number of MtF transsexual persons at our center in Catania. We feel this is a representative sample of patients presenting for medically supervised hormonal therapy, as we are one of the most frequented center in our area providing hormonal therapy for people with gender dysphoria. In our experience hormonal therapy for MtF patients with Oestradiol Valerate plus Cyproterone Acetate at different dosage was generally quite effective with almost none adverse events, even if the ability to induce full feminization can be variable depending on the patients genetic background.

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Endocrinological management of female-to-male (FtM) transgender persons: a single center experience during the last decade

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In FtMs testosterone (TE) therapy is used to pursue the dual objective of suppressing female secondary sex characteristics and inducing a male phenotype to the patient. Between October 2001 and December 2018, an heterogeneous group of 32 patients (Pts) with a mean age of 27.7 years presented to our Center for FtM Gender Dysphoria. We analyzed Body Mass Index (BMI), haemochrome and hormonal (LH, FSH, Prolactin) measurements comparing baseline levels to post-therapy. A total of 10/32 showed adrenal androgen levels above the upper reference range (TE, Δ4A, DHEAs); pre-therapy mean TE was 0.6 ng/ml. 25/32

Pts were treated with im TE enanthate (TEe) and 7/32 with im TE undecanoate (TEu) at different dosages; a total of 4 Pts were switched from TEe to TEu during the follow-up. Pts with a baseline BMI <30 kg/m^2 showed a mean BMI increase of 0.6–1.2 kg/m^2 after starting TE administration; we observed maximum BMI increase after 12-18 months of treatment. Two Pts with a pre-therapy BMI >30 kg/m^2 showed a BMI decrease of -7.9 and -1.1 kg/m^2 after 24 and 18 months of treatment respectively. Hematocrit (Hct), Haemoglobin (Hb), and Red Blood Cells count showed a similar increasing trend, with maximum values after 9–18 months of treatment; Hct reached values $>50\%$ (maximum 54.6%) in a total of 7 Pts, two of which treated with TEu; in those Pts Cardioaspirin was added to hormonal therapy (as suggested by haematologists). Each patient required, as was predictable, a different and tailored TE dose. TEe dosage ranged from 80 mg/21 days to 250 mg/15 days, whereas TEu one ranged from 1000 mg/12 weeks to 1000 mg/21 weeks. TEu therapy provided more stable levels of testosterone, whereas spikes and drops in testosterone levels were observed during TEe treatment. During the initial follow-up 8/32 Pts (25%) complained of persistent uterine bleeding; 7 of them were taking TEe, 1 TEu. In 5 Pts bleedings easily disappeared after increasing the testosterone dose. None of our Pts developed hypertension. No cases of ovarian pathology were detected; but it might be considered that bilateral ovariectomy could prevent the development of ovarian malignancies. The BMI increase of 0.6–1.2 kg/m^2 after treatment might be due to fluid retention, or an increase in lean body mass or fat mass. TE administration in FtM transsexuals appears to be effective in maintaining testosterone levels within physiological limits, well tolerated and very safe with no differences among the testosterone formulations used.

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Long-term outcome in young women treated for central precocious puberty

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Background
GnRH-analogs (GnRHa) are the recommended treatment for Central Precocious Puberty (CPP). Despite a normal long-term outcome is generally reported, reproductive function and emotional sphere in adulthood are still poorly evaluated.
Objective
To evaluate the general long-term outcome of young women with previous CPP treated with GnRHa.
Patients and methods
A cohort of 63 young women (25.5 ± 5.31 years) with history of CPP treated with GnRHa were enrolled. All subjects received diagnosis of CPP at a men age of 7.01 ± 1.35 years, and were treated for 2.02 ± 1.43 years. Mean chronological age and bone age (BA) at the end of treatment were 10.15 ± 0.87 and 12.1 ± 0.86 years respectively. Menarche occurred 15.5 ± 9.59 months (range 2-43) after treatment was discontinued. At the enrolment all subjects underwent the following evaluations: gynecologic and menstrual cycle pattern history; anthropometric measurements and physical examination including signs of hyperandrogenism; pelvic US; Female Sexual Function Index (FSFI) questionnaire to investigate sexual and emotional sphere.
Results
Adult height (AH) (158.4 ± 6.3 cm) was within the genetic target (158.1 ± 4.7 cm) and significantly higher than predicted stature at diagnosis (155 ± 5.4 cm; $P=0.0001$). Mean height gain ($+3.1$ cm) was negatively correlated with BA at the end of treatment (r: -0.3684; $P=0.0035$) and with uterine length at diagnosis (r: -0.29; $P=0.025$). Height gain was higher in patients treated under 6 years ($+4.3$ cm) compared to those treated between 6–8 years ($+2.0$ cm, $P<0.0001$). Overweight/obesity was detected in 36.5% of patients at diagnosis and increased up to 46% during treatment; however in adult age only 30.2% of subjects were overweight/obese. Gynecologic history revealed that 34.1% had menstrual irregularities and 27.3% received diagnosis of PCOS. Assessment of emotional and sexual sphere revealed dyspareunia in 100%, difficulties in reaching orgasm in 60%. Only 10% of patients planned pregnancy (due to young age of most women) and none of them reported fertility problems.
Conclusions
Our study confirms that AH is normal in girls with CPP treated with GnRHa and that height gain is higher in patients treated before the age of 6 years. An increase in BMI is observed during treatment, but this effect seems to be transient, with no increased risk of overweight/obesity in adulthood. We observed an increased prevalence of PCOS compared to general population, and problems in affective-sexual sphere. Whether these findings are intrinsic to CPP *per se* or to GnRHa therapy require further studies.

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Neurofibromatosis type 2 revealed by hypertension in a young woman: is there a link?

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Introduction
Neurofibromatosis 2 (NF2) is a rare genetic disease characterized by the development of multiple schwannomas and meningiomas. It has a very variable phenotype but the most common type of tumor to develop is the vestibular schwannoma. We report clinical case of NF2 which has been revealed by hypertension.
Observation
We report the case of a 25-year-old woman referred to our institution for evaluation of hypertension. She had no family history of neuroendocrine tumors or known phakomtosis. The clinical history included a past of chronic headache and *tinnitus* for 2 years. On a general examination, she had no deformity or abnormal pigmentation. On neurological examination, she had normal higher psychic function with left sixth nerve palsy and a mild cerebellar signs. She had no clinical manifestations of adrenal medullary or cortical hyperfunction. Biochemical, endocrine, and renal investigation of the hypertension was negative. Abdominal CT showed a bilateral Dumbbell-shaped tumor located around the L3 and L4 segments. Cranial and whole spine magnetic resonance imaging showed bilateral vestibular schwannomas, multiple meningiomas, and spinal neurofibromas. Based on clinical and imaging findings the diagnostic of neurofibromatosis type 2 was made. Genetic confirmation is underway.
Discussion
The clinical presentation of NF2 varies and approximately half of the patients seen are the first case in their families. Our patient is also the first case in her family. Few studies showed the increased incidence of hypertension in NF2 compared to an unaffected population.
Conclusion
The association of neurofibromatosis type 2 and hypertension is rare. The ethiopathogenic mechanisms of this association have not yet been elucidated. There may be an underlying renal vascular disease in NF2 patients, similar to NF1, and this requires further research.

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MiRNA-342-3p as a potential diagnostic biomarker in parathyroid carcinomas

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Introduction
Despite recent developments in biochemical, radiological and molecular techniques, a preoperative diagnosis of parathyroid carcinoma (PC) remains a difficult task. The main challenge of all studies in this area is a small number of cases based on retrospective data. The search for new blood biomarkers associated with PC could be important for early diagnosis and prognosis. Dysregulated microRNA (miRNA) levels are involved in tumorigenesis and may serve as diagnostic markers for PC.
Objective
To define specific miRNAs that can be used for differential diagnosis of PC.
Materials and methods
Serum samples were taken from patients with biochemically confirmed symptomatic primary hyperparathyroidism and frozen at $-20\,^{\circ}$C. After the parathyroidectomy the patients were divided into 2 groups based on the results of morphological analysis: patients with PC ($n=12$) and patients with PA ($n=12$) matched by age, sex, level of PTH and calcium. Total RNA isolation from plasma samples with on-column digestion of the genomic DNA was carried out with mirVana PARIS Kit (Ambion). Reverse transcription was carried out using a TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems). To

examine differential expression of 760 endogenous miRNAs, Real-Time PCR was performed on 'QuantStudio 12 K Flex' station (Life Technologies) with TaqMan OpenArray Real-Time PCR Master Mix and 'TaqMan OpenArray Human MicroRNA Panel' (Applied Biosystems). The data obtained were analyzed using Expression Suite Software v.1.1 (Applied Biosystems). MiRNAs in a PC group whose expression differed more than two times from the control PA group ($P = < 0.05$) were selected for subsequent analysis.
Results
We identified 10 miRNAs whose levels were significantly lower in PC group compared to PA (control) group: miRNA-342-3p ($P = 0.000$), miR-195 ($P = 0.021$), miRNA let-7e ($P = 0.049$), miRNA-744 ($P = 0.024$), miRNA-150 ($P = 0.028$), miRNA-19a ($P = 0.037$), miRNA-320 ($P = 0.047$), miRNA-16 ($P = 0.024$), miRNA-339-5p ($P = 0.05$) and miRNA-361 ($P = 0.046$); among those, downregulation of miRNA-342-3p (fold change $= 0.35$) also met the Benjamini-Hochberg adjustment criteria for multiple comparisons. In addition, some studies have showed, that miRNA-342-3p regulates the carcinogenesis of various types of cancers such as liver cancer, cervical cancer, and NSCLC and its overexpression inhibits the proliferation, migration and cell invasion.
Conclusions
Our study demonstrates that serum miRNA-342-3p is a promising preoperative diagnostic biomarker for distinguishing PC from PA. We plan to improve the differential expression analysis of the selected miRNAs with a larger number of samples in the future.

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Adaptation of hypothalamo-pituitary-adrenal axis and cardio-metabolic parameters to physical stress in professional athletes

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Introduction
Although intensive, repeated and perennial, physical stress of training generally does not represent a health hazard to professional athletes. Adaptation to such stress is presumed on multiple levels, but still not fully defined. Our aim was to analyze specificities of hypothalamic-pituitary-adrenal (HPA) axis response and adaptation to physical stress in professional athletes.
Subjects and methods
We exposed 55 professional male athletes to acute physical stress by performing cardiopulmonary exercise test on a treadmill. Cortisol and ACTH responses were measured at 4 points: B at baseline (during rest), S at the start of the test (the moment of stepping on a treadmill), MAX at the point of maximal effort, and R at the 3rd minute of recovery period. Oxygen consumption (VO_2) and heart frequency (f) were measured in parallel, as parameters of metabolic rate and cardiac function. Control group consisted of 20 sedentary male subjects matched by age. Statistical analysis was performed with SPSS software. Specifically, ANOVA for repeated measures was used to analyze difference in response.
Results
Although the athletes had higher baseline cortisol levels, cortisol response was attenuated during MAX compared to controls ($P = 0.010$). Significant difference was also observed during R ($P = 0.015$), with cortisol levels slowly declining in athletes, while they were still rising in controls. This was in line with significant difference in percent of change of cortisol level from S-MAX ($P = 0.010$) and from MAX-R ($P = 0.015$) between groups. Unlike cortisol, two groups had similar ACTH responses throughout the test ($P > 0.05$ at all points), with levels still rising during observed recovery period in both groups. Apart from neuroendocrine adaptation, the athletes had higher VO_2 ($P < 0.05$) in all points in test except in anticipation – S ($P = 0.740$), and significantly lower f at B ($P < 0.01$) and S ($P = 0.007$). There was no correlation between VO_2 and cortisol levels throughout test. On the other hand, cortisol values strongly correlated with f at S ($P < 0.05$ for all values). Heart frequency at S was a significant independent predictor of all cortisol values (B was 0.399, 0.245, 0.309 and 0.286 for B, S, MAX and R cortisol respectively, with P being 0.001, 0.044, 0.010 and 0.023 respectively).
Conclusion
Adaptation of HPA axis to repeated physical stress might be protective against hypercortisolism. It is dependent of training status, and in line with autonomous nervous system adaptation. Adaptation of metabolic rate seems to be an independent form of adaptation.

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Diagnotic value of Shear Wave Elastography in differentiating parathyroid adenomas from thyroid nodules

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Parathyroid adenomas are situated nearby thyroid gland or even intrathyroidal and could be confounded with thyroid nodules. Ultrasound elastography is a noninvasive technique that explores the elasticity and stiffness of different tissue.
Aim
To assess the value of 2D-shear wave elastography (2D-SWE), a new technique of sonoelastography, in the differentiation of parathyroid adenomas from thyroid nodules.
Subjects and methods
We studied 22 cases (F/M = 19/3) with primary or tertiary hyperparathyroidism, diagnosed by specific tests, and 32 patients (F/M = 28/4) with 52 thyroid nodules. Between patients with hyperparathyroidism, 20 cases presented a primary forms and two patients presented tertiary hyperparathyroidism due to chronic renal disease. In all the patients with hyperparathyroidism, the parathyroid lesions were detected by using ultrasound and at least another imaging technique (parathyroid scintigraphy or magnetic resonance imaging), postoperative pathology confirming the diagnosis. In cases with thyroid nodules, 13 lesions were malignant (25.5%). All the measurements were performed with an Aixplorer system (Supersonic Image Inc. France), using a linear high-resolution transducer 15-4 MHz. For each parathyroid lesion or thyroid nodule, three elastographic determinations were performed and a mean value of stiffness was quantitatively measured and expressed in kilopascals (kPa).
Results
The mean stiffness for parathyroid lesions was 10.18 ± 4.85 kPa (6.6–15.9). In benign thyroid nodules the mean stiffness was 21.78 ± 14.45 kPa and in malignant thyroid lesions -38.90 ± 23.03 kPa, $P = 0.0119$. The statistical analysis indicates that the mean stiffness assessed by 2D-SWE in parathyroid adenomas was significantly lower than in benign nodules ($P < 0.0001$) or in malignant lesions ($P = 0.0004$).
Conclusion
This new technique can quantitatively evaluate the stiffness of parathyroid adenomas, which was significantly lower when compared to that of thyroid nodules. These data indicate that the measurement of stiffness by 2D-SWE might be a new method that can help in preoperative localization of parathyroid adenomas.

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Differential regulation of 5β-reductase (AKR1D1) expression and activity by glucocorticoids in human and rodent liver

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The prevalence of metabolic syndrome and its hepatic manifestation, non-alcoholic fatty liver disease (NAFLD), continues to escalate. Glucocorticoids (GCs) and bile acids (BAs) are established regulators of metabolic phenotype. 5β-reductase (AKR1D1) is highly expressed in human and rodent liver, where it inactivates steroid hormones and catalyses a fundamental step in BA synthesis. We have previously demonstrated that AKR1D1 modulates hepatic GC availability and GC receptor (GR) activation in human hepatocytes, in addition to alterations in triglyceride accumulation, fatty acid oxidation, insulin sensitivity and intracellular inflammation. However, the potential role of GCs to regulate AKR1D1 expression and activity is completely unknown. *In vitro*, human liver HepG2 and Huh7 cells were treated with 500 nM dexamethasone for 24h and expression changes of key enzymes involved in steroid metabolism and BA synthesis were measured by qPCR and western blotting. As expected, dexamethasone induced the mRNA and protein expression of the GR-dependent genes *DUSP1* and *GILZ*. In both cell lines, dexamethasone down-regulated AKR1D1 mRNA and protein expression (vehicle: 0.82 ± 0.08 vs. dex: 0.64 ± 0.06, $P < 0.01$), with a parallel decrease in cortisone clearance (vehicle: $41.52 \pm$

5.26 vs. dex: 52.78 ± 4.69 nmol/g protein, $P < 0.01$). *CYP7A1*, *CYP8B1* and *HSD3B7* mRNA expression were significantly increased. Pharmacological antagonism of the GR with RU-486, reversed all the dexamethasone-induced changes in gene expression. In contrast to our cellular observations, hepatic AKR1D1 mRNA and protein expression were increased in C57BL6/J mice following corticosterone treatment (vehicle: 0.54 ± 0.08 vs. cort: 0.94 ± 0.07, $P < 0.01$). CYP7A1 and CYP8B1 mRNA and protein expression were also increased. However, in healthy male volunteers ($n = 14$), dexamethasone significantly decreased urinary 5β-tetrahydrocortisol (5β-THF) excretion (pre: 329.8 ± 23.15 vs. post: 155.8 ± 18.22ug/8h, $P < 0.001$) without alteration in 5α-THF excretion, consistent with decreased AKR1D1 activity. In conclusion, GCs differentially regulate AKR1D1 expression and activity in humans and rodents. In human models, down regulation of AKR1D1 activity, may act as a feed-forward mechanism, augmenting glucocorticoid action with the potential to drive adverse effects.

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CD27-IgD- memory B cells studied in polycystic ovary syndrome

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Background
Age-associated double negative (DN) B memory cells lacking surface expression of CD27 and IgD have been associated with proinflammatory characteristics, higher disease activity in autoimmune diseases and disease-specific autoantibodies. We studied the distribution of DN B cells in Polycystic Ovary Syndrome (PCOS), their surface markers and cytokine production.
Methods
CD19+ cell subpopulations on the basis of IgD and CD27 expression were phenotypically analyzed from normal-weight PCOS patients with clinical hyperandrogenemia [$n = 18$, age 27.5 ± 11.2 years, body mass index (BMI) 27.3 ± 14] and normal-weight controls (HD, $n = 17$; age 37 ± 16.3 years, BMI 25.1 ± 10.9) in order to evaluate significantly enhanced frequencies of DN B cells. The exclusion criteria were use of insulin-sensitizers, contraceptives, steroids, diabetes type 1 and chronic inflammatory bowel disease, recorded at clinical visits for hormonal and metabolic data. Flow cytometry for surface markers and intracellular cytokine staining was performed.
Results
Phenotypic analysis showed a significant remodeling of B cell repertoire in PCOS. The frequency of DN B memory cells was significantly higher in PCOS patients than in the HD ($P = 0.002$) along with declined IgD + B cell compartment ($P = 0.011$). Notably, absolute numbers of DN cells within PCOS cohort with 45.3 (±39.9) cells/μl were significantly different to HD 23.1 (±11.9) cells/μl ($P = 0.046$). DN B cells surface expression of IgG, CD38 and CD86, along with the analysis of cytokine production is ongoing. A positive correlation between the percentage of DN B cells and BMI has been found in PCOS patients ($P = 0.01$) but not in HD.
Conclusion
Our pilot cohort of PCOS patients showed increased peripheral expansion of DN B cells. The dominating isotypes remain to be clarified. We speculate these cells could contribute to inflammation by T cell induction and the production of proinflammatory cytokines. Though increased adipose tissue mass is a determining factor in inflammation, PCOS might trigger additional specific antigenic stimuli.

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Pan-cancer analysis of thyroid hormone signaling pathway reveals new possible targets for combinations therapy

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Introduction
Published studies suggest links between altered actions of thyroid hormones (TH) and cancer development and progression. It is not clear, however, whether these links are specific to cancer types or whether TH can globally affect cancerogenesis. Here, we performed PanCancer analysis of TH signaling pathway.
Material/methods
79 genes linked with TH signaling pathway, including genes encoding proteins involved in TH synthesis, transport, receptors, as well as key TH-regulated genes were selected basing on KEGG data. Transcriptomic, genomic, and clinical data of 10,967 cancer patients, 32 cancer types were retrieved from TCGA (The Cancer Genome Atlas) and analyzed using cBioPortal, Firebrowse, starBase.
Results
The expression of 29 genes was statistically significantly ($P < 0.05$; threshold: 30%) commonly increased while expression of 20 genes was commonly decreased in the vast majority of analyzed cancers when compared with non-tumoral control samples. Cancers with the highest number of genes with altered expression included: breast invasive carcinoma (64 genes), cholangiocarcinoma (66 genes), kidney renal clear cell carcinoma (62 genes), lung adenocarcinoma (58 genes) and squamous cell carcinoma (69 genes), thyroid carcinoma (58 genes) , and uterine corpus endometrial carcinoma (58 genes). The genes of which the expression was prevalently decreased in analyzed cancer types included TSHB, SLC16A2, ABCB1, THRB, ITGB3, TAAR1, PIK3R1, NCOA1, RCAN1, PLN. The genes of which expression was prevalently increased in cancers included SLC3A2, AKT1, PLCB3, HRAS, SRC, SLC2A1. Strong expression correlations were found for the following pairs of genes: DUOX1/DUOX2 (in 19 cancer types), SLC3A2/SLC7A5 (14 cancer types), SLCO1A2/SLCO1B1 (9 cancer types), SLCO1B3/SLCO1B1 (13 cancer types). Altered expression of 29 genes correlated with poor survival of patients in at least four types of cancer, including, among others, SLC7A7, ITGAV, SLC2A1, SLC7A5, SLC5A5, SLC3A2, DIO1, THRA and DUOX1. Mutation analysis revealed that the queried genes were altered in 7334 (67%) of analyzed tumor samples. Top 10% most frequently altered genes included PIK3CA, TG, MYC, CCND1, CREBBP, NOTCH1, ARNT, NCOR1. The analysis of 3081 pairs between tested 79 genes revealed co-occurring or mutually exclusive alterations of which more than 2800 were statistically significant. Top significant co-occurring alterations in gene pairs included TG and MYC, SLCO1A2 and SLCO1B1, SLCO1C1 and SLCO1B3, SLCO1B1 and SLCO1B3, THRA and MED1.
Conclusion
The study reveals global links between altered TH signaling and cancer, possibly contributing to patients survival rate. Co-occurrence of alterations in TH pathway genes and classical oncogenes suggest possible targets for therapy combinations.
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CYP11A1 inhibition as a therapeutic approach for the treatment of castration resistant prostate cancer

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Background
Prostate cancer is a major global challenge due to the increasing number of aging population and frequency of diagnosis. During the past decade new treatments have been targeted to the androgen signaling axis either by inhibiting the binding of androgens to androgen receptor (AR) and AR nuclear translocation, or by inhibiting androgen production via CYP17A1 enzyme. Despite the significant progress on the research and new therapies, CRPC is still incurable and there is urgent need for better, more effective treatments. ODM-208 is an oral, non-steroidal and selective inhibitor of CYP11A1 enzyme, suppressing the synthesis of all steroid hormones that could be potential agonistic AR ligands.
Methods
The inhibition of CYP11A1 was measured *in vitro* by the formation of radiolabelled isocapronic acid in a human adrenal cortex cell line (H295R). The tumor growth inhibition of ODM-208 was studied in VCaP castration-resistant prostate cancer (CRPC) xenograft model. At the end of the xenograft study, plasma ACTH and LH, and key steroid hormone concentrations were analysed from plasma and target tissues. In addition, full length AR (AR-FL) and AR-V7 were analysed from the tumors by western blot and key enzymes of androgen biosynthesis, CYP17A1, AKR1C3, SRD5A1 were quantified by qPCR. In dogs an ACTH stimulation test was done.
Results
ODM-208 potently inhibits CYP11A1 enzyme *in vitro.* In addition, *in vivo* in the VCaP CRPC xenograft model ODM-208 significantly inhibited tumor growth. Importantly, the amount of AR-FL and AR-V7 levels remained unchanged in the tumors after ODM-208 treatment. Slight increase of CYP17A1 and SRD5A1 enzyme levels was observed, indicating the activation of steroidogenesis in VCaP tumors *in vivo*. Treatment had no effect on plasma LH, whereas ACTH was

significantly increased demonstrating reduction in glucocorticoid levels by negative feedback. In line with ACTH, all measured steroid hormones were significantly reduced both in plasma and target tissues. In dogs ACTH-stimulated cortisol production was significantly inhibited after single oral dose of ODM-208.
Conclusions
ODM-208 shows promising antitumor activity in preclinical CRPC models and has favorable toxicological profile. Thus, ODM-208 might have potential for treating patients with CRPC. Based on the nonclinical results, a phase 1/2 clinical trial (NTC03436485) has been initiated.

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Neuroendocrine effects of stereotactic hypothalamotomy in humans

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Stereotactic hypothalamotomy in the treatment of morbid sexual deviation was first performed by Prof. Dr. Fritz Roeder 1966 in Univ. Göttingen and installed in University Hamburg-Eppendorf (UKE) by Neuropathologist Dr. Dieter Müller (DM) in the late 1970s. Dr. Dieter Lüdecke (DKL) agreed with Prof. Herrmann, Director of Neurosurgery, to give the Professor position to DM to join the Unit. It was known that the sex behaviour centre in the ventromedial nucleus of Cajal was distinct from the centre in the median eminence controlling pituitary secretion. The aim was to investigate the effect of hypothalamic stereotactic stimulation of the preoptic area (POA) and ventromedial nucleus (VMN) on the regulation of pituitary secretion in 27 patients referred for hypothalamotomy to cure hypersexuality. 27 patients (one female) were referred by a group of psychiatrists and a psychologist; 24 for compulsive hypersexualism. Neurosurgical access including air encephalography and hormonal investigations were performed by DKL and his Neuroendocrine Laboratory; including basal GH, ACTH, LH, FSH and prolactin and pre- and post-operative hormone responses to Metyrapone and Insulin Tolerance Tests. Patients were initially anaesthetised then woken up during the procedure. Electrostimulation to determine the exact location and to perform hypothalamotomy were both done by DM. All 27 patients could be improved. Four mild relapses occurred and three patients requested repeat stereotaxis. Only one woman was seen with extreme, debilitating hypersexuality. She also had severe acromegaly but hypersexuality had persisted after GH normalisation and in spite of multiple psychiatric medications. She returned to normal after a controlled partial hypothalamotomy.
Endocrine results
GH and ACTH rose after stimulation of the optic chiasma but stimulation of the pre-optic area POA and VMN suppressed GH secretion, showing for the first time the location of GH down-regulation in man. A distinct GH release was provoked by stimulation of the basolateral amygdala. ACTH response to metyrapone was impaired in the first seven patients but resolved by 6 months. Subsequent patients had lesions 1 mm more dorsally with normal ACTH responses. Slight increases in prolactin and decreases in testosterone were seen but still within the normal range. Importantly, no patient needed hormone replacement. Side effects were transient diabetes insipidus in 2/3 patients and one patient had an epileptic seizure after surgery. This well controlled series of medial hypothalamotomies was accepted with success at the World Congress of Neurosurgery, Sao Paulo 1977 and shows that the procedure has major psychiatric benefits with minimal side-effects.

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P669

Dyslipidaemia and altered hepatic function in males - consequences of androgen excess in fetal life

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Introduction
Adult male offspring of women with PCOS have increased dyslipidaemia, characterised by elevated triglycerides (TG), increased total and LDL-cholesterol (LDL-C), and hyperinsulinaemia. As altered intrauterine endocrine environments can 'programme' adverse health outcomes in adulthood we hypothesised that this dyslipidaemia was a consequence of a hyperandrogenic intrauterine environment. We used an outbred large animal model to identify if prenatal androgen excess could be causally linked to male hepatic dysfunction and investigate the underpinning mechanisms of dyslipidaemia.
Methods
Ovine fetuses were directly injected with a 200 µl bolus of testosterone propionate (PA; 20 mg) or vehicle control (C) at day 62 and 82 of gestation. Male adolescent offspring were studied at 6 months postnatal age (C, $n=14$; PA, $n=14$). Hepatic transcriptome and proteome were determined using Illumina RNA sequencing and liquid chromatography-mass spectrometer (LC-MS/MS), respectively. Plasma proteins and analytes were measured using LC-MS/MS, ELISA or benchtop biochemistry autoanalysers. Statistical analysis between C and PA groups was carried out using pairwise comparisons, with false discovery rate correction, accepting adjusted $P<0.05$ as significant.
Results
Adolescent PA ovine males had increased levels of total cholesterol, LDL-C, TG and insulin (all $P<0.05$), reproducing metabolic disturbances observed in sons of PCOS patients. Plasma protein analysis showed increased levels of circulating apolipoproteins, including APOA4, APOC3, APOD and APOM (all $P<0.05$) indicating altered cholesterol homeostasis. However, genes and proteins involved in cholesterol biosynthesis pathway were downregulated (all $P<0.05$) (*HMGCS1, HMGCR, MVD, FDPS, Q15LE, CYP51A1, HSD17B7, NSDHL* and *DHCR7*). There was upregulated expression of hepatic cholesterol transporters, *ABCG5* and *ABCG8* (all $P<0.05$) and decreased expression of *CYP7A1* ($P<0.05$), the rate limiting enzyme in bile acid synthesis.
Conclusions
Androgen overexposure *in utero* leaves a legacy in adolescent life of male offspring that is characterised by hypercholesterolemia. This is directly programmed in utero and suggests that dyslipidaemia in the sons of women with PCOS may have a significant environmental rather than genetic component. This effect is underpinned by altered expression of gene/protein pathways responsible for bile acid synthesis and *de novo* cholesterol synthesis in the liver. As the cholesterol biosynthesis pathway is decreased standard therapeutic strategies to reduce cholesterol may be less effective. In addition to providing understanding of molecular mechanisms underpinning such adolescent development of hepatic dysfunction and targets with utility for potential intervention, our data also provide potential biomarker identification.

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P670

The impact of new technologies in the future of health somatotropin: 100% therapeutic adhesion in oncological pediatric age survivors in the Ipolfg

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Introduction
The somatotropin deficit is one of the late consequences of cancer treatments. The administration of somatotropin implies treatment with daily injections, which hinders therapeutic adherence. This goal is a challenge for survivors and health professionals. Therapeutic education and new technologies are instruments that favor the training and development of control mechanisms that promote and motivate the behavior's change.
Objective
To evaluate the therapeutic adherence of pediatric oncologic survivors treated with somatotropin in the IPOLFG Rehabilitation Endocrinology Clinic.
Methods
Retrospective, descriptive and analytical study, reviewing of nurse and medical clinical records of children / adolescents under treatment with somatotropin of our Endocrinology Rehabilitation Outpatient Clinic from January/2015 to October/2018.
Development
At present, 57 children/adolescents with a record of 100% therapeutic adherence are under treatment with somatotropin. The use of differentiated and personalized strategies, communication techniques and new technologies in therapeutic education have promoted acceptance and motivation in a therapeutic commitment that has led, especially in the last three years, to a positive result in adherence to this treatment. The device used in Department, Easypod, allows the registration and consequent verification and control of doses prepared and administered giving precision and accuracy to the validation of the respective adhesion. The Easypod Connect platform, which has been recently integrated in the appointments, has proved useful in early detection of cases of non-adherence,

allowing a faster intervention in these cases. Nonadherence was identified at the beginning of the treatment, mainly due to the fear of the pain of the bite or due to saturation of treatment time. Sometimes, demotivation with the obtained results, may be also a negative interference. Five cases of partial adhesion and/or non adhesion were identified in this time period. Nursing appointments, were intensified, telephone contacts, adjustment of parameters in the devices (reduction of the time of injection), techniques of pain relief, teaching of distraction techniques, negotiation, positive reinforcement by the obtained results and development of the interpersonal relation for a involvement of children/ adolescents and parents in therapeutic goals.
Conclusion
Therapeutic education, new technologies and multidisciplinary teamwork are fundamental for skills development on training administration and consequent success in adherence. Only with this work we can get efficacy and decide about future adjustments of somatotropin doses in children / adolescents. This therapeutic success has repercussions not only on the stature but also on the present and future quality of life of survivors.

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P671

Clinical, malformative profile of turnersyndrome at mohammed VI university hospital centre oujda-morroco

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Introduction
Turner syndrome occurs in one out of every 2,500 to 3,000 live female births. The syndrome is characterized by the partial or complete absence of one X chromosome (45,X karyotype)[(1)]. Patients with Turner syndrome are at risk of congenital heart defects, and is defined by the association of a dysmorphic and malformative syndrome, the main elements of which are small size and gonadal dysgenesis[(2)].
Methodology
Descriptive, transversal study of 11 female patients followed for Turner syndrome in Mohammed VI University Hospital Centre Oujda.
Results
The mean age of our patients at the time of diagnosis is 10.6 years ranging from 2 to 22 years. Patients older than 10 years are the majority, accounting for 60% of cases. Statural delay is the main reason for consultation (67%), in more than 80% of cases it is less than 3 standard deviations; followed by pubertal delay in 40%, cases, Clinical manifestations vary and may be subtle, but they usually include short stature, a broad chest with widely spaced nipples, cubitus valgus, and nevi. The karyotype was mosaic in 40%, homogeneous 45 XO in 30% and structural abnormalities accounted for 20% of the total. Turner's syndrome is accompanied by variable malformations: heart disease in 3 patients, bone abnormalities were found in 2 patients and otological malformations in 4 cases. 2 patients presented with celiac disease, 2 cases of hypothyroidism and 1 case of diabetes. The treatment with recombinant growth hormone is initiated in 3 patients with a mean bone age of 9 years, 4 patients were treated with estrogen-progestins, with a good evolution.
Conclusion
Turner's syndrome also has many clinical implications that need to be identified, explained and treated to improve quality of life and prevent complications[(2)].
Bibliography
1. Paolucci DG1, et al. Turner Syndrome: Care of the Patient: Birth to Late Adolescence.Pediatr Endocrinol Rev. 2017 Jun;14 (Suppl 2): 454-461. doi: 10.17458/per.vol14.2017.pb.turner syndrome care.
2. Bondy CA; **Turner Syndrome** Study Group. Care of girls and women with **Turner syndrome**: a guideline of the **Turner Syndrome** Study Group. J Clin Endocrinol Metab.

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P672

The management of acromegaly: experience of the endocrinology

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Introduction
Acromegaly is a rare and misdiagnosed disease characterized by somatotropic hypersecretion. The purpose of this study is to describe the epidemiological, clinical, para-clinical, therapeutic features of Acromegaly disease.
Patients and methods
This is a retrospective study including 10 patients with acromegaly in the Endocrinology Diabetology Department of Oujda's Mohammed VI University Hospital, Morocco.
Results
The mean age at diagnosis was 49 years with a female predominance. The median diagnosis delay was 8 years. Acrofacial dysmorphic syndrome was the most frequent mode of revelation. Pituitary adenoma was the etiology in all cases, macroadenoma in nine patients and microadenoma in one patient. All our patients had complications at the moment of diagnosis: ante-pituitary insufficiency in 100% of cases, ophthalmological disorders in 70%, cardiorespiratory complications in 60%, diabetes mellitus was found in 50% and dyslipidemia in 30% of cases. All our patients had goiter. colic polyps was observed in 40%, bone deformities in 60% and arthralgia in 50%. 70% of patients underwent transsphenoidal pituitary surgery, and 80% have been treated by somatostatin analogs (Lanreotide LP 120 mg), given before surgery in four cases with non-invasive adenoma and in three cases as a second line therapy after incomplete tumor resection associated to radiotherapy (30%). Treatment with SA has normalized IGF1 levels in 62.5% of cases.
Conclusion
Early diagnosis of acromegaly is necessary to avoid complications. Its management should be discussed among multidisciplinary meetings.

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P673

Sheehan's syndrome: case report

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Introduction
In our country, Sheehan syndrome is one of the most common causes of pituitary insufficiency in female patients.
Case
A 54-year-old female patient developed cardiac arrest after an elective hip replacement surgery, and after 5 minutes of cardio pulmonary resuscitation, the rhythm returned to normal and the patient was intubated. Since she was hypotensive, she was given the infusion of noradrenaline after dopamine infusion, but despite this treatment, the patient continued hypotension. Her past medical history revealed that she had been using 100 µg LT4 for 1 year due to hypothyroidism and had not ingested her medication for 1 week. The patient had extensive hemorrhaging during the last birth, but no transfusion was performed. She subsequently did not lactate and never resumed menses. The patient was menopausal at the age of 36 years. She is usually hypotensive, tired and fatigued. The patient had hypoglycemia and hypotension. total pituitary insufficiency was considered as a result of evaluation of history and clinical findings. the hormone levels were found as cortizol: 1.22 µg/dl (6.02–18.4), Prolactin: 5.13 ng/ml (4.79–23.3), FSH:1.87 IU/ml (25.8–134.8), LH:0.676 IU/ml (7.7–58.5), Estradiol:17.96 pg/ml (5.0–138), IGF-1: $<$ 15 ng/dl (94–252), ACTH:12.3 pg/ml (0–46), sT4:0.3 ng/ml (0.93–1.7), TSH:2.58 mIU/ml. (0.4–4.1). The patient was diagnosed with Sheehan's syndrome and adrenal crisis. After basal blood withdrawal, hydrocortisone 400 µg and L-thyroxine 50 µg was started. When the clinical improvement improved, the dose was reduced to $10+5+10$ mg / day oral hydrocortisone. The patient was discharged after the sick day rule was told to himself and his family.
Conclusion
If TSH is normal or low in patients diagnosed with hypothyroidism, central causes should be investigated and questioned in terms of obstetric history and panhypopituitaryism.

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P674

First and second day cortisol levels as predictors of long-term hypocortisolism after pituitary surgery

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Introduction
Prediction of HPA (hypothalamus-pituitary-adrenal) activity after trans-sphenoidal pituitary surgery (NS) is essential for post-operative management. There is not unique behavior in this setting: most of specialists suggests 4-6 weeks of glucocorticoid supplementation and treatment interruption after demonstration of normal endogenous response. Some authors suggest early cortisol detection for the identification of patients requiring glucocorticoid therapy. Aim of study is to evaluate the ability of cortisol in first (FC) and second day (SC) after NS in predicting HPA axis function. Methods: we evaluated 71 patients (56 ± 14.8 years old, mean $\pm$ SD; 27 F) who underwent a 3D endoscopic endonasal approach to the sella between April 2013 and April 2018 in Neurosurgical Department of San Giovanni Battista Hospital for pituitary benign diseases (36 non-functioning pituitary adenoma; 20 GH-secreting; 3 PRL-secreting, 3 GH/PRL secreting, 5 FSH/LH positive and 4 Rathke cleft cysts). We excluded Cushing disease patients, those in antiallergic prophylaxis and those with hypocortisolism before surgery. For each patient we evaluated FC and SC levels (h. 8:00) after procedure and at 3 months. In all patients with cortisol levels <18 µg/dl, HPA axis was further assessed with a stimulation test (the ACTH 1 µg test or the Insulin Tolerance Test) at 3 months.
Results
None of the 71 patients had peri-procedural complications. At the discharge, 36 patients were on glucocorticoid therapy, 13 had indication to take glucocorticoid only in stress condition and 22 were dismissed without any specific therapy. At 3 months, 17 patients (23.9%) had a diagnosis of hypocortisolism (HP; 55.59 ± 14.53 years old, F6) whilst 54 (76.1%) normal HPA activity (NP: 55.78 ± 16.07 years old, F 21). FC levels (median; range: 25.7 µg/dl; 4.39 – 63.5 µg/dl) resulted higher than SC (15.75 µg/dl; 2.19–45 µg/dl, $P<0.001$). FC levels were significantly lower in HP compared with NP ($P<0.02$), also SC levels (HP lower than NP; $P<0.001$). Considering 15 µg/dl as the limit value to rule out hypocortisolism, we calculated ΔFC (FC-15) and ΔSC (SC-15). Only ΔFC resulted significantly higher in NP compared to HP (P 0.02), while no difference was detected in ΔSC (P 0.1).
Conclusion
in our study FC and SC levels have a significant strength in predicting hypocortisolism. Also ΔFC (but not in second day) could have a role in suggesting to clinicians the need of glucocorticoid treatment in patients who underwent pituitary surgery.

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P675

Preoperative predictors of Cushing's disease remission after transsphenoidal endoscopic surgery

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Purpose
Transsphenoidal endoscopic surgery (TSS) is the first-line treatment for Cushing's disease (CD). However, persistence of hypercortisolism after TSS considered important problem. In this case search for CD remission predictors is actual.
Aim
To study the role of preoperative oral high-dose dexamethasone suppression test (HDDST) and pituitary magnetic resonance imaging (MRI) in the prognosis of CD remission after TSS.
Materials and methods
101 patients (12 men, 89 women, mean age 41 years (15–72) with confirmed CD were included. HDDST and pituitary MRI were performed before the TSS in all cases. Invasive growth of adenoma was assessed by the Knosp classification. Postoperative examination was done one year after surgery. Remission criteria were: secondary adrenal insufficiency (the need for glucocorticoid replacement) or combination of normal midnight ACTH and serum cortisol levels, normal 24 hour urine free cortisol (UFC) excretion and serum cortisol suppression less than 50 nmol/l in 1-mg dexamethasone test. The optimal threshold value of serum cortisol suppression in the HDDST for prediction of CD remission after TSS was calculated by ROC-analysis.
Results
One year after surgery CD remission was confirmed in 63 patients, whereas in 38 patients hypercortisolism persisted. The optimal threshold value of serum cortisol suppression in the HDDST for prediction of CD remission after TSS was $\leq 74\%$. Test's sensitivity and specificity were 86.8% and 84%, respectively. The probability of wrong prediction was 16% ($P=0.0001$). The results of TSS did not depend on the MRI adenoma size: remission of hypercortisolism was achieved in 64% of microadenomas and in 56% of macroadenomas. However in patients with non-invasive adenomas (Knosp 0–2) 47 of 50 patients with adenoma size ≥ 3 mm developed remission (94%), in 24 patients who had MRI-negative or <3 mm adenoma CD remission developed only in 11 cases (45.8%).
Conclusion
According to our data serum cortisol suppression more than 74% in preoperative HDDST may be used as a prognostic criterion for CD remission after TSS. The adenoma size may be used as a prognostic criterion in patients with non-invasive adenomas: the lesion size ≥ 3 mm is associated with high CD remission rate after TSS.

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P676

An unexpected intrasellar meningioma in a patient with anosmia

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Introduction
Although meningiomas often occurs in parasellar regions such as the tuberculum sellae, olfactory groove, and sphenoid wing, pure intrasellar meningiomas are extremely rare. Patients usually present with gradual visual deterioration secondary to compression of the optic apparatus. Obtaining a correct preoperative diagnosis will likely require a thorough clinical assessment including neuroimaging and endocrine studies.
Case report
A 56 year-old woman with a 6 month history of anosmia was referred to the Neurology Department. A pituitary mass was found and she was referred to the Endocrine Department. A magnetic resonance imaging (MRI) scan revealed a $15 \times 16 \times 19$ mm enhanced homogeneous intrasellar mass with suprasellar extension. The optic chiasm was slightly displaced, as well as the anterior cerebral artery, and the pituitary stalk was not visualized. Formal visual field testing was normal, and laboratory data revealed intact pituitary axes. Total resection of the mass was attempted via the transsphenoidal route, and the surgery was complicated with meningitis, which resolved after a 3 week course of antibiotics. The histological report showed a grade I meningotelial meningioma. The patient developed hypopituitarism as evidenced by low levels of ACTH, Cortisol, FSH, LH, estradiol, TSH and FT4. Surgery was further complicated by diabetes insipidus and bilateral temporal hemianopsia. Intrasellar meningiomas are extremely rare, they may be easily confused with pituitary adenomas. They frequently cause visual dysfunction and rarely cause anosmia as the first manifestation. Some evidence suggests that the correct preoperative identification of an intrasellar meningioma is of value in order to appropriately decide the best surgical approach.
Conclusion
To our knowledge, this is the first case of an intrasellar meningioma causing anosmia. The presence of anosmia might aid in the correct diagnosis of an intrasellar meningioma mimicking pituitary adenoma.

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P677

Erectile dysfunction in diabetic men revealing an empty sella ($n=3$)

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Introduction
Erectile dysfunction (ED) is quite common. It poses a problem of diagnosis and management given the multiplicity of contributing factors and etiologies that can sometimes be unrecognized.
Observations
We report 3 observations of patients followed for insulin-requiring diabetes. The average age was 51. They had ED for 3.5 years on overage. The clinical examination of our patients showed obesity or weight excess. The impact assessment of diabetes showed diabetic retinopathy in all cases. HbA1c was 8.3%. Hormonal exploration has objectified a biological hypogonadism with a central look. The complete hypophysiogram did not show other abnormalities. Pituitary imaging revealed an empty sella. The dosage of PSA, ferritinemia and prostate ultrasound are normal. Ophthalmological examination and visual field did not show abnormalities. In addition, conversion enzyme assay, chest X-ray and abdominal ultrasound and salivary gland biopsy are normal. Androgenic treatment was initiated using the necessary precautions. Improvement of symptomatology is obtained in all cases. Clinical, biological and hormonal monitoring is planned.
Discussion
Our observation illustrates the interest of the hormonal exploration of ED for the diabetic. A hypothalamic-pituitary pathology can be at the origin of this symptomatology. The appearance of empty sella is rare in humans especially in men. Etiological exploration is necessary. A secondary empty sella must to be considered. The hypothesis of hemochromatosis, especially in diabetics, must be advanced. For our patients, the etiological exploration is negative but the hypothesis of diabetic microvascular involvement remains plausible in our patients since they have diabetic retinopathy.

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P678

Case report of pituitary adenoma with subclinical Cushing's disease

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Background
Subclinical Cushing disease is defined by mild hypercortisolism that results from a corticotroph pituitary adenoma, without any typical sign of the disease. The patients often have coexisting metabolic diseases such as diabetes mellitus, and hypertension. Conversely, silent corticotroph adenomas demonstrate normal cortisol secretion, but positive immunochemistry for ACTH, most usually without ACTH hypersecretion, although they and can progress to clinical Cushing disease. A subcategory of the corticotroph adenomas are the Crooke's cell adenomas characterised by cytoplasmic accumulation of cytokeratin filaments in $>60\%$ of the cells. These adenomas are usually invasive and recur frequently. We present a case of pituitary Crook adenoma with subclinical Cushing disease.
Case presentation
A 73-year-old male patient was diagnosed with a pituitary adenoma in the MRI performed for recent-onset headaches. He was on treatment for hypertension, atrial fibrillation and had a right-eye strabismus since birth. He did not report any symptom related to pituitary hormones deficiency or hypersecretion and the physical examination was also normal. Optical field test revealed a right-eye strabismus without eyelid ptosis and normal pupil reflex. MRI revealed 'a large pituitary adenoma with small optic chiasm pressure, small encapsulation of the right cavernous sinus, and extension to the borders of the left cavernous sinus.' 1st–2nd blood test results (normal range): morning serum cortisol: 23.9–23.1 μg/dl (5–25), ACTH: 128.7–105.7 pg/ml (7.3–63.3), night serum cortisol: 9.5 μg/dl (<7.5), urine 24-h cortisol: 195–163 nM, cortisol after overnight 1 mg-dexamethasone test: 4.4–4.6 μg/dl, FT3: 3.9–3.4 pmol/l (3.1–6.8), FT4: 11.7–11.4 pmol/l (12.0–22.0), TSH: 2.3–1.6 μU/ml (0.7–4.2), FSH: 0.9IU/L (1.0–9.7), LH: 0.5IU/L (1.0–8.0), Testosterone: 0.8 ng/ml (1.4–4.0), PRL: 27.1 ng/ml (3.3–11.9), IGF-1: 15ng/ml (40–400), urine osmolality: 942 mOsm/KgH2O (>300). The patient was diagnosed with subclinical Cushing disease because of the lack of signs of clinical Cushing syndrome and the non-suppressed cortisol level after the overnight 1mg-dexamethasone test, and with coexisting deficiency of the other pituitary hormones. The slight elevation of the PRL was probably due to stalk pressure. The patient received L-thyroxin and underwent a transsphenoidal resection of the pituitary adenoma. The pathology report described a corticotroph ACTH-secreting pituitary adenoma, compatible with a Crooke adenoma (Ki-67 2-3%).
Conclusion
Patients with a pituitary adenoma and elevated ACTH, without the clinical signs of Cushing syndrome, should be evaluated for the pituitary-adrenal axis function. A Crooke's adenoma can be the underlying aetiology of subclinical Cushing disease.

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P679

Giant empty sella and pituitary insufficiency 20 years after raditherapy for nasopharyngeal cancer

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Background
Empty sella (ES) is often an incidental imaging finding, associated or not with the following symptoms: headache, hypopituitarism or visual impairment. Two etiological forms are described: primary ES due to a combination of increased spinal fluid pressure and a defect in the sella diaphragm and secondary ES due to the shrinkage of the pituitary gland (after pituitary surgery, radiation, apoplexy, hypophysitis or neurosarcoidosis).
Clinical case
We present the case of a male patient diagnosed with giant empty sella and partial pituitary insufficiency 20 years after radiotherapy for nasopharyngeal cancer. A male patient, aged 37 years, presented in our service for daily headache, episodes of diplopia, memory and concentration disturbances, asthenia, dizziness, somnolence, weight gain and diminished libido. In the two months previous the consultation he had two alarming episodes of loss of consciousness. Hormonal dosages showed a partial thyrotropic and gonadotropic insufficiency with normal prolactin, IGF1 and cortisol. MRI investigation showed a giant empty sella invading the sphenoid sinus, with very scarce pituitary tissue. In the pathological history of the patient, an episode of radiotherapy at age 17 for nasopharyngeal cancer is noted followed by complete remission of the tumor. At the time and during the 10 years follow-up, no anomaly of the pituitary region was noted. Radiotherapy is probably the cause of the pituitary atrophy and the secondary empty sella. Substitutive treatment with thyroxin and testosterone was prescribed, resulting in significant clinical improvement: weight loss, remission of memory and concentration disturbances, asthenia, dizziness, somnolence, and diminished libido. The headache and the visual disturbances also improved. A yearly follow-up is recommended in order to assess the pituitary function and the substitutive treatment. As the empty sella is completely invading the sphenoid sinus, the occurrence of a nasal cerebrospinal fluid leak is a concerning perspective.
Conclusion
We present the very rare case of a giant empty sella and pituitary partial insufficiency, secondary to radiotherapy for nasopharyngeal cancer, showing the necessary follow-up of these patients, even longtime after the treatment.

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Acromegaly complications at the time of diagnosis

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Introduction
Acromegaly is an underdiagnosed condition that is responsible for multiple complications. The purpose of this work is to examine the prevalence of these complications at time of diagnosis.

Patients and methods
This retrospective study included 10 patients diagnosed with acromegaly followed in the endocrinology – diabetology department of Mohamed VI university hospital.
Results
Mean age at diagnosis was 49 years with a sex ratio (M/F) =0.66. The average diagnosis delay was 8 years. The pituitary adenoma was the etiological diagnosis in all our patients. In terms of endocrine function, 80% of the patients had gonadotropic insufficiency, 40% of them presented thyrotropic insufficiency, 20% had corticotropic insufficiency, and 50% had hyperprolactinemia. Cardiovascular complications were dominated by Left Ventricular hypertrophy in 60% of cases and hypertension in 40% of them. Only one case of valvulopathy complicated by atrial fibrillation was found. Sleep apnea syndrome was diagnosed in half of our patients. Concerning metabolic effects of acromegaly, 60% showed a carbohydrate metabolism disorder and 30% had dyslipemia. As for osteoarticular complications, 9 patients had extremities hypertrophy, 5 patients suffered from arthralgia and 1 patient presented carpal tunnel syndrome. Tumoral complications were also noticed: goiter was present in 100% of cases and colonic polyps in 40% of cases.
Conclusion
Several complications are already present at time of diagnosis of acromegaly hence the importance and necessity of their screening and specialized management.

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First case of mature teratoma and yolk sac testis tumor associated to inherited MEN-1 syndrome: a case report

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominantly inherited endocrine tumor syndrome characterized by development of cancer in various endocrine organs, particularly in pituitary, parathyroid and pancreas. Moreover, in some cases, also non-endocrine tumors can be diagnosed, developing atypical phenotypes.
Case report
We report herein the clinical history of a patient affected by MEN-1 syndrome who developed atypical features for this disease. The patient clinical history started on August 2015 when he referred, at the age of 23 years, to the Emergency Department of our Hospital for the occurrence of progressive asthenia, weakness, tremor and syncope. The biochemical test documented hyper-calcemia and severe hypoglycemia. The patient was referred to our Neuroendocrine Tumor and Pituitary Unit and he was diagnosed with pancreatic insulinoma, hypercalcemic hyperparathyroidism and a prolactin secreting pituitary adenoma. The MEN-1 syndrome was suspected and genetic test for mutation of menin resulted positive for the pathogenic variant c1548dupG. On January 2016, patient was diagnosed with intratubular germ cell neoplasia, consisting of mature teratoma and yolk sac tumor and he underwent a right orchiectomy.
Conclusion
This is the first case report showing the clear association of MEN-1 syndrome with the yolk sac tumors and teratomas, as in our case, the c1548dupG represents a pathogenic variant rather than a SNP. This case suggests the opportunity of an accurate evaluation of testis particularly in young MEN-1 affected patient and that a prompt screening for neoplastic disease should involve all the endocrine glands.

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Assessment of oro-dental manifestations in a series of acromegalic patients, the AcroDent study

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Objective
Maxillofacial manifestations of acromegaly are well described (prognathism, inter-dental space enlargement, occlusion disorder, macroglossia, prominent cheekbones…) [1] but the dental and periodondal impact of this disease has been poorly investigated. The scientific literature on this topic is scarce, with controversies about gingival and cement enlargement. Our goal is to describe the oro-dental state of these patients as precisely as possible and to study the impact of acromegaly on patients' reported oral health related quality of life (OHRQoL) at the same time.
Methods
We prospectively assessed the oro-dental status of acromegalic patients, whether cured or not. After collecting the characteristics of their disease, patients answered the GOHAI questionnaire assessing their OHRQoL, as well as the AcroQoL questionnaire assessing the acromegaly-specific quality of life and then benefited from a complete stomatological and radiological examination (orthopantomogram systematically, retro-alveolar radiography or Cone Beam Computed Tomography if necessary) by the same experienced specialist.
Results
29 patients aged 59.1±16.0 years were included, 52% had controlled acromegaly. The average DMFT index (sum of Decayed, Missing and Filled Teeth per patient) was 19.0±7.8. 55% of patients had a gingivitis and 62% had a mild to moderate chronic periodontitis, but no case of severe chronic periodontitis were found, probably because the frequency of a protective thick gingival biotype was increased (9/29, 31%). Contrary to previous reports [2;3], no case of generalized gingival hypertrophy or diffuse hypercementosis were observed. According to the Add-GOHAI score, 30% of patients only had a satisfactory OHRQoL. This parameter was correlated to the acromegaly-specific quality of life according to the AcroQoL score. Interestingly, 11 patients (37.8%) had bulky oral bony outgrowths (OBO) such as large maxillary or mandibular tori and multiple vestibular exostosis.
Conclusions
1. The unsatisfactory OHRQoL reported by patients contrasts with a rather good objective oro-dental state.
2. Huge OBO could be helpful signposts for the diagnosis of acromegaly, especially when a patient visits a dentist for another non-specific acromegaly-related oral symptom (occlusion disorder, temporo-mandibular joint pain…).
3. Taking our results into account, we advocate annual oral examination for acromegalic patients, as for the rest of the population.
References
[1] Chanson P. and Salenave S. Acromegaly. Orphanet J Rare Dis. 2008;3:17.
[2] Çapoglu I. *et al.* Gingival Enlargement in Acromegaly. Endocrine. 2002;18, 207–10.
[3] Kashyap RR. *et al.* Dental patient with acromegaly: a case report. Journal of Oral Science. 2011;53, 133–6.

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GHD children's stature evolution after one year of treatment with growth hormone

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Introduction
GH deficiency (GHD) is a rare etiology of short stature. The lack of early diagnosis and adequate treatment have adverse consequences, especially the small final height with the resulting psychological impact. The aim of this study is to identify some of the predictive factors influencing stature gain during the first year of GH therapy.
Materials and methods
This is a retrospective longitudinal study of 14 cases of complete GHD collected in the Endocrinology-Diabetology department between 2014 and 2018.

Results
The prevalence of patients with GHD is 8.33% among 170 cases with short stature requiring exploration. The mean chronological age (CA) at the start of treatment was 12, 41 years. Mean height Z-score at time of diagnosis was −4,92SD. The mean bone age (BA) at the time of diagnosis was 5, 46 years. The delay of BA over the chronological age was of 6, 75 years on average. The mean therapeutic dose was 0.025 to 0.035 mg/kg / day. The average stature gain at the end of the first year of GH treatment was 0.82 ± 0.24 SD. Correlation analysis showed that a change in height gain in the first year had a significant correlation with the age at the start of treatment ($P < 0.001$) and the severity of growth hormone deficiency (P: 0,045). No correlation was found between height gain and sex gender, body mass index, the presence of multiple pituitary hormone deficiencies, and abnormalities on pituitary magnetic resonance imaging.
Conclusion
Despite a very evocative clinical features, the diagnosis of GHD remains difficult and relatively late in some patients. The height gain is more important during the first year of GH therapy. The earlier the treatment is administrated, the better the results will be in case of a severe deficiency.

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Effects of growth hormone deficiency (ghd) and gh treatment on early markers of atherosclerosis in children

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Background
Endothelial dysfunction is considered an early step in the development of atherosclerosis, while an increased intima-media thickness (IMT) represents one of the earliest morphological changes in the arterial wall in the process of atherogenesis. Only a few studies have investigated endothelial dysfunction and IMT in GHD children and results are still inconsistent.
Objective
Aim of our study was to evaluate the effects of GHD and GH treatment on endothelial function and IMT in childhood.
Methods
24 GHD children (10.8 ± 2.7 years) and 24 age-, sex- and BMI-matched controls were enrolled into the study. At baseline all subjects underwent auxological and anthropometric measurements, evaluation of lipid profile [triglycerides, total-, LDL-, HDL cholesterol, atherogenic index (AI = total/HDL cholesterol), non HDL cholesterol (total cholesterol – HDL cholesterol)], evaluation of endothelial function by ultrasound assessment of brachial flow-mediated dilatation (FMD) and IMT of common carotid artery (cIMT) and of internal carotid artery (iIMT). These evaluations were repeated after 12 months of GH treatment in GHD children.
Results
At baseline GHD children had higher total cholesterol (162.83 ± 18.33 vs 149.83 ± 20.63 mg/dl, $P = 0.04$), LDL cholesterol (91.48 ± 21.73 vs 77.08 ± 19.73 mg/dl, $P = 0.02$), non HDL cholesterol (102.4 ± 20.23 vs 89.33 ± 18.03 mg/dl, $P = 0.04$) and AI (2.84 ± 0.5 vs 2.56 ± 0.4, $P = 0.03$) compared with controls. No differences were found in triglycerides and HDL cholesterol between patients and controls. GH therapy was associated with a significant reduction in total- (151.42 ± 14.90 mg/dl, $P = 0.03$), LDL- (74.44 ± 15.56 mg/dl, $P = 0.005$), non HDL cholesterol (86.42 ± 17.81 mg/dl, $P = 0.01$) and AI (2.29 ± 0.35, $P = 0.0001$), while triglycerides and HDL cholesterol did not change. Moreover, at study entry GHD children showed lower values of FMD (8.75 ± 2.44 vs 11.85 ± 5.98%; $P = 0.02$) compared to controls while no difference was found in cIMT (0.37 ± 0.08 vs 0.40 ± 0.06 mm) and iIMT (0.33 ± 0.06 vs 0.36 ± 0.07 mm). GH treatment was associated to a significant improvement in FMD (10.60 ± 1.69%, $P = 0.04$). cIMT and iIMT slightly reduced in patients after 12 months of GH treatment although these differences did not reach statistical significance. No correlations were found between changes in FMD and total-, LDL-, non HDL cholesterol and AI.
Conclusions
Our results suggest that GHD children may exhibit subtle lipid alterations and early markers of atherosclerosis as documented by negative changes in FMD values. GH exerts beneficial effects restoring endothelial function and abnormalities in lipid profile.

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Copeptin in differential diagnosis in polyuric states

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Introduction
Measurement of copeptin is proposed for use in the differential diagnosis of polyuric syndrome.
Aims
To evaluate the diagnostic value of copeptin levels in patients with polyuria syndrome.
Materials and methods
The study included 17 patients with central diabetes insipidus (CDI), 3 patients with nephrogenic diabetes insipidus (NDI), 7 patients with primary polydipsia (PP) and 26 control subjects. In all individuals blood samples were taken after 8 h fast. Copeptin levels were measured by BRAHMS CT-proAVP Kryptor.
Results
In 38% (10) of healthy volunteers, the level of copeptin was less than 5 pmol/l. The rest control individuals average levels were 8.5 ± 2.8 pmol/l (from 5.41 to 15.16). Patients with CDI in 82% had copeptin levels below 5 pmol/l, the rest 6.8 ± 0.8. Patients with PP in 71% had copeptin levels below 5 pmol/l, two patients had levels 5.3 and the 6.7 pmol/l. All NDI patients had measurable copeptin concentrations in the blood – 8.6, 12.9 and 14.5 pmol/l.
Conclusions
A large proportion of values in the range below the sensitivity of the method of determination in healthy people and patients with PP makes it difficult to differentiate them from ones with CDI. The increase in method sensitivity would be desirable.

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Delayed psychotic episod in a patient with panhipopituitarism and central diabetes insipidus after craniopharyngioma removal

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Introduction
Central diabetes insipidus is a rare disorder, characterized by a failure of the posterior pituitary to produce vasopressin that lead to hypotonic polyuria and polydipsia. Diabetes insipidus may be due to post-pituitary surgery, where sometimes the posterior lobe also has to be removed or damaged; other injury as fractures of the skull, trauma, infiltrative lesions, tumors/metastases, idiopathic or rare genetic causes. As the sensation of thirst is the key homeostatic mechanism that prevents hypernatraemic dehydration in patients with untreated diabetes insipidus (DI), adipsia leads to failure to respond with appropriate fluid intake. Marked hypernatremia can occur if a central lesion impairs both ADH release and thirst centre, this being the typical biochemical manifestation of adipsic DI. It poses a significant challenge to manage due to an absent thirst response and the co-existence of cognitive impairment in some patients.
Case presentation
A 50-year-old, normal weight male patient, known for 5-months with post-operative panhipopituitarism after craniopharyngioma removal and diabetes insipidus, probably adipsic, is transferred to our institute from a rural hospital for evaluation and treatment of severe hypernatremia (serum sodium 159 mmol/l). He was in substitution treatment, but in the past 2 months it was interrupted by the patient. The clinical exam revealed a confused, dehydrated, tachycardic, afebril patient with increased dimension and low pulse of the calf. Head and abdominal CT scans were performed and revealed pituitary tissue debris, minimal hydrocephalus and space-replacement processes in the pulmonary arteries that raised the suspicion of lung thromboembolism. The diagnose was confirmed in a cardiology service and anticoagulant therapy was initied. After the admission, hormonal tests confirmed the panhipopituitarism. The biochemical test revealed a severe hypernatremia which was corrected during his hospitalization, but his mental status degraded showing psychomotor agitation, agressive behaviour, both verbal and pysical, being diagnosed with organic behaviour disorder.
Particularities
Craniopharyngioma was probably clinical latent congenital form since endocrine features were lacking during chilhood. The psychiatric complications that occurs

in around 11–57%, either transient or permanent, started late after the sugery, despite the literature data. Also is known that women, not men, are an independent predictor of increased cardiovascular, neurological and psyhosocial morbidity.
Conclusions
Management of DI with cognitive impairment is complex and requires a multidisciplinary approach. The majority experience morbidity (severe hypernatremia, sleep apnea, venous thromboembolism and obesity) and an increased mortality risk. Recovery from it is very rare, but the prognosis is variable.
Keywords: Craniopharyngioma, hypernatremia, behavioral disorders
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Patient compliance, mainly due to lower socioeconomic status, is the principal predictor of effective acromegaly treatment: data from a single tertiary center

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Introduction
Effective acromegaly treatment in the era of somatostatin analog therapy may initially seem easy to apply. Several factors, modifiable or not, may be involved in every patient's treatment. The aim of this study was to evaluate possible factors affecting effective acromegaly treatment.
Methods
From the original pool of 25 patients, that were diagnosed with acromegaly in our department during the last 15 years, 18 are currently being followed and were evaluated in present study, with median (range) age 65 (34–84) years and 8 (44.44%) males. Demographic characteristics were recorded and clinical, biochemical, metabolic and hormonal parameters were evaluated. Treatment outcome was evaluated from baseline IGF-1 and GH values and GH nadir after 75 gr. OGTT under current treatment.
Results
All our patients harbored pituitary adenomas with initial maximal diameter of median(range) 10 (3–35) mm. Thirteen patients underwent selective transsphenoidal pituitary surgery, two received adjuvant radiotherapy with image-guided stereotactic radiosurgery, fifteen are currently receiving somatostatin analog therapy, six are treated with dopamine agonist co-administration and two are receiving pegvisomant. Twelve patients are considered to be adequately treated based on both IGF-1 (<220 ng/ml) and GH nadir (<1 ng/ml) values, whereas six patients are still out of normal IGF-1 range. These patients had higher GH nadir values upon initial diagnosis (Spearman's rho $=0.63$, $P=0.02$), are of lower chronological age (rho $=-0.56$, $P=0.013$) and they are less compliant to periodical assessment (rho $=-0.64$, $P=0.0039$), mainly due to lower socio-economic status and less access to health insurance benefits. These patients also suffer more from arthropathy (rho $=-0.56$, $P=0.014$) and have raised triglyceride levels (rho $=-0.51$, $P=0.03$), probably as a consequence of GH excess.
Conclusions
Lower socioeconomic status of acromegaly patients is probably associated with less patient compliance and poor treatment outcomes, affecting overall quality of life and eventually survival.
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Case of Pituitary corticotropinoma - from PCOS to obvious Cushing's

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Cushing's is a challenging disease to diagnose. The diagnosis is often delayed because Cushing's is frequently masked by its overlap with more common medical problems such as diabetes, high blood pressure, obesity and polycystic ovary syndrome. Cushing's may be more common than previously thought. The patient is a 15-year-old girl who developed symptoms of hyperandrogenia about 3 years prior to her visit to the Endocrine medical research Center, Uzbekistan. The problems with the girl began with the onset of the mensis, when she was 10 years old. She had experienced rapid weight gain from 40 to 55 kg, however had grown only by 7 cm in height in 2 years, while mensis was regular. An initial endocrine evaluation revealed some acne on her face; neither moon face nor buffalo hump was noted. Her growth rate was 1.1 cm/year during this period. Then, about 6 months later, her main complaints were of weight gain, seborrhea, buffalo hump, 'dirty' and greasy skin, acne, menstrual dysfunction, in spite of this thickened skin and absence of stretch marks gave false appearance of disease. Laboratory testing showed cortisol and ACTH values were normal, testosterone level was slightly high and LH/FSH ratio was changed. A pelvic ultrasound confirmed polycystic ovaries. The clinical and laboratory tests were consistent with PCOS. Therapy with life style changes (weight reduction), metformin, oral contraceptives (OC) was started. Without OC, the menstrual cycle was absent. When she was 16, she started suffering from hypertension, hump was very clear, single striae was there. Cortisol and ACTH levels were slightly high, but electrolytes were normal. MRI investigation showed hyperplasia of pituitary gland. PJD (Pubertal Juvenile Dyspituitarism) was suspected by doctor. After one year, she subsequently developed back pain and was found an osteopenia. MRI showed- corticotropinoma of pituitary gland. ACTH, cortisol values were high. The patient was scheduled for surgery and underwent transsphenoidal resection of her pituitary microadenoma. Patient was successfully treated with surgery and achieved remission from her Cushing's disease. After surgery, she lost 8 kg, menstrual cycles were regular, concentrations of cortisol, ACTH, testosterone and electrolytes were normal. She will be monitored for recurrence the rest of her life. In conclusion, pituitary corticotropinoma in early stages of life doesn't have specific symptoms. In our case, it masked by PCOS, lately PJD. Only after 6 years we were able to diagnose Cushing's Syndrome.
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Macroprolactinoma in apoplexy associated to 23 year-old Down's syndrome

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Introduction
Pituitary adenoma has been exceptionally reported in Down's syndrome (DS). We report the case of a 23 year-old patient diagnosed with Down's syndrome, who was admitted to the Endocrinology Department for a macroprolactinoma.
Case report
A 23 year-old woman, diagnosed with DS, presented with acute headaches and diplopia. She had no history of trauma, and physical examination showed signs of damaged third and sixth cranial nerves, along with provoked galactorrhea. Hormonal workup showed elevated levels of prolactin at 104 ng/ml with low levels of gonadotropin, and the MRI showed a pituitary lesion measuring 14mm, with a necrotic center recalling a pituitary adenoma in apoplexy. The posterior pituitary hypersignal was absent. The patient was then put on 30 mg of hydrocortisone per day, with 1 mg of cabergoline per week. The follow-up showed decreasing levels of prolactin two months after her admission, the cabergoline was then discontinued
Discussion
Down's syndrome is associated with increased risk of malignancies, most of which, however, are haematological. Pituitary functions in Down's syndrome have been studied and showed no significant difference while compared to other patients. Some cases of pituitary hyperplasia in patients with Down's syndrome presenting with primary hypothyroidism have been reported.
Conclusion
We report a macroprolactinoma in 23 year-old Down's syndrome in apoplexy. It remains to confirm if an ethio-pathological link exists between Down's syndrome and pituitary neoplasia.
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Radiologic and laboratory predictors for the surgical outcome in acromegaly

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Introduction
Perioperative assessment of surgical outcome in acromegaly patients is essential due to significant persistence rate even after total adenomectomy. Grade of adenoma invasiveness and basal growth hormone (GH) level in early post-operative period have been considered as important factors.
Aim
The aim of our study was to evaluate the correlation between the outcomes of surgery in patients with acromegaly and the grade of adenoma invasion assessed by Knosp classification, and the level of postoperative 24-hour GH.
Materials and methods
Patients with GH-producing pituitary macroadenoma were included in the study. All patients underwent transsphenoidal surgery (TSS). The grade of parasellar invasiveness was assessed according to Knosp classification. A 24-hour postoperative GH level was measured in all patients. The results of TSS were evaluated 9 months after surgery. The biochemical remission of acromegaly was defined as nadir GH level on an OGTT <0.4 μg/l along with age and gender normalized values of insulin-like growth factor 1 (IGF-1).
Results
Nineteen patients (12 women and 6 men), mean age 47.0 ± 13.2 years (27–64 years) were enrolled. The data on parasellar growth by Knosp classification was the following: Knosp grade 0 was in one patient; grade 1 in five; grade 2 in three; grade 3 in seven and grade 4 in three patients. Baseline GH level and adenoma size did not differ in patients with Knosp grade 0–2 and grade 3–4. Patients with Knosp grade 0–2 had lower 24-hour postoperative GH level than patients with Knosp grade 3–4 (2.3 ± 3.1 vs 6.8 ± 6.1 μg/l, P-value $= 0.041$). Nine months after surgery, acromegaly remission was confirmed in 9/19 patients (47%). Six of 9 (66%) patients with remission had Knosp grade 0–2 and 3/9 (33%) patients with remission had Knosp grade 3–4. Seven of 9 (77%) patients with remission had 24-hour postop GH level <2.0 μg/l and 2/9 (22%) patients with level ≥ 2.0 μg/l. The remission rate had tendency to be higher in patients with 24-hour postop GH level <2.0 μg/l compared to group with Knosp grade 0–2: 7/8 (87.5%) vs 6/9 (66%), respectively, P-value $= 0.07$. All patients with Knosp grade 3–4 and 24-hour postop GH level <2.0 μg/l had remission 9 months after surgery.
Conclusion
Our data suggests that 24-hours postoperative GH level <2.0 μg/l may be a stronger predictor of acromegaly remission after TSS than the grade 0–2 of adenoma invasion assessed by Knosp classification. These findings required further evaluation.

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Acquired bilateral cortical adrenal atrophy in a middle-aged male

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Introduction
While iatrogenic Cushing's syndrome is common, acquired isolated ACTH deficiency is a rare condition. Hypophysitis is the most common cause, and while most recently published cases are associated with immunotherapy, it may also be idiopathic. Hereby we present a case of cortical adrenal atrophy secondary to idiopathic acquired ACTH deficiency, in order to raise awareness about this condition.
Material and Methods
Review of the patient's clinical record and the relevant literature.
Results
A non-smoking 49-year old man complained of progressive weakness in the last 6 months, being presently unable to climb a flight of stairs or to stand from the sitting position without arm support. He had a history of iron deficiency anaemia, B12 vitamin deficiency, sporadic use of nasal decongestant, a head trauma at the age of 15 without any known sequelae, and a lack of any significant glucocorticoid intake. He reported no personal or family history of autoimmune disease. The patient was initially assessed by a cardiologist who could not find any cardiological reason that justified the symptoms. Therefore, he was referred to the Endocrinology and Internal Medicine departments. He also complained of progressive asthenia, frequent headaches and loss of about 10% of his previous body weight. He had no sexual dysfunction and his physical examination showed no hyperpigmentation, his BP was 136/78 mmHg, HR 69 bpm, and the rest of the examination was unremarkable as well. His lab test showed normal natremia, kalemia and blood count. Free T4, TSH, LH, FSH, testosterone, aldosterone, plasma renin activity and metanephrines were normal. Plasma cortisol was undetectable, and ACTH was 2.5 pg/ml (inadequately low). Anti-adrenal and anti-hypophysis antibodies were both negative. A CT scan showed marked bilateral cortical atrophy of both adrenals, without any other abnormalities. An MRI scan of the hypophysis and hypothalamus was normal. The patient's clinical condition improved markedly with standard oral hydrocortisone substitution (30 mg per day).
Conclusions
Acquired isolated clinical deficiency of ACTH is an elusive clinical condition that can be caused by hypophysitis in the absence of glucocorticoid intake, whose origin might be related to autoimmunity. In this clinical case hypophysitis could be excluded, and therefore the most likely diagnosis would be idiopathic acquired isolated ACTH deficiency, as the head trauma he suffered may play a role in the development of this condition. We recommend follow-up with lab and imaging tests in order to find new possible deficiencies and/or abnormalities.

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Osteoporosis with Multiple Vertebral Fractures in a 61-year-old Male Revealing a Cushing Disease

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Cushing disease is a rare endocrine disorder characterised by excess production of adrenocorticotropic hormone (ACTH) from a pituitary adenoma causing an excessive stimulation of the adrenal glands resulting in hypercortisolism. Most common clinical presentation includes a combination of signs like central obesity, facial plethora,ecchymosis, purple skin striae, hirsutism, acne, muscle weakness and atrophy. Hypertension, glucose intolerance and diabetes, hypokalaemia and osteoporosis are usual consequences of persistent uncontrolled hypercortisolism. Osteoporosis is a frequent pathology in elderly subjects mostly in menopaused women. It can be primary or, less frequently, secondary to another pathology. However, in male subjects, secondary osteoporosis is more frequent. We present the case of a 61-year-old male patient primary admitted for multiple vertebral fractures (T9, T10, T12, L1, L2, L3, L4, L5) requiring cementoplasty initially thought to be post traumatic (mild fall from his height) until a new fracture appeared without any trauma. Spinal MRI showed signs of osteoporosis and bone densitometry confirmed it with a T score L2-L4 of -4,5. Clinical re-evaluation during hospitalisation found very discrete signs of hypercortisolism: relative muscle weakness and atrophy, mild facial erythrosis and few bruising on the arms and legs. BMI was strictly normal as was the blood pressure. Biological analysis revealed increased 8 am cortisol and ACTH with loss on nictemeral secretion rhythm, 24h urinary cortisol up to six times the normal rate, no suppression after 1mg dexamethasone overnight suppression test, moderate hyperprolactinemia, hypogonadotropic hypogonadism. Blood glucose and potassium were in the normal range. Pituitary MRI revealed a macro adenoma with a slight expansion towards the left cavernous sinus and extension towards the sphenoidal sinus. Trans-sphenoidal surgery was performed after a 4 weeks Ketoconazole treatment. Pathological analysis confirmed a pituitary adenoma of $17 \times 24 \times 19$ mm with an estimated Ki 67 of 15%. One month post-surgery evaluation was consistent with high afternoon and midnight cortisol rate, normalization of 24h urinary cortisol and non-suppression after 1-mg overnight dexamethasone. Therefore, hypercortisolism is one of the possible causes to look for when diagnosing a severe osteoporosis especially in a male subject.The particularity of this case is the revelation of a Cushing disease by severe osteoporotic complications, without any metabolic abnormalities and a very poor clinical presentation.
Keywords: Cushing disease, hypercortisolism, osteoporosis

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Ectopic neurohypophysis: an unusual cause of growth hormone deficiency

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Introduction
The ectopic posterior pituitary is a rare condition which is characterized by the ectopic location of posterior lobe of pituitary, pituitary stalk abnormalities, and associated clinical manifestations of anterior lobe related growth hormone dysfunction or less commonly multiple anterior pituitary dysfunctions. We describe the case of a young female who presented with short stature and was found to have ectopic posterior pituitary.
Case presentation
A 17-year-old young female presented with short stature and amenorrhea. Her siblings and parents were healthy, with normal height. An examination showed her blood pressure was 90/60 mmHg, and her height, weight, and body mass index were 147 cm, 34 kg, and 15.73 kg/m^2, respectively. She had a B5 P3 Tanner Stage. Our patient showed no signs of diabetes insipidus. Her lab investigations showed that her thyroid stimulating hormone (TSH) was 2.4 uIU/ml (0.34 to 5.6), her free thyroid hormone level FT4 was 6 pmol/l (7.9 to 14.4), her prolactin was 157 mIU/l (70 to 566), and her baseline cortisol was 153 ng/ml (60 to 184). Her insulin like growth factor IGF-1 was 84 ng/ml (247.3 to 481.7), her Estradiol level was 43 ng/dl, her follicle stimulating hormone FSH was 10.08 uIU/ml, and her leutinizing hormone LH was 6.87 uIU/ml. A clonidine Stimulation test was conducted, and growth hormone(GH) serum levels were measured at 30, 60, and 120 minutes. The results showed a GH deficiency with a peak cut-off value of 10 µg/l. Her bone age was 17 years according to the Greulich and Pyle method, as shown by X-rays. The results from her pituitary magnetic resonance imaging scan were consistent with ectopic posterior lobe of pituitary gland.
Conclusion
Despite the fact that structural malformations in hypothalamo-pituitary region are a rare disorder, it should always be kept in the differential diagnosis of a patient presenting with short stature. Patients with this disease have an excellent opportunity to reach normal height if they present before the joining of epiphyses.

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P694

New markers of systemic inflammation and oxidative macromolecular damage in partial and total Adult Growth Hormone Deficiency

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It is known that adult growth hormone deficiency (GHD) is associated with oxidative stress (OS): both GH and IGF-1 exert antioxidant functions. OS is in turn related to systemic inflammation and cardiovascular/oncological risk. Discordant data concerning GH effects on antioxidants are reported. Moreover, no data are available in partial GHD, which can induce cardiovascular alterations. To evaluate oxidative damage on macromolecules and systemic inflammation, 80 patients, studied by GHRH + arginine test were enrolled. On the basis of GH peak, they were classified as: 26 total-GHD (t-GHD) (39–70 years, BMI 31.1 ± 2.6 Kg/m^2 with peak GH < 9 ug/l or < 4 ug/l when BMI ≥ 30 kg/m^2), 25 partial-GHD (p-GHD) (24–73 years; BMI 26.9 ± 1.5, with GH peak 9–16 ug/l). Finally, 29 subjects (aged 20–73 years, BMI 25.5 ± 1.1) with GH peak > 16 ug/ml were classified as controls (ctrl). A blood sample was collected for Total Antioxidant Capacity (TAC) evaluation, by spectroscopical method, expressed as latency time of appearance of radical species using the Metmyoglobin-H_2O_2-ABTS system. In t-GHD and ctrl we also evaluated k and λ free light chains (FLCs), produced by plasmacells and related to chronic inflammation, by turbidimetric method. A morning urine sample was collected for determination, by ELISA, of: Hexanoyl-Lysine (HEL) adduct, biomarker of lipid peroxidation; dityrosine (DT), biomarker of protein oxidation; 8-OH-2-deoxy-guanosine (8–OHdG), parameter of DNA damage. Concerning urine parameters, a trend to increase in HEL in t-GHD vs p-GHD and ctrl was observed, although not significant. 8-OHdG did not significantly differ among the three groups. On the contrary, significantly lower levels of DT in p-GHD vs t-GHD and ctrl were found (mean ± S.E.M, 0.41 ± 0.10, 1.07 ± 0.19 and 0.83 ± 0.24 umol/l, respectively, $P < 0.05$). The most important results were observed in TAC, which was significantly increased in p-GHD vs controls, with further significant increment in t-GHD (52.3 ± 2.9, 43.39 ± 2.2 and 67.7 ± 3.0 sec, respectively, $P < 0.05$). Concerning FLCs, t-GHD showed levels significantly higher than ctrl (k 37.21 ± 6.97 and 12.34 ± 0.85 mg/l; λ 19.44 ± 2.61 and 11.67 ± 0.77 mg/l, respectively). Our data show an increase in antioxidants, related to GHD severity; while in p-GHD such compensation is sufficient to counteract oxidative damage, leading to low DT levels, in t-GHD, oxidative and inflammatory parameters again augmented, despite further increase of antioxidants. These data suggest a condition of antioxidant reactivity also in p-GHD, hypothesizing a condition of OS, magnified in t-GHD. If partial and total-GHD represent different phases in the natural history of this condition requires further investigations.

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P695

Severe salt wasting syndrome due to spontaneous epidural haematoma

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Hyponatraemia is commonly encountered in neurosurgical units. Salt wasting syndrome is rare, and thought to occur due to ANP- and BNP-mediated natriuresis, leading to hypovolemic hyponatraemia. A 31 year old male was transferred to the National Neurosurgical Unit with a 12 hour history of back pain, progressive lower limb weakness and sensory loss. MRI demonstrated an epidural haematoma, extending from C7 to T3, and he underwent emergency decompressive laminectomy. Vasopressin, noradrenaline and 0.9% saline were administered for spinal shock; initial plasma sodium concentration (pNa) was normal, 139 mmol/l (RR 133–145 mmol/l). Within 24 hours of admission, he became polyuric (8000 ml/24 h) and pNa dropped to 122 mmol/l, accompanied by slurred speech. 3% saline infusion was commenced, and the rate quickly up-titrated to 100 ml/hr to maintain pNa in the normal range. Further investigations confirmed a large volume natriuresis (urine output (UO) 6 liters/24 h, urine sodium 205 mmol/l, urine osmolality 614 mOsm/kg) and BNP was elevated (2483 pg/ml, RR 0-97), in keeping with a diagnosis of salt wasting syndrome. Echocardiogram was normal. Aldosterone was undetectable (< 138 pmol/l), renin 7.2 mIU/l (RR 9-103), and co-peptin 1.7 pmol/l. On day 3 of admission, vasopressin infusion was stopped, resulting in a rapid aquaresis (4500 ml), and rise in pNa of 16 mmol/l in 4 hours. 3% saline was held to allow pNa to drop to prevent over-rapid correction, and vasopressin was restarted. BNP fell to normal limits over seven days, but he remained polyuric (6–14 liters/day) and hyponatraemic (pNa 120–130 mmol/l, despite 3% saline 100–200 ml/hour). This persistent aquaresis, despite normalisation of BNP concentration suggested not only BNP-related natriuresis, but also a loss of baroregulated vasopressin secretion, so that when vasopressin was held, significant hypotonic polyuria and rapid increase in pNa occurred. Oral fludrocortisone was commenced on day 12 and oral dDAVP on day 14. UO fell to 4–6 liters/day. Subsequently, indomethacin was introduced to decrease glomerular filtration rate. Over the next three weeks, UO fell and dDAVP was weaned down to stop, UO fell to 2–3 liters/day and pNa normalised. Aldosterone and renin concentrations remained undetectable, and fludrocortisone 100mcg was continued. He was discharged to his referring hospital 10 weeks from initial presentation. This case illustrates two discrete pathophysiological mechanisms of dysnatremia post-spinal injury (a) BNP-mediated natriuresis leading to hypovolemia, with lack of compensatory action of renin-angiotensin-aldosterone system, and of (b) baroregulated vasopressin release. Targeting these physiological derangements with volume repletion, aldosterone, plus dDAVP, was required to reduce urine volume and normalise pNa.

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P696

Endoscopic transsphenoidal surgery for Cushing's disease; a single surgeon experience

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Transsphenoidal surgery (TSS) to resect a corticotroph adenoma is the first-line treatment for Cushing's disease (CD); remission rates of up to 80% have been reported in cases of microadenomas. Endocrine Society guidelines define post-operative biochemical remission as morning serum cortisol <138 nmol/L within seven days of surgery. Our practice is to use a cut-off of <50 nmol/L at day 3 post-op to indicate biochemical remission. If serum cortisol on day 3 is 50–138 nmol/L, serial measurements are taken daily to determine if cortisol will fall further, and assessment for improvement/resolution of clinical signs of hypercortisolemia made, before repeat TSS is considered. Twenty-nine endoscopic endonasal TSS were performed in 27 patients with CD between January 2012 and April 2018. Patients with previous TSS prior to the study period were excluded. Twenty-one (78%) were female, median (range) age 37 (8–75) years. Pre-operative tumour localisation was determined on MRI in 17 of 27 patients; 15 microadenoma and 2 macroadenoma (1 with cavernous sinus invasion). Twenty-five patients (93%) underwent IPSS. Postoperative remission rates for initial surgery were 85% (23/27) when Endocrine Society cut-offs were used, 83% (24/29) when all TSS were included, and 88% (22/25) in patients with microadenoma/hyperplasia. Using a stricter cut-off of day 3 cortisol <50 nmol/L, overall remission rate was 61%. Four patients (15%) had persistent hypercortisolemia after initial TSS, two proceeded to second TSS, one received radiotherapy and metyrapone, and another underwent bilateral adrenalectomy. Remission rate after second TSS was 50% (1/2); the patient with persistent disease received radiosurgery and cabergoline. There was no statistical difference in rates of remission in those patients with or without tumour target on pre-operative MRI (15/17 vs 8/10, $P=0.6$). Eleven of 27 patients (41%) undergoing initial surgery developed transient DI, and 6 (22%) permanent DI. There were no cases of CSF leak requiring lumbar drain or meningitis. Post-operatively, there were four cases of TSH deficiency, and three cases of gonadotrophin deficiency (pre-menopausal). Seven patients were treated with GH. There were no cases of recurrence of CD; six patients recovered their HPA axis, at a median (range) follow-up of 25 (19-79) months. In conclusion, our series demonstrates satisfactory remission rates post-TSS for CD when Endocrine Society criteria are used, 85%, with higher rates for microadenomas/corticotroph hyperplasia, 88%. Permanent DI was the most common complication, occurring in 1 in 5 patients. Longer follow-up is required to determine recurrence rate, which is time dependent.

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P697

Therapeutic alternatives for acth secreting aggressive pituitary adenoma–case report

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Introduction
Cushing disease is the most common cause of endogenous hypercortisolemia and most frequently is caused by microadenomas, but rarely, only in 10% to 20% of cases, the adenomas are large enough to produce mass effect.[1]
Case report
We present the case of a 63 years old female patient, diagnosed in 2007 with a 22/18 mm non-secreting pituitary adenoma and panhypopituitarism. She undergone transsphenoidal surgery twice, followed by gamma knife irradiation, resulting in progressive tumoral regression and empty sella until 2014, when a follow-up CT scan revealed a 15/13/11 mm tumoral recurrence, with rapid tumoral growth in the next couple of months to 27/24/17 mm and invasion in the adjacent structures. The third transsphenoidal surgery and the second gamma knife irradiation followed, without much tumoral mass reduction. IHC revealed and biochemistry confirmed an ACTH secreting aggressive pituitary macroadenoma (ACTH = 70.2 pg/ml, 8 am serum cortisol after 1 mg dexamethasone suppression test = 13.8 mg/dl, Ki67 = 25%). Cabergoline therapy was tried without benefit on cortisol secretion (ACTH = 211.4 pg/ml, 24-hours urinary free cortisol = 1965 nmol/24h, 24 pm salivary cortisol = 18.75 nmol/l) or tumor mass which continued progressing to 31/35/34 mm and determined complications such as right eye blindness, right eyelid ptosis and severe trigeminal neuralgia. Pasireotide therapy was initiated but discontinued due to worsening of diabetes mellitus control, even though there were beneficial effects on cortisol secretion. In 2018 temozolomide therapy was decided. The clinical, imagistic and biological follow-up showed improvement on ACTH and cortisol secretion (ACTH = 148.8 pg/ml, 8 AM serum cortisol = 6.34 ug/ml and 24- hours urinary free cortisol = 286.58 nmol/24h), improvement of trigeminal neuralgia, excellent control of the secondary diabetes mellitus and high blood pressure with minimal therapy and stable tumor mass (38/30/29 mm). After five cycles of therapy, temozolomide had to be, at least temporary, discontinued because the patient developed venous catheter related sepsis.
Conclusions
ACTH secreting aggressive pituitary adenomas are rare, but due to their aggressive behaviour and high recurrence rate after surgery and radiotherapy, must be early diagnosed, appropriately treated and followed-up. Temozolomide is an effective therapeutic agent for aggressive pituitary adenomas, that showed significant improvement on clinical and paraclinical parameters and should be used when other treatment options fail.
Bibliography
1. Gandhi, C. and Post, K. (2019). *ACTH-Secreting Adenomas*. [online] Ncbi.nlm.nih.gov. Available at: https://www.ncbi.nlm.nih.gov/books/NBK12462/ [Accessed 3 Feb. 2019].

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P698

New diagnosis of Kallmann syndrome in an adult Fugitive

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Background
Innate, isolated hypogonadotropic hypogonadism is a rare disease and results in men in cryptorchidism and failed puberty. Migration leads to diagnosis of the disease also in developed countries only in adults.
Case
A 28-year-old man was sent for endocrine workup because of failed development of primary sexual characteristics and missing secondary sex characteristics. He grew up in a rural place in Sri Lanka, his brothers and sisters developed regular puberty. On his flight out of Sri Lanka he was diagnosed in an Arabian country for hypogonadotropic hypogonadism. They did a complete workup. An MRI scan showed an anatomically normal pituitary gland and normal pituitary function tests were found, except the gonadal axis. They could not detect any LH or FSH also Testosterone was below the assay detection limit. He received for several months treatment with choriogonadotropine. Subsequently treatment was not continued. Arriving in Switzerland he was sent to our department because of discrepancy between age and his juvenile appearance. On examination we found cryptorchidism, micropenis and absence of secondary sex characteristics. Sonography confirmed the clinical finding of not developed gonads (0.5ml volume) and cryptorchidism on the left side, chronological bone age was estimated of only 14 years after Greulich and Pyle. Pituitary function was intact except gonadal axis. We found him to be hyposmic. Fulfilling the criteria of a Kallmann syndrome. We started treatment with choriogonadotropine. After a few weeks his Testosterone rose (20 nmol/l) and the patient developed a puberty including vocal break. Notably was the descensus oft his gonads and the height gain in one year (159 cm to 164 cm). Genetic Evaluation is ongoing in a scientific study, results are pending.
Discussion
In hypogonadotropic hypogonadism endocrinological workup is essential to find the right diagnosis. Kallmann syndrome is a rare genetic disease, several genetic mutations are well known. These days in western countries the syndrome is often already diagnosed during childhood or in young males because of absent pubertal characteristics. A careful induction of treatment (testosterone or choriogonadotropine) is imperative because those adult men develop puberty. Treatment needs to be started early, so patients go through a normal pubertal development and reach a normal adult height.

Conclusion
In adults with clinical suspicion pituitary function tests have to be done and a careful workup is needed to ascertain the correct diagnosis. Rare diagnosis can be found in fugitives, presenting in older age with sicknesses diagnosed normally earlier in life.

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P699

Hypogonadotropic hypogonadism in a male patient with glycogen storage disease type 1A

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Introduction
The glycogen storage disease (GSD) is a rare disorder of carbohydrate metabolism resulting from the defective synthesis and utilization of glycogen. GSD-1a is a subtype of GSD caused by a deficiency in glucose-6-phosphatase activity, which leads to decreased conversion of glucose-6-phosphate to glucose. The dominant features at presentation are hypoglycemia and lactic acidemia. Long-term complications include blood glucose lability, lactic acidemia, short stature, decreased bone mineral density, delayed puberty, hypertension, dyslipidemia and hepatic adenomas. Hypogonadotropic hypogonadism has been hypothesized as a possible complication. It may be explained by recurrent hypoglycemia in GSD patients, as the subsequent elevation in cortisol may lead to suppression of GnRH, LH and FSH. Treatment with testosterone is directed at restoring levels to normal but must always be carefully considered.
Case report
A 20-year-old male was referred to our Endocrinology outpatient clinic due to suspected hypogonadotropic hypogonadism. The patient was diagnosed with GSD-1a at the age of 9 months and referred periods of poor therapeutic compliance during late childhood and adolescence. Since the age of 14, he was followed in a Pediatric Endocrinology outpatient clinic due to the absence of secondary sexual characteristics and at the age of 20 was medicated with testosterone enantate (50 mg every 4 weeks) during 4 months. The left-hand wrist X-ray before testosterone therapy showed bone age equal to chronological age. Family target height was 173 ± 8 cm and both parents reported normal pubertal development. In the Endocrinology first appointment (1 month after testosterone suspension), the physical exam revealed height 166 cm, Tanner stage 5 pubic hair, Tanner stage 3 axillary hair, testicular volume < 4mL and absence of facial hair. Blood analysis (3 months after testosterone suspension) showed low serum testosterone concentration with low serum LH and FSH and low GH and IGF-1. The other pituitary axis hormones, ferritin and iron saturation were normal. Pituitary and head MRI was normal. He initiated testosterone undecanoate therapy (1000 mg every 12 weeks) and has current normal testosterone values.
Discussion
Distinguishing between constitutional delayed growth and puberty and hypogonadotropic hypogonadism may be difficult. In this case, the absence of spontaneous pubertal development until the age of 18, the underlying disease, having no family history of delayed puberty and the fact that the bone age is equal to chronological age may be in favor of hypogonadism. Poor therapeutic compliance during childhood and adolescence may have contributed to recurrent hypoglycemia and hyperlactatemia and consequently hypogonadotropic hypogonadism.

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P700

Severe hyponatremia caused by secondary adrenal insufficiency in a patient with central diabetes insipidus: A case report

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Introduction
Hyponatremia is a common electrolyte disturbance in clinical practice, and is considered severe when $Na+ < 125$ mEq/L. In most patients, is caused by a single cause but, in selected cases, there are multiple factors that contribute together. Drugs are a common cause of electrolytes abnormalities and a careful drug history is important especially the interaction between them.
Case report
We report the case of a 60-year-old male patient who was admitted to our hospital with clinical symptoms and laboratory findings of severe hyponatremia ($Na+$ 115 mEq/l). Medical history: He was under treatment with desmopressin for diabetes insipidus diagnosed 34 years ago. Last 6 months, he was under treatment with inhaled glucocorticoid (Fluticasone 1000 mcg/day) for asthma bronchiale. After he was improved by breathing, he stopped Fluticasone himself, without doctor's advice. After 2 months, he was getting worse by lungs, so he restarted fluticasone at the same dose. He was improved by lungs but his general condition was getting worse day by day. After 2 weeks, he presented at emergency unit for medical help. He was hospitalized and treated with concentrated NaCl intravenous and fluid restriction, simultaneously it was worked to find up the cause of hyponatremia. MRI of head revealed aspect of partial empty sellae. TSH 1,4 (0.4-4.2UI/ml), Ft4 low. Firstly, we thought for overtreatment with desmopressin, but using lower dose, he had polyuria-polydipsia and not correction of hyponatremia. Secondly, we evaluated the function of the kidneys but they were normal. Finally, adrenal suppression due to inhaled high dose of fluticasone, was suspected and the level of cortisolemia was measured at 8 a.m that resulted low. It was started treatment with Hydrocortisone 20 mg/day and it was lowered dose of Fluticasone gradually from 1000 mcg/day to 500 mcg/day. It was started also 50 mcg levothyroxine/day. The situation started to improve day by day. He got out of the hospital under endocrinologist follow-up. After 4 weeks he was in a good health and normal blood levels of electrolytes.
Conclusion
In selected cases, there are multiple factors that can cause severe hyponatremia. Drugs interaction (Fluticasone may interact with desmopressin to potentiate its antidiuretic effect), central hypothyroidism, secondary adrenal insufficiency, all together could have contributed to severe hyponatremia, our case confirms that. The physicians should beware about inhaled fluticasone, to use the lowest effective dose, and to have under control all these patients that need to use other drugs with desmopressin for electrolytes anomalies, especially severe hyponatremia as a life-threatening complication.

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P701

Acromegaly in a 29-year-old woman: restored fertility after surgery and radiosurgery

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Acromegaly is a rare condition and is frequently associated with infertility. There are very few reported cases of pregnancy in these patients, particularly after surgery and radiosurgery. This is a case of a 29-year-old woman with a 1-year history of nasal obstruction, headache and amenorrhea. She was mother of a 5-year-old child and was trying to get pregnant again, unsuccessfully. Clinical examination revealed coarsening of the facial features, hand and feet enlargement, hypoacusis and bitemporal hemianopsia. No hypertension neither hyperglycemia were documented. Blood tests showed a marked elevation of Growth Hormone (GH 418 ng/mL, reference range 0–10) and Insulin-like Growth Factor 1 (IGF-1 796 ng/mL, reference range 117–329), establishing the diagnosis of Acromegaly. The Prolactine levels were in the upper limit of normality (PRL 28.8 ng/mL, reference range 2.8–29.0), and the remainder pituitary evaluation was normal, including the CRH, LH-RH and TRH stimulation tests. Cranial magnetic resonance imaging revealed a pituitary macroadenoma with left cavernous sinus extension and optic chiasm compression. Treatment with Octreotide was started and she underwent transphenoidal adenoma partial resection 2 months later, after which ophthalmological examination got progressively normal. At this time, treatment with Levothyroxine and Hydrocortisone was initiated. Nevertheless there was still biochemical and radiological evidence of disease. The patient underwent gamma-knife radiosurgery 4 months later. After that, GH and IGF-1 levels got reduced and became completely normal after 4 years. Few months after the intervention she restored menses. Then she got 3 uneventful pregnancies, the first of them 13 months after radiosurgery, and delivered at term 3 healthy babies. Facial and extremities features became softer. Octreotide and Hydrocortisone were suspended 2 years later. After 12 years she has no evidence of disease progression and is only medicated with Levothyroxine 50 mcg per day.

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P702

Cardiovascular and metabolic comorbidities in patients with Cushing's disease at diagnosis and after long term remission

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Introduction
Cushing's disease (CD) is associated with metabolic and cardiovascular comorbidities that can be incompletely resolved after disease remission. Our objective was to evaluate the metabolic and cardiovascular status of patients with MC in remission
Patients and methods
We performed a retrospective study including 15 CD patients cured by pituitary surgery. Patient's medical records were reviewed and information regarding blood pressure and metabolic abnormalities were collected.
Results
The study included 15 patients (10 women; mean age at diagnosis of 34.2 ± 11.3 years) who met the biochemical CD remission criteria after pituitary surgery. Thirteen patients (86.7%) developed adrenal insufficiency. The median duration of glucocorticoid replacement therapy was 28 months (IQR, 12 to 72). At diagnosis, the mean body mass index (BMI) was 28.6 ± 3 kg/m^2. Hypertension was present in 12 patients with mean systolic blood pressure (SBP) of 150 ± 26 mm Hg and mean diastolic blood pressure (DBP) of 84 ± 13 mmHg. The metabolic comorbidities were: obesity (7 patients), diabetes (9 patients), hypercholesterolemia (9 patients), and hypertriglyceridemia (9 patients).The mean levels for fasting glucose (FG), total cholesterol (TC), and triglycerides (TG) were 7.67 ± 1.97 mmol/l, 6.16 ± 1.33 mmol/l, and 2.90 ± 2.12, respectively. At the early evaluation (median of 12 months after surgery), many patients had persistent comorbidities: hypertension (8 patients), obesity (4 patients), diabetes (8 patients), hypercholesterolemia (5 patients), and hypertriglyceridemia (5 patients). SBP, FG, and CT significantly decreased but not BMI, DBP, and TG. At the late evaluation (median of 41 months), hypertension was persistent only in 2 patients with significant decrease of both SBP and DBP. Obesity was present in 3 patients, diabetes in 6 patients, hypercholesterolemia in 6 patients, and hypertriglyceridemia in 7 patients. Compared with mean levels at diagnosis, there was no significant difference in FG, CT, and TG mean's levels at the late evaluation.
Conclusion
After successful surgery, the improvement of cardiovascular and metabolic comorbidities is often incomplete and patients still have increased cardiovascular risk even after long term remission. Lifelong follow-up is necessary to control these persistent comorbidities.

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P703

Change of the response to cabergoline after pregnancy in a patient with partially resistant microprolactinoma

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Prolactinoma is the most frequent pituitary tumour among women of childbearing age. Cabergoline (CAB) is the treatment of choice for most of these patients. However there remain prolactinomas completely or partially resistant to standard therapy, which is rare in microprolactinomas. We present a clinical case demonstrating a positive change of the response to treatment of partially resistant microprolactinoma. A female patient, born in 1989, initially presented with dysmenorrhea/galactorrhea at the age of 18 yrs. Elevated prolactin (PRL) level of 150 ng/ml (upper limit of normal $\leq$ 25 ng/ml) and microadenoma of 8 mm in maximal size at pituitary MRI were revealed. The diagnosis of microprolactinoma was established and CAB was initiated at 0.25 mg twice weekly. PRL was reduced but its normalization was not achieved despite stepwise titration of CAB dose up to 4.0 mg/week. PRL varied from 770 to 1294 mIU/l (upper limit of normal $\leq$ 557 mIU/l, macroprolactinemia was excluded). Maximal adenoma size increased to 10 mm. In 2011-13 she was taking 4.5-5.0-4.5 mg/week regularly, but PRL remained elevated (856-800-618 mIU/l). In December 2013 she got pregnant at dose of 4.5 mg/week. CAB was discontinued, but spontaneous abortion occurred at 8–9 weeks of pregnancy. CAB was restarted at the same dose with much more pronounced effect. Achieving of normal PRL level had made it possible to reduce the dose to 2.5 mg/week. In July 2014 she got pregnant for the second time. CAB was discontinued again. No complications during pregnancy were observed, and a healthy male infant was delivered at term in 2015. After cessation of breastfeeding moderately elevated PRL and some reduction of maximal adenoma size (to 6 mm) were registered. CAB was restarted and PRL was controlled on standard dose of 1.0 mg/week. In 2018 she became pregnant for the third time. CAB has been cancelled. The fetal growth to date is appropriate for gestational age. Only a few studies have addressed the outcome of prolactinoma after pregnancy pointing the remission (mostly of micro-prolactinomas) after delivery in some patients. This case (11 yrs of follow-up) demonstrates a better response to CAB of partially resistant microprolactinoma in a compliant patient after the first pregnancy despite its unsuccessful outcome. After miscarriage hyperprolactinemia has been controlled on standard doses of CAB resulting in restoration of fertility, subsequent pregnancies and some reduction of microadenoma size after delivery and cessation of breastfeeding.

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P704

Sex differences in presentation but not in outcome for ACTH-dependent Cushing's syndrome

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Background
Sex differences in clinical picture of ACTH-dependent Cushing's syndrome are controversial, except for the known higher prevalence in females. We compared a broad range of potential differences to enable a more accurate understanding of the clinical picture of sex-specific ACTH-dependent Cushing's syndrome.
Design
Cohort study.
Methods
We included consecutive patients with ACTH-dependent Cushing's syndrome from Leiden and Berlin diagnosed between 2000–2016, comparing clinical presentation, biochemical parameters, diagnostic tests, surgical outcome, and comorbidities between men and women.
Results
We included 130 patients: 37 males and 93 females. With similar serum cortisol levels, ACTH levels were higher in males than females at time of diagnosis (median: 116 ng/L versus 57 ng/L). The prevalence of osteoporosis was higher in males than in females (48.6% versus 25.0%), persisting after surgery, with more vertebral fractures (16.2% versus 5.4%) before surgery. Males showed more anemia (75.9% versus 36.8%) after surgery. There were no differences in etiology, pituitary tumor size, diagnostic and therapeutic strategy, or surgical outcome between sexes.
Conclusions
Based on this study, males and females with ACTH-dependent Cushing's syndrome present different clinical patterns. However, these differences do not justify different diagnostic strategies or treatment based on sex, considering the similar surgical outcome. Clinicians should be alert to diagnose accompanying osteoporosis (with fractures) and anemia in male patients with ACTH-dependent Cushing's syndrome.

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P705

Adrenal crisis in treated patients with Cushing's syndrome

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Background
Adrenal crisis, the most feared complication of adrenal insufficiency, is a potentially life-threatening situation of acute glucocorticoid deficiency. After

successful surgery, many patients with Cushing's syndrome develop (transient) adrenal insufficiency. The incidence of adrenal crisis in patients treated for hypercortisolism is unknown.
Methods
Cohort study including consecutive patients with Cushing's syndrome with adrenal insufficiency after surgery from Leiden and Berlin from 2000–2015. We summarized incidence of adrenal crisis, compared patients with and without adrenal crisis regarding potential risk factors for its occurrence, and assessed the effect of better education in time on incidence of adrenal crisis.
Results
We included 106 patients, of whom 19 had in total 41 adrenal crises. There were 9.0 crises per 100 patient-years at risk (95% confidence interval [CI]: 6.7–12.0). All crises occurred while on hydrocortisone substitution. The risk ratio for a recurrent crisis was 2.3 (95% CI: 1.2–4.6). No clear change in incidence of adrenal crisis due to better education in time was observed. There was no difference in recurrence rate between patients with and without any crisis, but patients with adrenal crisis had more complications (anterior pituitary deficiency and diabetes insipidus).
Conclusions
Previous adrenal crisis is a risk factor for recurrent crisis. However, further risk factor analysis is needed. Effective education methods to prevent adrenal crises should be identified, including nursing staff education for prevention of adrenal crises during hospital stay immediately after surgery.

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P706

Visualisation characteristic of the inactive pituitary adenoma (IPA)

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Early diagnostics it is IPA treats difficult questions of a modern neuroendocrinology as even highly informative computer tomographs and the magnetic resonant imaging (MRI) don't give the correct answer to 30–55% of cases, and at microadenomas to 90% of cases.
The purpose
Studying of structure it is IPA at MRI-research at patients with the verified diagnosis.
Material and methods
Research included 325 patients with is IPA (145 women and 180 men at the age of 18 till 70 years (44.5 ± 3.85 years). Middle age of 15–70 (43.6 ± 3.84) years. Disease duration from the moment of establishment of the diagnosis on the basis of the anamnesis and MRI-researches from 1 year to 15 years.
Results and discussion
The studied patients had adenomas with intrasellar – 74, parasellar – 41, infrasellar – 23, infraparasellar – 26, suprasellar – 14, supraparasellar – 25, suprainfrasellar – 13, suprainfraparasellar – 12, suprainfrapararetrosellar distribution – 97. At MRI – research structure it is IPA had mainly soft tissue ($n = 269$) and a cystic ($n = 56$) structure. In 55 cases structure it is IPA was it is presented by a hemorrhagic component, and at 12 from them there were both cystic and hemorrhagic components. In 271 cases the structure of a tumor was rather uniform, in 54 – non-uniform. MRI of the image of 54 patients with is IPA had a hypointensive signal on T1-and an isointensive signal on the T2-weighed images, 204 cases were hypointensive and on T1-and on the T2-weighed images, 28 tumors were hypointensive on the T1-weighed images and hyperintensive on the T2-weighed images, 11 cases were izointensivna on the T1-weighed images and hypointensive on the T2-weighed images, and 9 cases – izointensive on the T1-weighed images and hyperintensive on the T2-weighed images.
Conclusions
Thus, at MRI research the majority it is IPA had intrasellar (29.8%) and suprainfrapararetrosellar (19.7%) distribution, in 82.8% of cases — solid structure, in 7.7% – contained cystic inclusions, in 9.5% – a hemorrhagic component contained. The MR-signal from the IPA tissue is predominantly hypointensive, as on the T2-weighed images (66.2%), and T1-weighed images (88.0%). Difference on MR-images depending on the sizes and from extent of distribution it is IPA are not revealed.

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P707

A case of isolated adrenocorticotropic hormone deficiency diagnosed with ventricular fibrillation by prolonged QT interval

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Introduction
Isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) is a rare disease, which is characterized by secondary adrenal insufficiency with low cortisol production, and normal secretion of pituitary hormones other than ACTH. Although it is known that QT prolongation is sometimes observed in patients with IAD, reports on IAD in which the QT interval was sufficiently prolonged to cause Torsades de Pointes (TdP) are rare. We described the case of a patient with IAD and arrhythmia with prolongation of QT interval.
Case report
A 48-year-old woman was rushed to the hospital with fever and syncope. She had similar episodes at the age of 39 years. The electrocardiogram (ECG) showed prolongation of QT interval (QTc 0.64 sec). The ECG monitoring registered polymorphic VT (TdP); thus, she received basic life support. However, due to recurrent TdP, we performed Implantable Cardioverter Defibrillator (ICD) implantation. She initially had two ICD operations for fever, and subsequently for ventricular fibrillation. Echocardiography showed normal cardiac size and left ventricular function. In addition, she had hypotension, hyponatremia, seizure, and hypoglycemia. Therefore, we suspected adrenal insufficiency. Endocrinological examination showed low plasma ACTH (< 2.0 pg/ml) and cortisol (1.16 μg/dl). Brain computed tomography of the pituitary gland showed no remarkable findings. A combined stimulation test for corticotropin-releasing hormone (CRH), gonadotropin-releasing hormone, and thyrotropin-releasing hormone showed a poor response to CRH stimulation. The other pituitary hormones responded well to their superordinate hormones, thus, a diagnosis of IAD was made. After hydrocortisone replacement therapy, her symptoms disappeared completely, and her ECG showed improved QT interval (QTc 0.46 sec), and ICD operation was not required.
Conclusion
We believe that the adrenal insufficiency contributed to the long-QT syndrome causing TdP, because the ECG changes improved after the initiation of steroid replacement therapy. Congenital long-QT syndrome was excluded by gene mutation screening (KCNQ1, KCNQ2, and SCN5A), and by the absence of QT prolongation in her family. Although precise mechanisms of QT prolongation by glucocorticoid insufficiency are not known, it might have been associated with glucocorticoid, which is important for the maintenance of membrane calcium transport function in the cardiac sarcoplasmic reticulum, and which extends the duration of action potential by up-regulating the expression levels of various ion channels. Based on our findings, we believe that the possibility of adrenal insufficiency should be considered in patients with QT prolongation and TdP, particularly when they have unexplained hypotension, hyponatremia, and hypoglycemia.

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P708

Hypophysitis secondary to anti-pd1/pd-l1 blockade: variations in presentation, four distinct cases

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PD-1/PD-L1 pathway is a key regulator in T-cell activation and tolerance. Nivolumab, pembrolizumab (a PD-1 inhibitors) and atezolizumab (a PD-L1 inhibitor) are monoclonal antibodies approved for treatment of advanced cancers. Autoimmune thyroid diseases are the most common immune-related adverse effects (IrAEs) occurring after anti-PD-1 or anti-PD-L1 therapy, whereas autoimmune hypophysitis is described more frequently in patients treated with anti-CTLA-4. IrAEs can be isolated manifestations or more rarely occur in combination. We report 4 cases of hypophysitis secondary to anti-PD-1/PD-L1 therapy, one case with isolated ACTH deficiency, one case characterized by an autoimmune polyglandular syndrome type 2 (APS-2), one case with isolated ACTH deficiency associated with autoimmune thyroiditis, and the last one with

panhypopituitarism. Case 1 is a 60-year-old man with metastatic lung adenocarcinoma treated with atezolizumab. After the fourth dose, type 1 diabetes mellitus presented with ketoacidosis, Addison disease (AD) associated with isolated ACTH deficiency presented with severe hyponatremia. 21-hydroxylase and pituitary antibodies were found positive whereas islet cells antibodies were negative. Sellar MRI was negative for pituitary lesions. Atezolizumab was withdrawn and conventional chemotherapy was started. Tumour progression was documented on a CT scan three months later. Case 2 is a 68-year-old man with non-small cell lung cancer (NSCLC) treated with Nivolumab. After six cycles, he presented with adrenal insufficiency due to isolated ACTH deficiency; MRI showed no lesions in the hypothalamic-pituitary region. Hydrocortisone replacement therapy was started and Nivolumab was withdrawn. Tumour progression was documented at CT scan after three months. Case 3 is an 80-year-old man affected by metastatic melanoma treated with Pembrolizumab. After two cycles, he presented autoimmune hypothyroidism. Pembrolizumab was discontinued and reintroduced after four months. After 20 weeks of treatment, he was diagnosed with adrenal insufficiency secondary to isolated ACTH deficiency. MRI revealed no abnormalities in the anterior pituitary. Hydrocortisone replacement therapy was started and immunotherapy was continued. No tumour progression was documented after six months. Case 4 is a 70-year-old man with NSCLC and a secondary stalk lesion with normal anterior and posterior pituitary function. After two cycles of Nivolumab, he was diagnosed with panhypopituitarism. At sellar MRI the lesion was unmodified. Hormone replacement therapy was started and Nivolumab has withdrawn. Rapid tumour progression was documented with CT-scan 3 months later. In conclusion, although some endocrine IrAE may be life-threatening, a promt diagnosis and institution of proper hormonal replacement therapy might avoid immunotherapy withdrawal and a likely tumor progression.

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P709

Protein expression of convertases involved in POMC processing in silent and functioning corticotroph tumors

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Introduction
Previous results of our group, presented in the ECE last year, showed a lower gene expression of proconvertase PC1/3, involved in the processing of *POMC*, in silent corticotroph tumors (sCT) than in functioning ones (fCT), overall and in microadenomas. The aim of the present study was to quantify the protein expression of convertases involved in the processing of *POMC* (PC1/3) and in the degradation of ACTH (PC2, CPE and PAM) in a series of CT.
Methods
We selected 15 sCT, 15 fCT and 14 silent gonadotroph tumors (sGT) (control group). Previously, the gene expression of these convertases was quantified by quantitative PCR. The quantification of protein expression was carried out by Western Blot.
Results
Similar to gene expression studies, sCT showed lower PC1/3 protein expression than fCT ($P=0.078$), especially than fCT microadenomas ($P=0.028$). Moreover, we observed a strong positive correlation between PC2 and CPE gene and protein expression ($\rho \geq 0.670$, $P<0.009$) in sCT but a lack of correlation in the case of PC1/3.
Conclusion
The difference in PC1/3 expression between sCT and fCT remains at the proteins level. This low gene and protein PC1/3 expressions and the efficient post-transcriptional processing of PC2 and CPE in sCT compared with fCT could explain the lack of Cushing symptomatology in sCT. Moreover, we confirmed that the macro CT represent an intermediate state between silent and micro fCT.
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P710

Lymphocytic hypophysitis with disturbance of both anterior and posterior pituitary function preceded by headache, diagnosed as meningitis

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Introduction
Lymphocytic hypophysitis (LH) is a heterogeneous inflammatory condition in the pituitary gland, which may cause hormonal deficiency. However, some patients with LH initially present with headache.
Case
A 63-year-old woman complained of a severe headache for 1 month. Examination of cerebrospinal fluid (CSF) showed increased lymphocyte counts, indicating meningitis. Contrast-enhanced magnetic resonance imaging (MRI) revealed an expanding sellar mass with homogeneous enhancement. One month later, MRI showed enlargement of the pituitary mass and formation of a cyst within the mass; however, the patient's headache had recovered naturally. Seven months later, the patient exhibited loss of appetite and malaise. Cortisol was significantly lowered (ACTH 3.0 pg/ml, cortisol 1.59 μg/dl); therefore, hydrocortisone therapy (15 mg) was initiated. MRI showed a thickening pituitary stalk with a mass, but no cystic lesion in the sellar mass. The patient's physical condition improved, but she developed polyuria. Water deprivation test confirmed central diabetes insipidus (DI), due to increased urinary excretion (approximately 6 l/day), low specific urinary density (<300 mOsm/l), increased serum sodium (147 mEq/l), increased osmolality (298 mOsm/l), and no change in AVP (0.5 pg/ml). Thus, DI was revealed after steroid therapy, which diagnosed masked DI. Anterior pituitary function was assessed through exogenous administration of releasing hormones and peptide (TRH, CRH, LH-RH, and GHRP); it was disturbed (baseline GH 0.27 ng/ml, stimulated 5.55 ng/ml; IGF1 30 ng/ml; baseline LH <0.10 U/l, stimulated <0.10 U/l; baseline FSH 0.28 U/l, stimulated 0.88 U/l; baseline ACTH <0.20 pg/ml, stimulated 21.7 pg/ml; baseline TSH 0.047 μIU/ml, stimulated 0.237 μIU/ml). MRI indicated shrinkage of the thickened pituitary stalk and accompanying mass. Thus, replacement therapy was initiated: levothyroxine, GH injection, and desmopressin, combined with hydrocortisone. Differential diagnosis included sarcoidosis, IgG4-related disease, and malignant tumors. Chest radiography and examination of IgG4 and angiotensin I-converting enzyme were normal. Changes in the pituitary lesion on MRI were not typical of malignant tumors. Therefore, we diagnosed this patient with LH. In this patient, meningitis preceded LH. However these two diseases might exhibit a casual relationship, CSF findings might be influenced by LH. There is the possibility that meningitis might be a symptom of LH.
Conclusion
We encountered a patient who exhibited LH with disturbance of both anterior and posterior pituitary functions. In this patient, meningitis preceded and might have been a symptom of LH.

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P711

Whole genome demethylation status of somatic DNA extracted from different pituitary adenoma types

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Background
Although the role of hypermethylation of certain tumor suppressor genes are known in pituitary adenomas little information is available regarding whole methylation-demethylation status and especially regarding its correlation with clinical parameters. High-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) is an easy and accurate method to detect the level of methylcytosine (5 mC) and the demethylation intermedier hydroxymethylcytosine (5 hmC) too.

Material and methods
Overall, 44 fresh frozen pituitary adenoma tissues (29 gonadotroph, 12 somatotroph, 3 corticotroph). were collected and categorized according to the 2017 WHO classification After DNA extraction cytosine (C)%, 5mC% and 5 hmC% and (5 hmC/5 mC)*100) ratios were determined by HPLC-MS/MS system. Results were correlated with clinicopathological parameters.
Results
Higher level of 5hmC% and 5hmC%/5mC% ratio was confirmed in hormone-negative (HN) HN-SF1+ and HN-Tpit+ groups compared to FSH/LH+ and GH secreting adenomas. Significant difference between HN-SF1+ gonadotroph and FSH/LH+ gonadotroph adenomas was found but there was no alteration between HN-SF1+ and HN-Tpit+ tumors. In samples with higher proliferative index (Ki-67>4% vs 1–2% or 3–4%) significantly lower 5 hmC% and 5hmC%/5mC% were detected regardless of tumor type ($P=0.009$). However, after dissecting histological groups this phenomenon was most characteristic of GH+ and HN adenomas and it was absent in FSH/LH+ adenomas (by two-way ANOVA both Ki-67 and histological group factors reached significance levels ($P=0.003$ and $P=0.029$, respectively)).
Conclusion
5hmC% and 5hmC/5mC ratio indicating demethylation status can be reliably detected by HPLC-MS-MS method in somatic DNA extracted from pituitary adenomas. HN adenomas show increased demethylation compared to FSH/LH+ and GH+ adenomas independently from their transcription factor status. Adenomas with higher Ki-67 indexes exhibit gradually lower demethylation. 5 hmC/5 mC ratio may be used as prognostic tissue biomarker but these data need to be further investigated on higher sample set.

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P712

Does silent pituitary neuroendocrine tumors show lower specific adenohypophyseal gene hormone expression than functioning ones?

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Introduction
Pituitary Neuroendocrine Tumor (PitNET) subtypes present functioning and silent variants but the silencing mechanisms are still unknown. One of the possible hypotheses could be a decrease in the expression of the specific adenohypophyseal hormone genes. The aim of the present study was to analyze the expression of adenohypophyseal hormone genes in a series of PitNETs, in order to evaluate differences between functioning and silent PitNET subtypes, taking into account demographic and radiological variables such as age, gender, tumor size and invasiveness.
Material and methods
Molecular analysis was performed on 268 tumor samples. The different PitNET subtypes were identified according to their immunohistochemical profile. We quantified the gene expression of *POMC, AVPR1B, CRHR1, GH1, PRL, TSH, FSH* and *LHB* by quantitative real-time-PCR (qRT-PCR). The data were expressed as mean and standard deviation (SD) of the Fold Change (FC). Qualitative variables were expressed as relative frequencies. T-Student, Mann-Whitney and Chi-squared tests were used to analyze the differences between functioning and silent tumors.
Results
268 PitNETs (161 (60.1%) silent), were analyzed. Sixty percent of the patients were women, 95.5% were over the age of 25 (mean age and SD at diagnosis 49.74±15.37 years), 89.61% of the tumors were macroadenomas and 56.3% were invasive. Silent somatotropinomas and silent lactotropinomas showed lower expression of *GH* and *PRL* genes than their functioning variants ($P<0.001$ and $P=0.023$ respectively). Unusual silent plurihormonal PitNETs showed lower expression of *POMC* and *AVPR1B* (all $P<0.05$) and higher FSH expression than their functioning variant ($P=0.001$). Mixed silent somatotropinomas presented less expression of GH ($P<0.001$) but not of *PRL* genes ($P=0.33$) than mixed functioning ones. There were no statistically significant differences in the expression of *POMC*, *AVPR1B* and *CRHR1* between functioning and silent corticotropinomas (all $P>0.05$). In the global series there were statistically significant differences between functioning and silent tumors according to gender, with a high frequency of men having silent tumors ($P=0.007$). The mean age was higher in silent than in functioning tumors (54.71 vs 42.25 years; $P<0.001$). Finally, silent PitNETs showed higher frequency of macroadenomas ($P<0.001$) and invasiveness ($P<0.001$) than functioning ones.
Conclusions
A lower expression of adenohypophyseal hormone genes could contribute to the silencing mechanisms of some subtypes of PitNETs. Silent tumors are bigger than functioning ones, more prevalent in men, and more invasive.

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P713

Characterizing the microenvironment of pituitary neuroendocrine tumours, new approaches and tools to explore the function and contribution of folliculostellate cells

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Background
Tumour microenvironment (TME) can comprise >50% of the tumour mass and includes non-tumour cells like immune cells and fibroblasts, as well as extracellular matrix, signaling molecules, and blood and lymph vessels. In recent years, TME has begun to be considered both a prognostic tool and a therapeutic target. While the existence of TME is well accepted and described in numerous cancers, little is known about the TME of pituitary neuroendocrine tumours (PitNETs). Recent work highlighted the existence of tumour infiltrating lymphocytes and tumour-associated macrophages within PitNETs. Interestingly, besides the above-mentioned populations, folliculostellate cells (FSCs), which are resident cells of the normal anterior pituitary, are also found in PitNETs' TME.
Hypothesis
Besides the role FSCs have in the normal anterior pituitary, their identification in PitNETs suggests they may have a major implication in these tumours. Therefore, better characterizing PitNET-associated FSCs and understanding their contribution and their functional interactions with tumour cells and tumour-associated stroma may provide important indications regarding the mechanisms that drive tumourigenesis-associated processes.
Materials and methods
Exploration of the histological characteristics of gonadotroph and somatotroph PitNETs through the use of immunostainings of paraffin-embedded tumours, followed by whole slide scanning and automated imaging analysis using a software that allows for single-cell characterization, coupled with the exploration of the cellular properties of PitNETs' TME through the use of derived FSC cultures from human gonadotroph and somatotroph PitNETs. Correlation of this data with matching histopathological and clinical data.
Results
Single-cell analysis of immunostainings of paraffin-embedded PitNETs is feasible and allows for the quantification and mapping of cells, and for the identification of the clustering of FSCs with other cells. Also, the isolation of PitNET-derived cell lines that have FSC characteristics is feasible from both gonadotroph and somatotroph tumours. Our preliminary analysis highlighted differences between gonadotroph and somatotroph PitNETs, but also intra-tumour heterogeneity concerning the FSCs.
Perspectives
This kind of combined approach will allow us to better characterize FSCs and their heterogeneity in PitNETs. In the future, by deepening these insights and by better understanding the biology of FSCs within the TME, the field will be one step closer to the potential discovery of new diagnostic and prognostic markers and of new and/or personalized treatments.

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P714

Low arginine vasopressin levels in patients with central diabetes insipidus is not associated with anaemia

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Background
Arginine vasopressin (AVP) is released upon osmotic stimulation or hypovolemia in order to maintain water balance. A recent study showed a role of AVP in haematopoiesis by stimulating red blood cell precursors, suggesting a higher risk of anaemia in patientis with AVP deficiency. The aim of this study was to explore the effect of low AVP levels in patients with central diabetes insipidus (cDI) and primary polydipsia (PP) on haemoglobin and the prevalence of anaemia.
Methods
We analysed data of 164 patients with either cDI (70, 43%) or PP (94, 57%) and of 30 healthy volunteers collected in the context of two prospective diagnostic studies. In all participants, a standardized work-up was performed including assessment of medical history, drugs, clinical parameters and laboratory values including copeptin, haemoglobin and haematocrit. Anaemia was defined according to WHO criteria as haemoglobin values of <120 g/l in women and <130 g/l in men.
Results
Patients with cDI (61% female, mean age: 46 years) were older than patients with PP (69% female, mean age: 36 years) and healthy volunteers (57% female, mean age: 31 years), $P<0.001$. Basal meancopeptin values were lower in patients with cDI (2.63 pmol/l ($\pm$1.08)) than with PP (13.91 pmol/l ($\pm$42.76)) and healthy volunteers (24.76 pmol/l ($\pm$57.49)), $P=0.02$. The prevalence of anaemia was low in all participants, *n* (%): 5 (7.1), 2 (2.2) and 3 (10) in cDI, PP and in healthy volunteers, $P=0.15$. Mean haemoglobin values were similar in all groups: 139 g/l ($\pm$15.85), 140 g/l ($\pm$13.16) and 139 g/l ($\pm$13.05) in patients with cDI, PP and healthy volunteers, respectively, $P=0.90$, as were mean haematocrit values with 0.41% in all three groups ($P=0.85$).
Conclusion
Chronically low AVP levels in patients with cDI and PP do not to affect haemoglobin levels and prevelance of anaemia in a stable situation.

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P715

Silent somatotroph tumors

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Introduction
Silent somatotroph tumors (sST) are a pituitary neuroendocrine tumor subtype with positive immunostaining for growth hormone (GH) but without the presence of acromegaly. Unlike silent corticotroph tumors, there is little information in the literature on sST. The aim of the present study was to study the demographic, clinical and molecular characteristics in a series of ST in order to compare sST and functioning ST (fST).
Methods
We have studied 72 ST. Immunohistochemically 62 fST and 10 sST have been identified. The immunohistochemistry was performed with the anti-GH polyclonal antibody of Novocastra and the quantification of GH and PRL gene expression was carried out by quantitative PCR with TaqMan probes. The following variables were evaluated: gene expression of GH and PRL, gender, age, maximum tumor diameter, ki67, pre-surgical IGF1 and invasiveness.
Results
fST showed higher gene expression of GH and PRL ($P<0.001$, $P=0.032$, respectively) and higher levels of pre-surgical IGF1 ($P<0.001$). On the other hand, sST presented higher maximum tumor diameter ($P=0.010$). No differences were found between fST and sST according to gender, age, ki67 and invasiveness (all $P>0.05$).
Conclusion
fST express more GH and PRL than sST and presented higher levels of pre-surgical IGF1. By definition, there are changes in tumor diameter since all sST are macroadenomas. On the contrary, there are no differences in the invasiveness behavior. Age and gender do not contribute to the functionality of this subtype.

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P716

Giant prolactinoma: a case with thirty-five years of follow-up

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Introduction
Giant prolactinomas are rare pituitary tumours, more frequently found in men (9:1), defined by an unusually large size (>4 cm), significant extrasellar extension and prolactin levels above 1000 ng/ml. Although dopamine agonists (DA) are the first-line treatment, combined therapy with DA and surgery, or rarely radiotherapy, may be necessary particularly when tumour volume control is not achieved.
Case presentation
A 60-year-old woman, was referred to our Endocrinology department (March 2016) due to a prolactinoma. The diagnosis had been made in another institution, at patient age 25, because of amenorrhea, galactorrhoea and headaches. At age 20 she had had a full-term pregnancy and two voluntary miscarriages between 20 and 25-year-old. She has a medical history of hypertension, dyslipidaemia, depression and obesity (submitted to gastric bypass surgery). Her family history was unremarkable. When diagnosed with prolactinoma, bromocriptine was prescribed, latter switched to cabergoline in unknown dosages. She had a poor compliance to treatment and was lost for follow-up between 2008–2016. In March 2016, due to change of city of residency, her new general practitioner referred to us and she reported a progressively visual impairment. CT scan revealed a large pituitary mass ($31\times25\times47$ mm), with infra and suprasellar growth, invading sphenoid and cavernous sinuses and compressing optic chiasm. Laboratory evaluation revealed hyperprolactinemia (7010 µg/l; normal range: 5–23 µg/l) and FSH/LH deficiency. Bitemporal hemianopsia was confirmed by visual campimetry. Bromocriptine was titrated up to 30 mg/day and subsequently changed to cabergoline (3 mg/week) due to persistently high prolactin levels and lack of tumour size reduction. After 3 months of cabergoline, prolactin remained high (3804 ng/mL) and MRI showed a tumor size of 31×48 mm. She underwent transsphenoidal surgery in November 2016 with no visual improvement. Histopathological examination revealed a prolactin adenoma without cytological atypia or mitotic figures, negative p53 immunoreactivity and Ki67 index <2%. The patient missed several appointments and keeps postponing surgical reintervention.She is currently medicated with cabergoline 3 mg/week, maintaining high level of prolactin (1749 ng/mL) and persistence of intrasellar tumour ($21\times20\times20$ mm) with optic chiasm compression.
Conclusion
In this case, the poor patient compliance could have been responsible for clinical outcome. Histopathological features of the tumour did not anticipate an aggressive behaviour and immunostaining analysis of quantitative expression of dopamine receptors could have been elucidative of inefficacy of medical therapy. In the future, radiotherapy may be considered if uncontrolled tumour progression occurs after additional surgical debulking.

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P717

Glycogenosis and hypofisis pathology, importance of a multidisciplinary management

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Introduction
Glycogenosis is a group of hereditary diseases affecting the glycogen metabolism, due to mutations in enzymes involved in the transformation and synthesis of glucose (liver and muscle glycogenosis). Brain germ tumors are very infrequent. They are located mainly in pineal and sellar region. Central diabetes insipidus is the most frequent manifestation. Their prognosis and response to combined chemo/radiotherapy treatment are favorable.
Case report
16-year-old woman referred from pediatrics to follow-up a panhypopituitarism and diabetes insipidus secondary to brain germinoma treated with chemotherapy and radiotherapy, in 2012. Personal history: cavernous angioma in pale nucleus followed up by neurology and oncology and admission in 2014 due to decompensation of glycogenosis (pending to be filied). She received treatment with: Levothyroxine 200 mcg/day, Hydrocortisone 20 mg/day and Ursodeoxycholic acid 300 mg/12h. Physical examination: weight: 57 kg, blood pressure 97/67 mmHg, non-painful hepatomegaly. She presented primary amenorrhea and abdominal ultrasound showed an atrophic uterus, linear endometrium with preserved tubes and atrophic ovaries. The gynecologist advised gonadal function restoration if not contraindicated other way. She was also referred to the Metabolopathy Unit where they requested a genetic study, densitometry and advised against hormone replacement therapy to reestablish sexual function. Blood tests: Glycemia 96 mg/dl, Creatinine 0.32 mg/dl, Na 142 mEq/L, K 3.99 mEq/L, normal lipid profile, calcium 9.69 mg/dl, plasma osmolarity 329 mOsmol/kg, TSH 10.3 µUI/ml, T4L 0.4 ng/ml, FSH 1.3 mUI/ml, LH 0.46 mUI/ml, Prolactin 11.5 ng/ml, Estradiol $<$11.8 pg/ml, Cortisol basal 0.5 ng/ml, ACTH 16 pg/ml, GH 0.03 ng/ml, IGF-1 $<$25 ng/ml, urine osmolarity 212 mOsmol/kg. She had polydpisia-polyuria, and recognice correct therapeutic compliance so we requested a malabsorption study and Levothyroxine absorption test with 200 g during a week (day 1: TSH 7.38 µUI/ml, T4L 0.5 ng/ml and day 7: TSH 1.5 µUI/ml, T4L 1.06 ng/ml). We confirmed hormonal imbalance due to poor adherence to treatment. We adjusted treatment: Levothyroxine 150 µg/day and Desmopressin flash 120 µg/day (according to diuresis). Supplementary tests included: densitometry (normal), pituitary MRI (no tumor remnants with empty sella) and analytical (TSH 0.01 µUI/ml, T4L 1.8 ng/ml, normal ions and lipid profile, GH 0.02 ng/ml, IGF-1 $<$25 ng/ml). We started treatment with 0.4 mg/day growth hormone, titrating doses according to IGF-1 levels, up to the current dose of 0.6 mg/day), but persisting without restoration of the gonadal axis (due to its contraindication in glycogenoses). In the last medical visit, the patient presented good general condition, without hypoglycaemia, good therapeutic compliance and nutritional recommendations. Genetic study still pending. In these cases, the multidisciplinary approach of the patient is important for an adequate diagnostic-therapeutic orientation.

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P718

A rare case of a TSH/GH secreting pituitary macroadenoma

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Introduction
Thyrotropin (TSH) secreting pituitary adenomas (TSHomas) are very rare and account for less than 2% of all pituitary adenomas. They present with elevated levels of fT4 and normal to high levels of TSH. About 25% of TSHomas co-secrete other anterior pituitary hormones. Growth hormone (GH) is the most commonly co-secreted hormone, followed by prolactin (PRL) and gonadotropins. Herein, we report a case of pituitary adenoma with simultaneous secretion of TSH and GH.
Case presentation
A 58 year-old man, with complete atrioventricular block, was assessed for thyroid function and was found thyrotoxic [fT4: 38.4 (12.0–22.0 pmol/l)] with inappropriately normal levels of TSH [TSH: 3.51 (0.27–4.20 mIU/l)]. He was not in any medication affecting thyroid function or thyroid hormone tests. He was started on methimazole, underwent implantation of a heart pacemaker and then referred to our department. The patient showed no clinical signs of hyperthyroidism. MRI imaging revealed a macroadenoma with suprasellar extension, in contact with the optic chiasm but with unaffected visual fields. Further assessment of pituitary function was diagnostic of growth hormone (GH) hypersecretion: abnormal GH suppression on a 75 g oral glucose tolerance test (OGTT) (nadir GH = 2.11 ng/ml) with increased IGF-1 levels (524 ng/ml; age and sex specific reference range 71–350). Corticotroph and gonadotroph pituitary reserve was normal. Further workup, following discontinuation of thyreostatic drugs, confirmed the diagnosis of TSHoma: increased a-subunit and blunted TSH response to TRH. Patient was diagnosed with TSH/GH co-secreting pituitary macroadenoma and was set to treatment with a somatostatin receptor analogue (SSA, Sandostatin LAR 30 mg/28 days) that rendered him euthyroid but failed to normalize IGF-1 after 6 months of follow up. Thus, he was referred for neurosurgical evaluation and under-went transsphenoidal resection of the adenoma. Histopathology showed tumor cells with abundant cytoplasmic positivity for GH and TSH on immunohistochemical staining. After surgery, thyroid hormone and IGF-1 levels were normalized and GH was normally suppressed on OGTT. Patient is now on complete biochemical remission, 10 months post-operatively.
Discussion
TSHoma is a rare pituitary tumor and GH co-secretion renders our case even more unusual. These tumors usually lack prominent clinical manifestations. An SSA managed to promptly control TSH hypersecretion, but not GH even after prolonged use. Complete biochemical remission was finally achieved with pituitary surgery.

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P719

Control of hyperglycemia in a young male patient with gigantism during transition: a case report

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Introduction
In acromegaly GH excess leads to impaired insulin sensitivity with an alteration of beta-cell function. The consequent hyperglycemia leads to a further increased cardiovascular risk and mortality.
Case report
A 16 years old patient was first referred to the Department of Pediatrics in 2014 with accentuated growth since the age of 10. The reason of the first referral was a sport injury (head trauma during playing basketball). Sella MRI depicted hypophysis macroadenoma and a concomitant severe hyperglycemia was found therefore human conservative intensified insulin therapy (ICT) was initiated. The diabetes could be insufficiently controlled and ceased only after hypophysis surgery. Residual tumor was diagnosed and consequent recurrent GH and IGF-1 elevation occurred followed by gamma-knife radiosurgery and repeated transsphenoidal hypophysis operation. After the second operation first generation somatostatin analogue (SSA) lanreotide treatment was initiated. After the second surgery hyperglycemia was treated with metformin initiated at the age of 18. After two years the patient was referred to adult endocrinology department with severe hyperglycemia (HgA1c: 12%), high GH and IGF-1 levels and a 5 mm microadenoma remnant. As during the earlier ICT recurring episodes of hypoglycemia were present leading to a decline in quality of life our patient rejected introduction of ICT regime. Trying to control hyperglycemia first a triple combination of metformin, sitagliptin and dapagliflozin was tested, which failed to control the symptoms, as he was admitted with severe recurrent hyperglycemia. Within a month thoroughful reeducation and administration of fixed injectable combination of degludec insulin and GLP1 analogue liraglutide led to a better control of hyperglycemia accompanied by a significant improvement in quality of life. Meanwhile Glutamic Acid Decarboxylase Autoantibodies (GADA) were found to be elevated with high level of C peptide, suggesting that the patient has a mixed type of diabetes mellitus.
Conclusion
hyperglycemia is a consequence of insulin resistance and a relative insulin deficit in acromegaly. Pharmacological therapy of acromegaly can alter glucose homeostasis. First generation SSAs reduce pancreatic insulin and glucagon secretion. In a rare case of mixed diabetes an ultra-long acting insulin analogue combined with a long acting GLP-1 analogue and metformin can result in sufficient glucose control with an improved quality of life.

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P720

Central diabetes insipidus revealing Langerhans cell histiocytosis

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Introduction
Langerhans cell histiocytosis (LCH) is a rare disease that occurs mainly in childhood. In its multifocal form, the central nervous system may be affected, but rarely as the primary site of the disease. The prevalence of central diabetes insipidus (CDI) ranges from 10% to 50% and in most cases is established after the diagnosis of LCH. We report 2 cases of CDI that revealed a LCH.
Observations
Case 1: A one-year old male patient was admitted for polyuropolydypsic syndrome with a fever evolving in the long course. The water restriction test was positive with a positive response to Desmopressin. The diagnosis of CDI was retained. Hypothalamic-pituitary MRI showed thickening of the pituitary stalk. In addition, the child had hepatosplenomegaly and rash on clinical examination, cytolysis with hepatic cholestasis, and bicytopenia on biology.The liver biopsy showed sclerosing cholangitis with presence of histiocytic cells and positive PS 100. The BRAF mutation search is underway. The diagnosis of LCH in its multi-systemic form was retained. The patient was prescribed with Desmopressin substitution and underwent chemotherapy protocol with good progress. Case 2: A two-year old female patient was admitted for polyuropolydypsic syndrome evolving since 2 months. The examination on admission was without anomalies. The water restriction test was stopped after 8 hours because of a weight loss of 5% and a serum level of natremia of 146 mmol/l. The Minirin test was positive. The diagnosis of CDI was therefore retained. Cerebral MRI showed extensive enlargement and contrast enhancement of the pituitary stalk, absence of the spontaneous hypersignal of the post-pituitary and presence of an osteolytic lesion of the left occipital cranial vault. Bone scintigraphy showed bifocal bone involvement of the occiput and left scapula. The histological diagnosis of LCH has been confirmed. The child was prescribed with nasal Despopressine. The chemotherapy was not proposed in the absence of other locations.
Discussion
CDI may be the first manifestation even before LCH diagnosis. The endocrine system may be affected by LCH because Langerhans cells can migrate to the lymph nodes and affect the hypothalamic-pituitary axis. This can lead essentially to an irreversible CDI. CDI is more common in patients with BRAFV600E.

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P721

Endocrine manifestations during Langerhans cell histiocytosis

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Introduction
Langerhans cell histiocytosis (LCH) is a rare disease characterized by non-specific granulomatous deposits in many tissues. The hypothalamic-pituitary region is infiltrated in 5 to 50% of patients with LCH but most often in those with the multifocal form. Diabetes insipidus (DI), the most common hormonal abnormality, occurs in 15–50% of patients. Anterior pituitary deficiency occurs only in 5 to 20% of patients. We report the case of a patient with LCH who has dissociated anterior pituitary deficiency.
Observation
A one-year old male patient was admitted for polyuropolydypsic syndrome with a long-term fever. The water restriction test was positive with a positive response to Desmopressin. The diagnosis of central DI was therefore retained. Pituitary MRI showed thickening of the pituitary stalk. In addition, the child had hepatosplenomegaly and rash on clinical examination, cytolysis with hepatic cholestasis, and bicytopenia on biology. The liver biopsy showed showed sclerosing cholangitis with presence of histiocytic cells and PS 100 positive. The diagnosis of LCH in its multi-systemic form was therefore retained. The patient received a chemotherapy regimen and Desmopressin substitution. The evolution was marked by an improvement in hepatic and hematologic manifestations but the patient exhibited a break in the growth curve during monitoring with persistent hyponatremia despite the dose adjustment of Desmopressin. The hormonal assessment showed a collapsed IGF1 level, a low cortisolemia and a low ACTH. The diagnosis of a somatotropic and corticotropic deficiency was therefore retained and the patient was put on hormone replacement therapy.
Discussion
ACTH deficiency is usually present in panhypopituitarism and rarely as an isolated deficiency. The incidence of ACTH deficiency in patients with LCH ranges from 30% to 50%. GH deficiency may precede the onset of all other endocrine deficiencies or may occur after radiotherapy treatment. Gonadotropin deficiency was the second most common pituitary hormone deficiency. A moderate disconnection hyperprolactinemia can be seen. Thyroid status is usually normal.
Conclusion
Anterior pituitary deficiency should be considered in all patients with LCH who require therefore close follow-up and appropriate substitution treatment.

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P722

Growth hormone therapy in Noonan syndrome

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Introduction
Short stature is a common manifestation of Noonan Syndrome (NS) that affects up to 70% of patients with this syndrome. We present 2 observations of NS associated with growth hormone (GH) deficiency.
Observations
Case 1: A 7-year-old female patient was admitted for a growth delay (height at −4 SD and weight at -1 SD). On examination, she had a dysmorphic syndrome suggestive of NS: triangular face, hypertelorism, low-implanted ears, a webbed neck, an enlarged thorax, and small hands with deep palmar folds. The ophthalmological examination was without abnormalities. Cardiac ultrasound was normal. The karyotype returned normal. The causal mutation has not been identified. Dynamic tests confirmed a partial GH deficiency. Pituitary MRI was normal. The patient was put on GH replacement therapy at the age of 8 years with a dose of 0.04 mg/kg/day with an improved velocity growth and a gain of +1 SD in height after 2 years of treatment. The dose was increased to 0.05 mg/kg/day. She has not yet started puberty. Case 2: A 5-year-old female patient was admitted for a stature delay (height at −3 SD and weight at −2 SD). On examination, she had a dysmorphic syndrome suggestive of NS: a triangular face with curly hair, hypertelorism and low implanted ears. The ophthalmological examination was without abnormalities. Cardiac ultrasound was normal. The karyotype returned normal. The causal mutation has not been identified. Dynamic tests confirmed a complete GH deficiency. Pituitary MRI was normal. The patient was put on GH replacement therapy at the age of 6 years with the dose of 0.045 mg/kg/day with improvement of velocity growth and a gain of +2 SD in height after 2 years of treatment.
Discussion
Possible mechanisms of short stature in NS include GH deficiency, neurosecretory dysfunction, and GH resistance. The PTPN11 mutation had IGF-1 levels similar to those without the PTPN11 mutation, as was the case for our 2 patients who had a normal karyotype. Early initiation and long-term GH treatment were associated with improvement in final height, whereas sex, GH dose and clinical severity did not show a significant association with final height. The delayed initiation of treatment could therefore explain the poor outcome of treatment in the first patient.

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P723

Elevated Chromogranin A levels in a patient with acromegaly – who is the culprit?

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Background
Chromogranin A (CgA) belongs to the family of granins, proteins which are an integral part of the secretory granules of neuroendocrine cells in endocrine glands and the diffuse neuroendocrine system. While it has become standard clinical practice to measure serum CgA in neuroendocrine tumors, various other non-endocrine conditions may increase this marker's concentration and lead to diagnostic problems.
Case report
We present the case of a 57-year-old female patient who was diagnosed with acromegaly based on the typical clinical, hormonal, and imagistic criteria in 2007. She underwent surgery, radiation therapy, and medical therapy with a

somatostatin analog until the disease was finally controlled in 2012. She also presented with an important co-morbidity – rheumatoid arthritis. During an annual follow-up for acromegaly, she presented with skin flushing, and purplish-red skin lesions on the neck and cheeks, which raised the suspicion of carcinoid syndrome. This was disproved by normal serotonin and 5-HIAA levels, but the patient's CgA level was, by contrast, twice the normal. This prompted us to screen for MEN 1 syndrome, but the diagnosis was refuted by normal calcium, iPTH, and prolactin levels, and a normal abdominal CT scan. We looked for other common causes of high CgA, but the patient had no history of proton pump inhibitor therapy, gastric disorders, or heart disease, and her kidney function was normal. Of great importance was the dermatologic evaluation, which concluded that the patient's skin lesions were highly suggestive of cutaneous lupus erythemathosus. Since her underlying rheumatic condition was severe, with a DAS-28-ESR score of 5.8, and generalized manifestations of the disease, including pulmonary fibrosis, rheumatoid nodules, and secondary osteoporosis, the patient was referred to a rheumatology clinic for further investigations and treatment.

Conclusions

Although CgA is a useful tool in the evaluation of neuroendocrine tumors, there are several other causes of potentially false positive results, the majority of which are related to proton pump inhibitor therapy, impaired renal function, and autoimmune gastritis. Rheumatic diseases, such as rheumatoid arthritis and lupus erythemathosus, are rarer causes of elevated CgA. The reason for this, while still partially unknown, is presumed to be the generalized inflammation, suggested by the correlation between CgA and tumor necrosis factor-α levels. It was also observed that CgA levels are unusually elevated in patients with generalized manifestations of rheumatoid diseases, which was also the situation of our patient.

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P724

The influence of acromegaly treatment on subclinical left ventricular dysfunction assessed by two-dimensional speckle tracking echocardiography (2D-STE)-preliminary results

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Introduction

Cardiac disease called acromegalic cardiomyopathy may be present in patients with acromegaly at diagnosis, however most echocardiographic studies showed that systolic function, measured by ejection fraction (EF), in these patients is normal. Speckle tracking echocardiography (STE) is a novel method that allows for the study of global longitudinal strain (GLS), a marker of early and subclinical left ventricular (LV) systolic dysfunction. Some studies show subclinical systolic dysfunction in the untreated acromegalic patients. It cannot be ruled out that the LV function measured with GLS improves as an effect of acromegaly treatment.

Objective

To assess the effect of acromegaly treatment on left ventricular GLS in patients with normal EF.

Patients and methods

Twenty consecutive patients (mean age 49 ± 14 years) with naïve acromegaly admitted to our department in 2018 were enrolled in the prospective study. The patients were preoperatively treated with somatostatin analogs (lanreotide autogel or octrotide LAR) while awaiting for pituitary surgery. All patients with normal systolic LV function measured by ejection fraction (EF) underwent 2D-STE at baseline and after 3, 6 months of medical treatment and 3 months after pituitary surgery.

Results

The median GH was increased at baseline [in ug/l, 5.06 (IQR: 0.6–69.3)] and decreased significantly after 3 and 6 months of somatostatin analog treatment and after surgery [in ug/l 1.29 (IQR: 0.05–34.9), 1.24 (IQR: 0.1–20.9), 0.31 (IQR: 0.05–4.92), $P<0.05$, respectively]. The mean IGF-1 level was increased at baseline (in xULN, 2.89 ± 1.06) and decreased significantly after 3 and 6 months of somatostatin analog treatment and 3 months after surgery (in xULN, 1.54 ± 0.92; 1.86 ± 1.24; 1.47 ± 0.86, $P<0.05$, respectively). The mean GLS in patients with acromegaly at baseline was below the normal range (in%, -18.74 ± 2.64) and increased 3, 6 months after somatostatin analog treatment and 3 months after surgery (in%, -19.38 ± 2.76; -19.21 ± 2.88; -20.88 ± 1.75, respectively), although statistical significance ($P<0.05$) was reached only between GLS at baseline and GLS measured in patients 3 months after pituitary surgery. There was no statistical significant correlation between baseline GLS and GH or IGF-1 concentrations.

Conclusions

Untreated acromegalic patients presented with subclinical systolic dysfunction expressed by decreased GLS. Systolic LV function improves as an effect of acromegaly treatment, particularly after pituitary surgery along with the decrease of GH and IGF-1 concentrations. The effective medical and surgical treatment of acromegaly may be responsible for prevention of development an overt cardiac insufficiency in acromegalic patients.

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P725

Remission rate of acromegaly after somatostatin analogs withdrawal: an update

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Objective

Several studies reported that a long-time therapy with somatostatin analogs (SSTa) in acromegaly could induce persistent remission event after drug withdrawal. The aim of this study was to evaluate GH/IGF-I secretion after SSTa discontinuation in a series of acromegalic patients.

Materials and methods

Data of 21 patients regularly referred to our Centre and previously included in a multicentre study, have been updated at the last available follow up. We then extended the analysis to other 7 acromegalic patients selected for SSTa withdrawal from 2008 and 2018. We retrospectively analysed all biochemical data prior and after SSTa withdrawal, including the last follow up available. Drug suspension was suggested after sustained reduction of IGF1 levels towards the lower limit of normal range concomitant with a progressive reduction of the SSTa therapy. Previous irradiation was considered as an exclusion criteria.

Results

We analysed data of 28 patients, mean age 51 ± 14 years, 9 (32%) males, 9 (32%) de novo and 19 (68%) previously operated. After SSTa withdrawal, 23 (82%) patients had a disease relapse after a mean time of 10.9 ± 11.1 months (median 6 months). After a mean time of 9 ± 4 years (median 10 years) from drug withdrawal, 5 (18%) patients are still on remission. In the long term remission group, 2 (7%) patients had been described in the first multicentre study and are still in remission since 12 and 13 years respectively, the remaining 3 (11%) patients are in remission since 10, 9 and 2 years respectively. Overall, the mean duration of treatment before withdrawal was 5 ± 3 years. In a subgroup of 4 (14%) patients who needed to restart therapy, a second trial of withdrawal was possible, but it failed again. We did not observe any difference between patients with and without relapse, in terms of mean dosage, mean time of treatment, GH and IGF1 levels before drug suspension.

Conclusions

our data challenge the previously held concept that medical therapy is always a lifelong requirement and suggest that a successful withdrawal of SSTa is possible, at least in a subset of acromegalic patients.

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P726

Detection of pituitary adenoma specific circulating tumour DNA using semiconductor sequencing

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Objective

The most common type of pituitary diseases are pituitary adenomas (PA) of different origin. Although non-metastasizing, they still cause increased mortality

and morbidity. Clinically significant PAs affect around 0.1% of population during lifetime. Circulating cell free DNA (ccfDNA) is approximately 165 bp long DNA fragments which are released in bloodstream upon cell death. ccfDNA has been used to investigate presence and properties of various cancers. Data on ccfDNA detection of adenoma of any type and localization is sparse in current literature. The primary objective of this study was to explore usability of semiconductor sequencing and CAST-PCR for detection of ccfDNA in PA using two different molecular methods.
Design
Tissue samples from adenoma of different origin of ten PA patients were screened for *GNAS* R201C mutation. The three positive samples were used in CAST-PCR to detect mutation in the ccfDNA. Five of the ten PA patients had exomes of germline DNA and adenoma tissue somatic DNA sequenced. Somatic mutations discovered in the exome of adenoma were also used in detection of ccfDNA.
Methods
Blood samples were collected from patients before resection of PA. Plasma, obtained by double centrifugation, were frozen within 2h after sampling. After resection, tissue samples were stored in RNAlaterSolution. ccfDNA, germline DNA and somatic DNA was extracted using QIAamp Circulating Nucleic Acid Kit, chloroform-phenol method and AllPrep DNA/RNA Mini Kit, respectively. Presence of *GNAS* R201C in somatic DNA was confirmed using Sanger sequencing. CAST-PCR was performed on somatic DNA and ccfDNA from positive samples, using TaqMan® Mutation Detection Assay GNASc.601C>T/ and real-time PCR. NGS Libraries were prepared with Ion Plus Fragment Library Kit. Sequences were aligned to GRCh37 using BWA. Each patient provided informed consent. Study has been approved by Central Medical Ethics Committee of Latvia (No. 22.03.07/A7, 01.29.1/28).
Results
Sixteen amplicons containing somatic mutation from five PA patients were sequenced (average coverage 6191X). Five mutations from two patients were found in approximately 50% of sequencing reads. Alternate alleles of somatic mutations located in *MPRIP* and *RYR1* genes were detected at 3.7% and 2.3% levels, respectively. These mutations were not detected in germline DNA. Nine mutations were not detected in ccfDNA above level of technological error. CAST-PCR of *GNAS* R201C in plasma ccfDNA yielded negative results.
Conclusions
For the first time we demonstrate possibility to detect somatic mutations found in ccfDNA from PA patients. Whether source of mutation containing ccfDNA is PA should be studied further.

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P727

Is idiopathic mild hyperprolactinemia a cardiovascular risk factor?

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Aim
In our study, we aimed at investigating cardiovascular risk predictability by conducting arterial stiffness measurement in patients with idiopathic hyperprolactinemia.
Material – Method
The biochemical parameters and arterial stiffness analyses of 54 patients with idiopathic hyperprolactinemia, who had applied to our polyclinic in 2017 and 2018, and 55 healthy volunteers having similar characteristics with regard to age, sex and body mass index.
Findings
The median prolactin level of the idiopathic hyperprolactinemia patients with a median age of 31 was found 45 ng/mL. The periphery and central blood pressures and pulse wave velocities (PWV) of both the patient group and the control group were found similar. Any relations between prolactin levels and blood pressure and arterial stiffness could not be found.
Conclusion
Our study showed that arterial stiffness did not increase in young patients with idiopathic mild hyperprolactinemia. However, the long-term effects of this mildly elevated prolactin are not known. Prospective randomized studies are required, that could reveal more clearly the prolactin-cardiovascular risk relation, and the clinical effects of extra-pituitary hyperprolactinemia.

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P728

Acromegaly in McCune-Albright Syndrome: case report

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Introduction
McCune-Albright syndrome (MAS) consists of at least two of the following three conditions: polyostotic fibrous dysplasia (PFD), *café-au-lait* skin pigmentation and autonomous endocrine hyperfunction. The most common form of autonomous endocrine hyperfunction is precocious puberty, but other syndromes may be present, including acromegaly, hyperthyroidism, and Cushing syndrome. Acromegaly is seen in approximately 20% of patients with MAS. Treatment options are medical, surgical and radiotherapy, but surgical treatment is difficult because of fibrous thickening of the skull floor.
Case report
A 33-year-old man, black race, natural of Guinea-Bissau, living in Portugal since the age of 30. Referred to Rheumatology outpatient clinic in July of 2016 with the history of deformity of the lower limbs, hip pain in the right and staggering gait, since de age of 14, and worsening progressively. No pathological history, without reference to precocious puberty and no usual medication. No family history. After physical examination and radiography exams made the diagnosis of PFD. Requested the collaboration of Endocrinology by analytical alterations: GH 12 ug/L (<1) and IGF1 428 ng/ml (115–307). Placed the hypothesis of MAC with acromegaly. Physical exam: stature 158 cm, weight 68 Kg (BMI 27.2 Kg/m^2), no endocrinopathy stigmas. Imaging study: pituitary MR 'fibrous dysplasia polyostotic facial skull with extensive facial mass changes. Presence of left lateral pituitary adenoma with 8 mm height'; GH at the OGTT 11 ng/mL. Acromegaly was diagnosed. Genetic test shows somatic mutation in the GNAS1 gene – variant c.601C that confirms the MAS diagnostic with acromegaly. Due to widespread bone involvement in the cranium and facial skull surgical treatment was not planned. Octreotide LAR therapy was started with 20 mg every 4 weeks, and after 4 months GH decreased to 5.1 ng/mL and IGF1 to 253 ng/mL. The patient is still under monitoring by our clinic, with no symptoms of disease having relapsed.
Conclusion
Medical treatment is considered the first line in patients with acromegaly associated with the McCune-Albright syndrome. Somatostatin analogues improve GH/IGF1 levels in most patients although remission has been only achieved in 30% of patients. The malignancy of fibrous dysplasia is very low and occurs in a small percentage of patients, possibly due to irradiation of bone lesions. Pituitary therapeutic irradiation should therefore be avoided in these patients and diagnostic irradiation should be kept to a minimum. The follow-up of comorbidities associated with acromegaly in the McCune-Albright syndrome is similar to that of patients with classical acromegaly.

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P729

Muscle dysfunction is associated with poor quality of life in patients with Cushing's syndrome long-term after remission

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Background
Residual morbidity in patients with Cushing's syndrome (CS) in remission significantly affects Quality of Life (QoL). While sustained muscle weakness is a frequent complaint in these patients, the impact of muscle dysfunction on their psychophysical wellbeing is currently unknown. Patients & methods: We included 28 female patients [mean(±SD) age, 50±12 years; mean (±SD) BMI, 26.7±3.8] and 26 age- and BMI-matched healthy controls. Mean (±SD) duration of remission was 132±87 months and mean (±SD) delay to diagnosis was 32±23 months. QoL was assessed using both generic (SF36) and disease-specific (CushingQoL) questionnaires. Muscle function was assessed using the following tests: gait speed velocity (GS), timed up and go (TUG), walk 3 meters,

30-second chair stand and hand grip strength measured by a manual dynamometer in both hands.
Results
The mean (±SD) CushingQoL total score was 58±19. GS was associated with both total score and several specific items on CushingQoL, including sleep, pain, mood, self confidence, body appearance, social functioning, and daily activity ($P<0.01$). GS was also associated with several items of the SF36 (physical functioning, general health, vitality, social functioning, role emotion and mental health) in patients but not in controls; $P<0.01$. In patients, hand grip strength and performance on 30-second chair stand were associated with physical functioning, role physical and body pain on SF36; $P<0.01$. Duration of TUG was negatively associated with physical functioning, role physical and body pain on SF36 in patients only. Duration of TUG was also associated with body pain and social functioning of CushingQoL; $P<0.01$. Longer duration of remission was negatively associated with both 30-second chair stand and physical functioning on SF36 ($P<0.05$). In a multiple linear regression model, GS velocity predicted the CushingQoL total score, independent of age and length of remission (ß 0.65, $P<0.001$). Duration of TUG negatively predicted social activities on CushingQoL, regardless of age and length of remission (ß -0.41, $P=0.031$).
Conclusions
Muscle dysfunction is associated with impaired quality of life in patients with Cushing's syndrome in remission.

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P730

Trial-in-progress: A multicenter, dose-titration, open-label phase 2b study of nevanimibe hydrochloride, A novel ACAT1 inhibitor, for the treatment of classic congenital adrenal hyperplasia

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More than 90% of classic congenital adrenal hyperplasia (CAH) patients have defects in the cytochrome P450 enzyme steroid 21-hydroxylase, resulting in the inability to produce cortisol as well as the overproduction of androgens and androgen precursors such as 17-hydroxyprogesterone (17-OHP). Management of classic CAH can be challenging since patients are often unable to adequately balance the supraphysiologic doses of exogenous glucocorticoids required to suppress excess androgen production while avoiding the iatrogenic side effects of high-dose glucocorticoids. Nevanimibe hydrochloride, also known as ATR-101, is a novel, orally-administered adrenal-specific acyl-CoA:cholesterol acyltransferase-1 (ACAT1) inhibitor. Nevanimibe inhibits adrenal steroidogenesis by decreasing cholesteryl esters, the substrate required for steroid synthesis. This inhibition of adrenocortical steroidogenesis at an early step suppresses steroid production across all pathways (i.e., mineralocorticoid, glucocorticoid and androgens), resulting in improved control of hyperandrogenemia. In a previous Phase 2 study in patients with classic CAH and elevated 17-OHP levels (NCT02804178), nevanimibe decreased 17-OHP levels within 2 weeks of treatment. Millendo Therapeutics is now conducting a Phase 2b study to evaluate the efficacy and safety of nevanimibe in treating patients with classic CAH over a longer time period (NCT03669549). At approximately 12 sites in the EU, Israel, and Brazil, 20–24 adult patients with classic CAH will be treated with nevanimibe at doses of 1000-2000 mg twice per day for 12 weeks. There are two patient cohorts: (1) patients with elevated 17-OHP and (2) patients with controlled levels of 17-OHP but requiring supraphysiologic dosing of glucocorticoids. During the screening period, patients who are on a high glucocorticoid dose and have suppressed 17-OHP levels may undergo a reduction in their supraphysiologic glucocorticoid dose to allow their 17-OHP levels to increase to $>$ 4x the upper limit of normal (ULN). All eligible patients will be started on nevanimibe 1000 mg BID, and nevanimibe doses will be titrated based on 17-OHP levels. The primary efficacy endpoint is the proportion of patients who are able to achieve a reduction of 17-OHP to $\leq$ 2x ULN. Safety endpoints include the incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs), as well as values and changes from baseline in clinical laboratory tests, vital signs, physical examinations, and electrocardiogram parameters. Nevanimibe, an adrenal-specific ACAT1 inhibitor, presents a novel therapeutic approach to the treatment of classic CAH that may allow patients to more easily achieve balance between replacement glucocorticoid doses and control of hyperandrogenemia.

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P731

Therapeutic decisions in acromegaly according to disease control in patients with acromegaly with or without prior treatment: data from baseline analysis of the SAGIT® validation study

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Background
The SAGIT® instrument, designed to assist clinicians in staging and managing acromegaly, is undergoing validation. A descriptive analysis of SAGIT Validation study baseline data revealed discrepancies between investigator-evaluated disease-control status, disease activity, hormonal control, and treatment decisions in acromegaly.
Objective
To describe the baseline characteristics of patients in the SAGIT® validation study.
Methods
Patients with acromegaly were enrolled in a 2-yr prospective non-interventional study in 9 countries (NCT02539927). Investigators determined acromegaly control status at baseline (clinical global evaluation of disease control [CGE-DC]). The study aimed to recruit evaluable controlled and non-controlled patients ($n=82$ per group). Data collection included: demographic and baseline disease characteristics; medical/surgical histories; concomitant acromegaly treatments; investigators' evaluation of clinical activity of the disease; growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels; and investigators' therapeutic decision (preferred intention: continue current treatment[s] with no change/no treatment initiation; intensify current treatment[s]/initiate a treatment; decrease the current treatment[s]; other). Patients were considered naïve to treatment if they had no previous pituitary surgery, radiotherapy, or medications for acromegaly.
Results
Of 228 patients enrolled, CGE-DC status was controlled in 110 (48.2%), not controlled in 105 (46.1%), and yet to be clarified in 13 (5.7%). All CGE-DC controlled patients had received prior treatment, while 31 patients were treatment naïve (not controlled, $n=29$; yet to be clarified, $n=2$). Investigators considered 48.2% patients in the controlled and 95.2% in the not controlled subgroups to have clinically active disease. In the controlled subgroup, 29.7% of patients did not exhibit hormonal control (GH $\leq$2.5 µg/L; normalized IGF-1) and 47.3% did not have strict hormonal control (GH $<$1.0 µg/L; normalized IGF-1). In the CGE-DC not controlled group, these proportions were 93.1% and 98.0%, respectively. In the CGE-DC controlled group, acromegaly treatment was continued with no change in 91.8%, intensified/initiated in 2.7%, and decreased in 5.5%. In the not controlled group, treatment was continued with no change in 40.0%, intensified/initiated in 58.1%, and 'other' for 1.9%.
Conclusion
These real-world findings suggest that opportunities to take active therapeutic decisions in patients with acromegaly may be missed, including in a number of patients with not controlled disease for whom no treatment change was made. Although there may be multifaceted reasons for lack of action, better tools to assist clinical decision making may make a difference for patients.

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P732

Assessing clinical meaningfulness of quality of life (qol) change in patients with Cushing's disease: calculation of minimal important difference estimates for the cushingqol using anchor and distribution-based approaches

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Purpose
Patients with Cushing's disease (CD) experience a wide range of physical and psychosocial health impacts. This can have a profound effect on patient's quality of life (QOL), impairing areas such as body image, personal relationships and work performance. The CushingQoL is a valid and reliable disease-specific

patient-reported outcome (PRO). When using a PRO in an interventional context it is critical to understand whether reported change is clinically meaningful. This study aims to derive estimates of the minimal important difference (MID) for the CushingQoL.
Methods
Anchor-based methods explore the association between change on a PRO and a related variable that identifies patients with an important change in their condition (the anchor). An improvement in CushingQoL score >10.1 has previously been estimated as an initial threshold for a clinically meaningful change, based on a distribution based method (using 0.5 SD) for defining the MID. This study will use data from SOM230G2304 to calculated anchor and distribution-based MID estimates and compare these to available estimates. SOM230G2304 is a Pasireotide LAR, phase III, randomized, double-blind, multicenter, study evaluating the efficacy and safety of two Pasireotide LAR regimens in patients (≥ 18 years old) with CD ($n=148$).
Results
The appropriateness of potential anchor variables was investigated (moderate correlation ($r>0.4<0.7$) as criterion). The following anchors met this criterion: SF12v2 Physical components scale used for CushingQoL total and psychosocial issues, SF12v2 Mental components scale used for CushingQoL total and psychosocial issues. A triangulation approach was used to discuss the estimates provided by both this anchor-based approach and distribution-based approaches.
Conclusions
This is the first known evaluation using clinical trial data to determine anchor-based MID values for the CushingQoL. The implications of these MID values for research and clinical practice are discussed along with guidance on best practice for evaluating the clinical meaningfulness of change scores on PROs.

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P733

Moderate hyponatremia at discharge is associated with increased risk of recurrence in patients with community-acquired pneumonia

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Background
Hyponatremia is the most common electrolyte disorder in hospitalized patients with pneumonia. Different studies have shown an association of admission hyponatremia and worse in-hospital outcome, but no data are available about the impact of hyponatremia at discharge on outcome.
Material and methods
Data from a double-blind randomized study including 725 patients hospitalized with community-acquired pneumonia were analyzed. The primary aim of the original study was to compare time to clinical stability upon prednisone treatment as compared to placebo. The aim of this subanalysis was to compare patient-relevant outcomes (i.e. mortality, rehospitalization and recurrence rate) within 180 days in patients with hyponatremia at discharge and normonatremic patients.
Results
Of the 725 patients, 187 (25.8%) were hyponatremic on admission. Of these, 159 (85%) normalized during the hospitalization and 28 (14.9%) were still hyponatremic at discharge. 34 patients developed hyponatremia during hospitalization despite being initially normonatremic. Of these, 17 (50%) were still hyponatremic at discharge. In total, at discharge, 45 (6.2%) patients were hyponatremic and 663 (91.4%) normonatremic. Patients with hyponatremia at discharge had a higher risk of recurrence of pneumonia compared to normonatremic patients at discharge (OR 2.68; 95% CI 1.09-6.95; $P=0.037$), independently from prednisone treatment (adjusted OR 2.9; 95% CI 1.03-6.96; $P=0.027$). In contrast, recurrence rate was not affected in patients who were hyponatremic during hospitalization but had normal sodium levels at discharge ($P=0.99$). There was no association hyponatremia at discharge and mortality or rehospitalization ($P>0.05$), but the number of events was low.
Conclusions
Hyponatremia at discharge is associated with an increased risk of recurrence in hospitalized patients with pneumonia, independently from in-hospital sodium levels and prednisone treatment.

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P734

A phase 2 study assessing osilodrostat in children and adolescent patients with Cushing's disease – Rationale and methods

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Background
In children, Cushing's disease (CD) presents with a combination of weight gain and slowed linear growth. First-line pituitary surgery is the treatment of choice for most patients. In paediatric patients, the transsphenoidal surgical success rate is 60%–98% when performed by an expert pituitary surgeon. There is a need for additional pharmacological interventions to control hypercortisolaemia, which are currently limited, in children and adolescents. In phase 2 and 3 trials in adult patients with CD, treatment with osilodrostat, an oral 11β-hydroxylase inhibitor, was effective and was generally well tolerated. The present phase 2, multicenter, open label, non-comparative study aims to evaluate the pharmacokinetics (PK), pharmacodynamics, safety/tolerability of osilodrostat in patients aged 6–<18 years with CD (NCT03708900).
Methods
Patients aged 6–<18 years with confirmed CD for whom pituitary surgery is not an option, for whom surgery has failed, or who are awaiting surgery are eligible for enrolment. The target enrolment is 12 patients. CD will be confirmed by the clinical criteria of decreasing growth percentiles with increasing weight (defined by height standard deviation score [SDS] <0, body mass index SDS >0 and a strong clinical suspicion of CD), an abnormal low-dose dexamethasone suppression test, measurable morning adrenocorticotrophic hormone levels and two 24-hour urinary free cortisol (UFC) measurements $>1.3\times$ULN (upper limit of normal). The study comprises a 4-week screening period, a 12-week core phase and an optional 9-month extension period for patients who obtain clinical benefit from osilodrostat as judged by the investigator. The starting dose of osilodrostat will be 1 mg once daily and 1 mg twice daily, for patients weighing 30-60 kg and ≥ 60 kg, respectively. The dose will then be titrated based on mean UFC (mUFC) and body weight. The primary objective is to assess the PK of osilodrostat. The primary endpoint is to evaluate the PK parameters (C_{max} and C_{trough}) up to week 12 core study. Secondary endpoints include the proportion of patients with normal mUFC (two 24-hour UFC samples) at weeks 6 and 12, change in mUFC during week 12, safety/tolerability up to week 12 of the core phase and month 12 of the extension phase and assessment of efficacy up to month 12.
Conclusion
This phase 2 study will be the first study of osilodrostat in children and adolescent patients with CD. The findings from this multicentre, open-label, non-comparative study may allow further clinical development of osilodrostat in this population.

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P735

The changing face of cushing disease in the 21st century: mood disorders and body image perception

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Introduction
Cushing's Disease (CD) has been associated with the occurrence of psychopathologies, the most frequent of which are depression and anxiety. However, the extent of psychopathological disturbances of CD in the 21st century is elusive.
Objectives
To explore psychopathologies and body image uneasiness (BIU) in untreated CD patients.
Patients & methods
It was a prospective observational study enrolling 23 consecutive naïve CD and 23 matched subjects with a non-functioning pituitary adenoma (NF), used as

controls. All subjects underwent a psychiatric evaluation and psychological questionnaires to explore the occurrence of psychopathologies (SCL-90R), mood (POMS, BDI-II), anxiety (SAS, STAI-2Y), body image uneasiness (BUT), and QoL (SF-36). Four CD have been preliminarily excluded due to a treated psychiatric disorder ($n=2$) or to a lack of reliability of surveys replies. Psychological inventories were evaluated as continuous as well as categorical variables according to the questionnaires interpretation rules. We used group comparison to differentiate between CD and NF and association analysis to examine the relationship between clinical and biochemical features of CD and psychological results.
Results
CD patients had higher scores than NF in almost all psychological scales. Similarly, when subjects were categorized according to the distress degree emerged from the questionnaires, we observed a generalized tendency toward the higher score classes in the CD cohort for the majority of the domains. However, when patients were grouped on the basis of the achievement of the pathological thresholds indicated by questionnaires, CD differed from controls only for the somatization and obsessive-compulsive subscales of SCL-90R and the anger subscale of POMS. CD and NF did not differ for the presence of pathological depressive and anxiety symptoms. Likewise, the psychiatric evaluation did not show differences between CD and NF for the prevalence of depression (9 vs. 0%) and anxiety (4 vs. 0%). Naïve CD showed a profound disturbance in BIU that was mainly related to body areas that change following CD (i.e., face, abdomen, and skin). Sex, age, BMI, the educational level, and the severity of CD did not have a role in the occurrence of psychopathologies and BIU of CD.
Conclusions
Untreated CD patients had overall distress in all assessed psychopathological domains compared to NF. However, the analysis of symptoms severity suggests that the psychopathological impairment of the CD remains subclinical in most cases. A disturbance of the body image characterizes CD patients and can contribute to the occurrence of psychopathologies and the reduced QoL of CD.

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P736

Prevalence of silent acromegaly in prolactinomas (PASP): an Italian experience

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Patients with prolactinomas may develop acromegaly during D2-agonists (DA), suggesting the existence of somatomammotroph adenomas with asynchronous secretion of GH and PRL. This may be due to the acquisition of somatotroph characteristics by lactotroph cells or to GH co-secretion by somatommammotroph cells unmasked after PRL inhibition by DA. The prevalence of silent acromegaly in prolactinomas during DA is 4.1%. The purpose of this study was to evaluate the somatotroph axis in a large series of patients with prolactinomas on DA. N 144 patients were enrolled in an Italian multicenter study (8 centers) [43 ± 12.5 year, 93F/64.6%, macroadenomas 50/34.7%]. Ninety patients [43.6 ± 13.0 year; 58 F/64.4%, macroadenomas 33/36.7%] were on DA and enrolled in a Cross-Sectional arm (CS), with a single PRL, GH and IGF1 determination after at least 3 months of treatment, whereas 54 untreated patients [42.3 ± 11.8 year; 35 F/64.8%, macroadenomas 17/31.5%] were enrolled at diagnosis in a Prospective arm (PR), PRL, GH and IGF1 being measured before and after 6 and 12 months of treatment. In the presence of high IGF1, DA was withdrawan for 3 months and basal GH, IGF1, PRL as well as GH during oGTT were measured. As expected, PRL was lower in CS ($P < 0.007$). High IGF1 (ULN 1.01-1.56) was found in 9 patients (6.25%, 5F; 4 CS and 5 PR). In CS, high IGF1 was observed after 5–144 months of therapy. In PR, IGF1 increased after 6 months of therapy. After DA withdrawal, IGF1 returned to normality in 6/9 patients, abnormal GH secretion was excluded through oGTT in 7/9 cases (GH nadir 0.1–0.3 ng/ml). In one patient oGTT was unavailable, but basal GH was < 0.4 ng/ml. One patient had slightly elevated IGF1(1.01 ULN) and no GH inhibition during oGTT on DA. Re-evaluation on DA treatment was performed in 7/9 cases. In one patient, IGF1 was mildly elevated (1.2 ULN) but GH hypersecretion was excluded at oGTT. In 5 patients IGF1 normalized. The patient showing no GH inhibition during oGTT on DA was re-tested with similar results: she underwent neurosurgery with pathological diagnosis of GH/PRL adenoma.
Conclusions
High IGF1 may be encountered in prolactinomas during DA. Drug withdrawal determines IGF1 normalization in most cases. Such alteration may be due to the stimulatory effect of DA on normal somatotroph cells, or may reflect assay variability. Rarely, persisting high IGF1 may reveal silent acromegaly. oGTT appears to reliably distinguish between both conditions.

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P737

A multicentre, randomized, open-label, Phase IV study investigating management of pasireotide-associated hyperglycaemia with incretin-based therapy or insulin in patients with acromegaly or Cushing's disease (CD)

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Background
Pasireotide has proven efficacy in acromegaly and CD, although pasireotide-associated hyperglycaemia occurs in some patients. This Phase IV, randomized, open-label study investigated optimal management of pasireotide-associated hyperglycaemia uncontrolled by metformin/oral antidiabetic therapy (OAD) [NCT02060383].
Methods
Adults with acromegaly or CD were enrolled and treated with long-acting pasireotide 40 mg/28 days or subcutaneous pasireotide 600 µg bid, respectively. Patients with increased fasting plasma glucose (≥ 126 mg/dl on three consecutive days) in the first 16 weeks that continued despite metformin/OAD were randomized 1:1 to incretin-based therapy (sitagliptin followed by liraglutide; rescue therapy: insulin) or insulin for another 16 weeks. Primary objective: assess incretin-based therapy versus insulin for glycaemic control at end of randomized period. Secondary objectives: assess glycaemic control, sustainability of glycaemic control, and safety in both treatment arms.
Results
249 patients were enrolled (acromegaly, $n=190$; CD, $n=59$), 103 (41%) did not require OAD, 46 (19%) were managed on OAD, 19 (8%) had prior insulin; 81 (33%) were randomized to incretin-based therapy ($n=38$) or insulin ($n=43$). Twenty-four (63%) patients receiving incretin-based therapy and 29 (67%) receiving insulin had diabetes at baseline (not receiving insulin). Median (range) months of exposure to pasireotide: acromegaly, 5.5 (3.7–8.0); CD, 4.1 (1.9–6.8); exposure was similar between treatment arms. With incretin-based therapy, rescue therapy (addition of insulin to existing medication) was administered in 12/38 (32%) patients for a median (range) duration of 1.8 (0.5–3.7) months. Estimated difference in adjusted mean change in HbA_{1c} between treatment arms at end of study was –0.28% (95% CI –0.63, 0.08) in favour of incretin-based therapy: acromegaly, –0.36% (95% CI –0.74, 0.02); CD, –0.01% (95% CI –0.96, 0.95). Mean change in HbA_{1c} from baseline to end of study was –0.12% (95% CI –0.36, 0.13) and 0.26% (95% CI –0.01, 0.53) with incretin-based therapy and insulin, respectively. Adverse events (AEs) were reported in 36 (95%) patients receiving incretin-based therapy and 35 (81%) receiving insulin, most commonly hyperglycaemia (incretin-based therapy, $n=11$ [29%]; insulin, $n=8$ [19%]); grade 3/4 AEs were recorded in 14 (37%) and six (14%) patients and serious AEs observed in four (11%) and one (2%) patient. Three (8%) patients discontinued treatment because of AEs (all on incretin-based therapy).
Conclusion
Antidiabetic medication is not required in many patients treated with pasireotide. For patients in whom hyperglycaemia occurs, metformin/OAD is an effective first-line treatment. For hyperglycaemia uncontrolled by metformin/OAD, incretin-based therapies are an effective treatment option.

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P738

Hemangiopericytoma mimicking a pituitary adenoma: a case report

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Introduction
The differential diagnosis of sellar masses is broad and includes - apart from the most common pituitary adenomas - other neoplasms such as craniopharyngiomas, germinomas, gliomas, meningiomas, and others. Hemangiopericytoma (HPC) is a rare vascular tumor arising from pericytes that may appear at any site of the body. We report an unusual case of an intrasellar HPC.
Case Report
A 63-year-old woman was admitted to our hospital complaining about headaches for twelve, frequently occurring orthostatic dizziness for six and progressive visual field defects for two months. Kinetic perimetry confirmed bitemporal hemianopia, and magnetic resonance imaging (MRI) revealed a sellar mass (27 mm) which compromised the optic chiasm. The sellar mass appeared homogenous, hyperintense on T2-weighted and isointense compared to brain parenchyma on T1-weighted MRI. On admission, pituitary insufficiency was diagnosed (random cortisol 160 nmol/l; TSH 2.4 mU/l; fT4 5.7 pmol/l; prolactin 121 ug/l; IGF-1 139 ug/l). Fluid intake and thirst were adequate. Cortisol and thyroxine were replaced. The patient underwent transsphenoidal resection. Intraoperatively, the tissue had an unusual consistency with an increased bleeding tendency as compared with typical pituitary adenoma. The intraoperative frozen section revealed tissue compatible with pituitary adenoma. After surgery, headaches and bitemporal hemianopia disappeared but adrenal insufficiency and hypothyroidism persisted. The final histo-pathological examination revealed a pleomorphic, highly vascular and cellular tumor. The tumor cells were immune-positive for STAT6, negative for CK8a, synaptophysin and TTF1. The proliferation index Mib-1 (Ki-67) was 10%. Based on these findings, the diagnosis of an HPC grade 2 was made.
Discussion
HPC are very rare intracranial tumors (<2.5% of all meningeal and <1% of primary intracranial tumors). However, a few cases of HPC presenting as a sellar mass have been described. Often they mimic a pituitary adenoma. The reported patients presented with visual field defects (reported in seven of twelve, just one with normal visual field) and headaches (reported in six of twelve). Data on pituitary function was available in six of twelve: two with normal pituitary profile; one with elevated prolactin; one with hypogonadism and adrenal insufficiency; one with adrenal insufficiency. In five of twelve cases visual field defects and pituitary insufficiency improved after surgery. Anyway, surgical resection is mandatory due to a high risk of progression, metastasis and relapse rates (up to 70%). Postoperative radiotherapy might be discussed in tumor boards with decision based on imaging and histopathological findings, and clinical aspects.

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P739

Investigation of the role of miR-126-3p in pituitary insufficiency following traumatic brain injury

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Aim
Traumatic brain injury (TBI) is known to be associated with pituitary insufficiency (PI). We have recently shown that there was a relationship between miR-126-3p, miR-3610 and PI developing in follow up of patients with TBI. In this study, we aimed to test the effects of miR-126-3p on hypothalamus pituitary-adrenal (HPA) and Growth hormone-Insulin like growth factor (GH-IGF-1) axes.
Materials and methods
miR126-3p microinjection was performed to mouse embryos and mild-TBI was applied to these mice at 2 months of age. Tissue expression levels of corticotrophin releasing hormone (CRH), propiomelanocortin (POMC), corticosterone (CORT), GH genes and serum levels of CRH, corticotrophin (ACTH), CORT, GH and IGF-1 were determined in acute (24 hours after trauma) and chronic (a month after trauma) periods of TBI.
Results
miR126-3p microinjected mice had similar hypothalamic CRH, higher pituitary POMC and higher adrenal CORT expression; similar serum CRH, higher ACTH and similar CORT levels compared to controls. In acute TBI, miR126-3p microinjected mice had similar hypothalamic CRH, higher pituitary POMC and similar adrenal CORT expression; higher serum CRH, ACTH and CORT levels than controls with acute TBI. In chronic TBI, miR126-3p microinjected mice had similar hypothalamic CRH, similar pituitary POMC and higher adrenal CORT expression; similar serum CRH, ACTH and CORT levels compared to controls with chronic TBI. miR126-3p microinjected mice had higher pituitary GH expression, higher serum GH and similar serum IGF-1 levels compared to controls. In acute TBI, miR126-3p microinjected mice had higher pituitary GH expression, higher serum GH and similar serum IGF-1 levels compared to controls with acute TBI. In chronic TBI, miR126-3p microinjected mice had higher pituitary GH expression, higher serum GH and similar serum IGF-1 levels compared to controls with chronic TBI.
Conclusion
miR126-3p may have a protective role in HPA axis functions after acute TBI, but this protective effect is not seen in chronic TBI. miR126-3p is associated with higher GH levels in mice with acute and chronic trauma and without trauma. Similar IGF levels despite higher GH levels may show a state of GH resistance in miR126-3p microinjected mice.

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P740

Secretory and proliferative activity of GH-secreting pituitary adenoma

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The aim
To estimate secretory and proliferative activity of pituitary adenoma (isolated somatotropinoma (ST) and somatomammotropinoma (SMT).
Subjects and methods
The study included 133 patients (total group: 45 male/88 female), aged 44.0 ± 12.5 year old with acromegaly (95 – with ST and 38 – with SMT). There were estimated patient's age, age of manifestation of acromegaly ($age_{manifest.}$), duration of period before diagnosis (DPD) and duration of disease (DD), total secretory activity of adenoma (TSA) (ng/ml), secretory activity of pituitary adenoma unit (SAUPA) (ng/ml per cm^3) and tumor growth rate (TGR) (cm^3/years). The data are given as Me and nonlinear regression model equations parameters.
Results
In the total group the tumor volume (VT) was associated with $age_{manifest.}$ ($r=-0.41$; $P=0.006$), plasma GH ($r=0.37$; $P=0.041$); TSA ($r=0.38$; $P=0.004$), TGR ($r=0.82$; $P<0.00001$) and SAUPA ($r=-0.36$; $P=0.006$). In the SMT-group VT was higher, than in a ST-group (Me 5.21 cm and 2.42 cm^3, respectively; $P=0.002$) and associated with GH level ($r=0.53$; $P=0.03$), but not with prolactin (PRL). The TSA in ST/SMT-group is associated with TGR ($r=-0.36$; $P=0.008$) and SAUPA ($r=0.54$; $P<0.0001$). It's identified association between TGR and SAUPA ($r=0.56$; $P<0.0001$). It's set that in a SMT-group TSA were higher, than in a ST-group (Me 28.9 and Me 12.5 ng/ml, respectively; $P=0.02$). The VT is associated with TSA both in ST-group ($r=0.54$; $P=0.0006$) and in SMT-group ($r=0.47$; $P=0.04$). SAUPA in ST and SMT groups did not differ, however VT is associated with SAUPA in both groups (($r=-0.54$; $P=0.0007$) and ($r=-0.75$; $P=0.0002$), respectively). In a SMT-group the VT is associated with PRL ($r=0.79$; $P<0.00001$), which determines 63.4% his dispersion, in that time as a GH only 22.1%.
Conclusion
The presence of association between the clinical flow of acromegaly and secretory and proliferative activity of GH-secreting adenoma, in particular connection between «aggressive» clinical flow a SMT with their high secretory and proliferative activity. It is set that considerable duration of DPD and DD is inherent the of high «benign» clinical flow of acromegaly at in relation to low TSA, to «malignant» – insignificant DPD and DD at high TSA of GH-secreting pituitary adenoma. The intensity of the tumor process in patients with acromegaly is associated with the age of manifestation, which results in a decrease in the proliferative and secretory activity of a GH-secreting pituitary adenoma with age.
Keywords: acromegaly, secretory, proliferative activity, pituitary adenoma, tumor growth rate.

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P741

Ongoing challenges in treatment of cushing's disease due to pituitary macroadenoma

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Introduction
Cushing's disease (CD) is five to six times more common than Cushing's syndrome, with a peak incidence at 20–40 years. It is usually an ACTH-secreting microadenoma, the local invasion being associated with one third of macroadenomas. The treatment of choice is the transsphenoidal surgery, but nearly 50% of the patients with macroadenomas ultimately require additional treatment. Cabergoline appears to be an attractive treatment option for CD, considering its efficacy comparable with that of ketoconazole, pasireotide, radiotherapy and repeat surgery.
Case report
We describe the case of a 63 years-old female patient whose case was presented in the early evolution of her Cushing's disease in 2016. She was diagnosed with an ACTH-secreting invasive pituitary macroadenoma in 2015, based on the typical clinical and hormonal signs of hypercortisolism. After transsphenoidal surgery and Gamma-knife radiation in 2016, her urinary free cortisol and ACTH were still elevated, so Pasireotide was initiated but, despite her excellent response to this therapy, Pasireotide was discontinued after 2 months due to side effects. Since then, the hypercortisolism reoccurred in 2018, and considering the surgical and radiological contraindications, she was started on Cabergoline 1 mg/week. After 3 months she developed corticotropic insufficiency in need of substitution, which was interpreted at that time to be more likely the result of stereotactic radiosurgery. Unfortunately, after another 3 months, the patient was hypercortisolemic again and restarted Cabergoline, this time at a lower dose – 0.5 mg/week, which seems, at the moment, to control the hypersecretion, without inducing insufficiency.
Conclusion
Our patient had a variable pattern of hypercortisolism which was difficult to control until the effect of Gamma-knife, because of the side effects to Pasireotide and the lack of medical therapy. As the latest studies reveal, Cabergoline is an attractive treatment option via its inhibitory effect on Dopamine 2 receptors in CD and the strongest predictors for response are previous surgery, prolonged duration of cabergoline therapy (at least 6 months) and lower doses (2 mg/week).
Keywords: Cushing disease, Cabergoline
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Thyroid 2

P742

An unusual case of skull metastasis of thyroid carcinoma in an adolescent

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Introduction
Thyroid carcinoma accounts for 1% of all thyroid tumours. Bone metastasis occurs in 10 to 40%, with skullmetastasis accounting for 2.5 to 5.8% of bone metastases. The largest series of skull metastasis from thyroid carcinoma described a frequency of only 2.5% among 473 patients. The majority of skull metastasis from thyroid cancers is of the follicular subtype. She can occur at any age, the youngest patient was just 18 years old but most patients are between 60 and 70 years old. We report an unusual case of an adolescent girl of an 16-year-old with a metastatic thyroid follicular carcinoma of the skull.
Case report
16-year-old M.A presents with a swelling in the parietal region of the skull. She incidentally noted the swelling which then gradually increased in size. Patient consults for cephalgias, sensation of intracranial hypertention and right parietal hump appeared six months rather. The spinal IRM concludes a solidokystic osteolytic process of the right parietal worm with endocranial development and a local pachy meningeal reaction. Thoracoabdominopelvic CT without abnormalities. The patient underwent total exeresis of the tumor with cranioplasty. Histological examination revealed the diagnosis of a bone metastasis of vesicular carcinoma of the thyroid.with positive staining for thyroid transcription factor -1 (TTF-1) and thyroglobulin (TG). The thyroid echography found two suspicious nodules TIRADS5. The patient was operated on and underwent a total thyroidectomy with recural lymph node dissection and bilateral jugulocarotidien. The histological study of the piece is in favor of a bilateral papillary microcarcinoma of 4 mm at left and of 3 mm on the right classified PT1m N0 M1.Totalized isotopically by 100 mCi I131 and suppressive treatment with thyroxine.
Discussion – Conclusion
Anatomically, skull metastatic lesions are most frequently located over the occipital region, It's wase noticed that this lesion is osteolytic on CT scan. Histological examination commonly reveals follicular carcinoma, usually well-to-moderately differentiated, but occasionally a mixed follicular-papillary pattern has been noted. The treatment of children and adolescents with differentiated thyroid carcinoma is more controversial than the treatment of adults. Primarily because of the rarity of skull metastasis with thyroid carcinoma, the role of standard postoperative therapy for this situation has not been definitively established.
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P743

The prevalence of anti-parietal cell and tissue-transglutaminase antibodies in patients with autoimmune thyroid disease: a preliminary report

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Background
The association between autoimmune thyroid disease (AITD) and other autoimmune diseases is well-known. The prevalence of concurrent autoimmune gastritis and celiac disease in AITD has been estimated at approximately 20–25% and 2–5% respectively. Although both conditions have significant morbidity including malignancy and may necessitate dietary modifications and endoscopic evaluation, no recommendation exists to screen AITD patients for these autoimmune disorders.
Objective
To assess the prevalence of anti-parietal cell antibodies (APCA) and celiac antibodies (tissue-transglutaminase antibodies, tTg) in ambulatory patients with autoimmune thyroid disease.
Methods
Due to the high prevalence of celiac disease and autoimmune gastritis in AITD patients presented in prior studies, it is standard practice in our clinic to recommend serological screening to AITD patients for these conditions. A retrospective study was performed including patients with AITD who presented to our clinic between 01/01/2016 and 31/12/2018. AITD was defined by positive thyroglobulin or thyroid-peroxidase antibodies. AITD patient charts were searched for thyroid disease presentation (hypothyroid, hyperthyroid, mixed or euthyroid) and for tTg and APCA test results. We present a preliminary report of our data.
Results
Our preliminary cohort included 118 AITD patients, of whom 100 (84.7%) were female and 18 (15.3%) were male. Sixty-six presented clinically with Hashimoto thyroiditis, 40 with Graves' disease, three with mixed Hashimoto-Thyrotoxicosis, and nine were clinically euthyroid. Ninety-three patients had undergone assessment for celiac antibodies and 53 for APCA. Anti-parietal cell antibodies were positive in 10 of 53 patients tested (18.9%), 6 of whom were female; 7/10 had vitamin B12 deficiency and two were diagnosed with type 1 gastric neuroendocrine tumor. Two of 93 patients who performed celiac serology (2.2%) had a positive tTg; a third patient had known celiac disease. All three patients were female; one had both APCA and celiac antibodies.
Conclusion
The frequency of tTg and APCA in our preliminary study is concordant with results of similar prior studies and alludes to a higher prevalence of celiac disease and autoimmune gastritis in AITD. However, our study may have overestimated disease prevalence, as not all patients performed serological screening, and some may have been evaluated due to suggestive symptoms rather than as screening. The increased prevalence of these conditions reported in several studies, and their important associated morbidities and treatment implications advocates for a role for screening in AITD patients.
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P744

Levothyroxine treatment of subclinical (SH) and overt (OH) hypothyroidism in children with autoimmune hashimoto thyroiditis (AHT): defining the TSH cut-off level

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Objectives
Assess the dose of levothyroxine in relation to TSH and FT4 at diagnosis of AHT in children with SH and OH.
Methods
Two hundred one children (155 girls) with AHT were devided according to TSH and FT4 levels at diagnosis of hypothyroidism [SH-FT4 >1.0 ng/dl: Group 1: TSH: 5–7.5 mU/l, Group 2: TSH: >7.5 mU/l, OH: Group 3: TSH >7.5 mU/l and FT4 ≤ 1.0 ng/dl]. Mean L-T4 dose was reported in μg/Kg per day at diagnosis and at 2.9 years of follow up and TSH targeted levels under treatment were 1–4 mU/l.
Results
Mean age at diagnosis was 9.6 yrs (SD, 2.6). Main characteristics are shown in table 1. At diagnosis, TSH, FT4 levels and L-T4 dose were significantly different ($P<0.05$) between SH (groups 1 and 2) as opposed to OH (group 3). At follow-up all patients were euthyroid and TSH and FT4 levels did not differ significantly between groups. L-T4 dose was significantly higher in OH as opposed to group 1 but not group 2. Table 1. Data are shown as means (S.D.).

	Group 1 ($n=70$)	Group2 ($n=72$)	Group 3 ($n=59$)	*P
AT DIAGNOSIS				
Age (yrs)	10.4 (2.6)	8.9 (2.6)	9.6 (2.4)	
Height *z*-score	0.55 (0.9)	0.52 (1.0)	0.43 (0.9)	
BMI *z*-score	0.87 (0.9)	0.93 (0.9)	0.92 (1.1)	
TSH (mU/l)	6.1 (0.7)	10.9 (5.6)	47.9 (74.2)	*
FT4 (ng/dl)	1.2 (0.2)	1.3 (0.16)	0.85 (0.1)	*
L-T4 (μg/Kg/day)	1.1 (0.4)	1.3 (0.51)	1.5 (0.6)	*
AT FOLLOW UP (yrs)	2.8 (1.4)	3.16 (1.6)	2.98 (1.6)	
Age (yrs)	13.2 (2.4)	12.1 (2.7)	12.6 (2.4)	
Height *z*-score	0.56 (1.0)	0.59 (0.9)	0.43 (0.8)	
BMI *z*-score	0.82 (0.8)	0.76 (0.9)	0.92 (0.9)	
TSH (mU/l)	2.2 (1.2)	2.6 (1.2)	2.2 (1.1)	
FT4 (ng/dl)	1.4 (0.2)	1.4 (0.4)	1.3 (0.2)	
L-T4 (μg/Kg per day)	1.1 (0.3)	1.4 (0.4)	1.6 (0.7)	*

*One-Way Analysis of variance (ANOVA), $P<0.05$.

Conclusions
At diagnosis, L-T4 needs are significantly lower in subclinical hypothyroidism patients as opposed to overt hypothyroidism patients. At 2.9 yrs, children with overt hypothyroidism receive significantly higher LT-4 doses than those with SH and TSH $<$ 7.5 mU/l but similar with those of SH and TSH $>$ 7.5 mU/l.

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P745

Evaluation of ultrasonographical and cytological features of thyroid nodules in patients treated with radioactive iodine for hyperthyroidism

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Aim
Radioactive iodine (RAI) is one of the treatment approaches in Graves and toxic nodular or multinodular goiter (TNG/TMNG) with low cost and high efficacy. In this study, we aimed to evaluate ultrasonographical and cytological features of thyroid nodules in patients who were treated with radioactive iodine for hyperthyroidism years ago.
Methods
Patients who had a history of RAI treatment for hyperthyroidism and had thyroid nodules that were evaluated with fine needle aspiration biopsy (FNAB) were included in the study. Ultrasonographical features, and cytological and histopathological results of nodules were obtained from the records.
Results
There were 27 patients (22 female and 5 male) with a mean age of 59.3 ± 13.5. The indication for RAI treatment was Graves in 5 (18.6%), TNG/TMNG in 16 (69.2%) and unknown in 6 (22.2%) patients. A total of 48 thyroid nodules were evaluated with FNAB and cytological diagnosis were benign in 24 (50.0%), nondiagnostic in 15 (31.2%), atypia of undetermined significance in 5 (10.4%), suspicous for malignancy in 2 (4.2%) and malignant in 2 (4.2%) nodules. Mean duration between RAI treatment and FNAB was 76.4 ± 63.1 months. Thyroidectomy was performed in 10 patients and 5 were benign (50.0%) and 5 (50.0%) were malignant histopathologically. FNAB result was benign in 1 (20.0%), atypia of undetermined significance in 1 (20.0%), suspicious for malignancy in 1 (20.0%) and malignnt in 2 (40.0%) nodules with malignant histopathology. Ultrasonography features of 31 cytologically/histopathologically benign and 5 cytologically/histopathologically malignant nodules were compared. Rates of nodules with anteroposterior/transverse diameter ratio higher than 1, solid structure, presence of peripheral halo, marginal irregularity and microcalcification were similar in benign and malignant nodules ($P=0.303$, $P=0.684$, $P=0.829$, $P=0.973$ and $P=0.621$, respectively). There were 1 (20.0%) isoechoic, 1 (20.0%) hypoechoic and 3 (60.0%) iso-hypoechoic nodules among malignant nodules, while 24 (77.4%) of benign nodules were isoechoic, 3 (9.7%) were hypechoic and 4 (12.9%) were isohypoechoic ($P=0.025$). Macrocalcification was observed in 4 (80.0%) of malignant and 10 (32.3%) of benign nodules ($P=0.042$).
Conclusion
In patients treated with RAI due to hyperthyroidism, thyroid nodules with suspicious ultrasonography features, particulary hypoechoic appearence and presence of macrocalcification, should be evaluated with FNAB irrespective of the period after RAI treatment. Atypia related with previous RAI treatment might cause diagnostic problems in cytological evaluation.

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P746

External beam radiotherapy in differentiated thyroid cancer: clinical experience in a large spainish multicentre study

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The role of adjuvant external beam radiotherapy (EBRT) in differenciated thyroid cancer (DTC) is controversial. It remains unknown whether EBRT in the neck following conventional treatment might improve progression-free survival (PFS) and overall survival (OS).
Objective
To assess EBRT outcomes in patients with locally advanced DTC in terms of local disease progression, PFS and OS.
Material and Methods
A multicentric retrospective study was performed including all those patients diagnosed of DTC and treated with EBRT in the neck or mediastinum as a consequence of incomplete resection, extrathyroidal extension (ETE) and/or local

recurrence after surgery. Quantitative variables expressed as median [interquartile range].
Results
Sixty-seven patients (48 women; age at diagnosis 62 [51–70] years) from 11 different hospitals in Spain were included. 32.3% ($n=23$) of cases had an aggressive histologic variant. 75.8% ($n=50$) of tumours had the resection margins involved, 86.4% ($n=57$) had ETE and extranodal extension was present in 43.8% ($n=28$). Iodine-refractory patients were 73.8% ($n=48$). Age at EBRT time was 68 [59–77] years. Radiotherapy was administered mainly in the neck (74.6%), followed by neck and mediastinum (22.4%). Conventional EBRT was used in 38.6% of patients, followed by IMRT (35.1%) and 3DRT (19.3%). The median dose was 60 [50–66] Gy. Indications of EBRT were ETE in 50.7%, disease persistence/recurrence after surgery (34.3%), extranodal extension and high-risk histology (7.5% each one). The median follow-up period after EBRT was 41 [18–69] months. Thyroglobulin decreased or stabilized in 84.6% of patients without distant metastases during the follow-up. In this group (M0, $n=39$) radiotherapy stabilized or reduced structural local disease in 96.8%, 96% and 92.9% at 1, 2 and 5 years, respectively. In M1 patients ($n=25$), EBRT stabilized or reduced cervical/mediastinal disease in 64.3%, 56.2%, 50% at 1, 2 and 5 years. OS rate was 68.7% (mean OS 10.9 years; CI 95%, 8.8–12.9). EBRT dose $\geq$60 Gy was associated with an increase in mean OS compared with dose $<$60Gy (11.2 *vs* 6.9 years, $P=0.01$). Patients $<$55 years had longer mean OS than those $\geq$55 years (15.7 *vs* 7.2 years, $P=0.004$). The location of EBRT (neck or mediastinum) was associated with different means of OS. Type of histology or positive surgical margins were also related with different mean PFS.
Conclusions
In our experience, adjuvant EBRT was useful to control local disease in aggressive DTC. Location of therapy (neck), age $<$55 and EBRT dose $\geq$60 Gy could be predictors of better clinical response to treatment.

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P747

Patient with graves disease and antithyroid drugs allergy: when endocrinology becomes an art

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Introduction
First treatment in Graves' disease consists in the administration of antithyroid drugs. The most common side effect is a rash, which affects about 5% patients and clears up if the drug is stopped. The other drug may then be used. The intolerance to both drugs is very rare, but in this situation early radioactive iodine or surgery may be the answer.
Case report
Woman of 61 years old who developed primary hyperthiroidism, with levels of thyrotropin (TSH) 0.01 µUI/ml (laboratory reference values 0.4–4.2) and free T4 (fT4) 2.19 ng/dl (laboratory reference values 0.93–1.7). Thiamazol 15 mg daily was iniciated. After twenty days, she developed an itchy rash with erythema, which dissapeared when the drug was discontinued. Then we iniciated propylthiouracil 150 mg daily. Three weeks later, she referred similar symptons, and we stopped medication. Consequently, fT4 elevated again. We decided the best treatment was total thyroidectomy, because Radioiodine therapy has a late onset of action and this procedure in our hospital is delayed for several months. In this context, she underwent renal arteriography with iodinated contrast material. To avoid thyrotoxicosis, we iniciated Lugol's iodine solution Forte 5%, 8 drops every 6 hours, five days before the study. A stent was placed in renal artery, and clopidogrel was indicated for two months. So anesthesiologist recommended delaying surgery until clopidogrel was discontinued and thyroid function was normalized. The only therapeutic option we found was to maintain Lugol until surgery, and monitorize hormone levels every two-three weeks. We reduced empirically Lugol dosage to 5 drops every 6 hours, and fifteen days later the thyroid function was normalized (TSH 0.5 µUI/ml, fT4 1.53 ng/dl). Five weeks after the start of Lugol, she developed mild hypothyroidism (TSH 11.39 µUI/ml, fT4 0.89 ng/dl). Again empirically, we maintained same dose of Lugol and added low-dose of levothyroxine. Eight weeks after start of Lugol, TSH was 5.43 µUI/ml and fT4 1.33 ng/dl. She undergone total thyroidectomy ten weeks after starting Lugol. The only complication was transitory hypoparathyroidism. Actually her thyroid function is adequately replaced with 100 µg of sodium levothyroxine.
Conclusion
Iodine solutions were used in the 1930s as the sole therapy for mild hyperthyroidism before the introduction of tionamides. Today, they still play a minor role in the treatment. We recovered this therapy and demonstrated that this 'obsolete' drug could have a rol in selected cases.

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P748

Risk factors of cervical lymph node metastasis of differentiated thyroid carcinoma

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Background
Differentiated thyroid carcinoma (DTC) has an excellent prognosis with a relatively low recurrent and mortality rate, but a small portion of DTC patients suffers from an aggressive form of the disease with tumor invasion and metastasis. Accurate identification of this group of DTC patients is of crucial importance to optimizing individualized DTC treatment. This study aimed to retrospectively investigate the clinicopathologic predictive factors of cervical lymph node metastasis.
Methods
Methods is was retrospective study. Patients who underwent total thyroidectomy with central lymph metastasis due to DTC were included into the study.
Results
There were a total of 150 patients who met the inclusion criteria of the study: 134 women (89.3%) and 16 men (10.7%). The age of these 150 patients ranged from 19 to 76 years (mean 50.9 ± 12.99 years). The age 45 years and less was the only independent factor identified using univariate logistic regression as statistically significantly affecting the well – differentiated thyroid cancer metastasis to the neck lymph nodes. Other factors such as male gender, ultrasound changes in the lymph nodes before surgery, more than one node in the thyroid and multifocal tumor were not statistically significantly related to metastatic cancer in the neck lymph nodes. After applying multivariate logistic regression model to these factors, it was found that the factors acting together, tumor metastasis to neck lymph nodes also increases the likelihood of only a younger age of patients.
Conclusions
Our findings don't suggest to use such factors as gender, tumor's size, multifocality as predictive factors for cervical lymph node metastasis. According to our results only age $<$ 45 years could be a predictive risk factor for lymph node metastasis.
Keywords: lymph node metastasis, risk factors, differentiated thyroid carcinoma
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P749

Effectiveness of radiofrequency ablation of the large benign thyroid nodules

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Introduction
The aim of the study was estimate RFA efficacy of large benign thyroid nodules.
Material and Methods
This is a retrospective analysis included the results of RFA treatment of 54 patients with large benign thyroid nodules at the Samara Oncology Center from November 2014 to December 2017. Patients were seeking the alternatives to thyroid surgery because of the unwillingness to be operated on. The mean volume of nodules was 48.5 (36.1–89.7) mL. Before the treatment the following studies were performed: a symptomatic evaluation, a cosmetic evaluation, an ultrasound examination of the thyroid with an evaluation according to TIRADS system, laboratory tests, a fine needle biopsy (twice) under the ultrasound navigation with the cytological evaluation by Bethesda system.. RF ablation was performed using an 18-gauge, internally cooled electrode, length 10 cm, working part 0.7 cm using 'moving shoot' technique. During the follow-up nodule volume, thyroid function, compressive symptoms, cosmetic concerns were evaluated.
Results
Median thyroid nodule volume reduction induced by RFA was 56.6% (49.1–81.3). The mean follow-up was 32.3 ± 7.6 months. The therapeutic effect was achieved in 2–7 sessions. The RFA procedure was repeated three months after the first session, the next sessions were performed every 3 months. Compressive symptoms resolved

in all patients. Cosmetic concerns improved in 52 patients. The procedure had no sustained complications.
Conclusion
RFA was effective and safe for treating large benign thyroid nodules. It reduced nodules volume and improved compressive and cosmetic symptoms. According to the archived results RFA might be recommended for treating benign thyroid nodules as alternative to conventional treatment.

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P750

Presentation of thyrotoxicosis in hospitalized elderly patients

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Introduction
Thyrotoxicosis in the elderly may present differently than in younger indeviduals, and with the aging of the worlds' population it is imperative to obtain data in this age group.
Aim
Our aim was to identify and characterize clinical and biochemical parameters of thyrotoxicosis in the elderly and to compare them to those of younger patients.
Methods
We retrospectively evaluated files of patients older than 40 who were admitted to Rabin Medical Center in the years 2000–2018, and had suppressed TSH levels and increased thyroid hormone levels at admission. Clinical characteristics were compared between those older and younger than 70 years.
Results
After exclusion of 42 patients (7 had non thyroidal illness, and 35 for multiple admissions) our cohort included 277 patients of which 157 were older than 70 (57%, mean 81.2 ± 6.1) with a female predominance. TSH levels, thyroid hormone levels and heart rate at admission were comparable between the groups. Etiology was more likely to be Graves' disease or thyroiditis among those younger than 70 years, and toxic adenoma/toxic multinodular goiter or amiodarone induced thyrotoxicosis in those older than 70 years. Weight loss, fatigue, apathy, new and chronic fibrillation and goiter were all significantly more common in the elderly. Similar results were obtained when we excluded those who were treated with thyroxine before hospitalization.
Conclusions
Hospitalized elderly individuals with thyrotoxicosis more commonly present with non-classical symptoms and atrial fibrillation, compared to younger patients. Low threshold for evaluation might be appropriate in this age group.

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P751

Differences between EU and ACR TI-RADS in identifying potential malignant thyroid nodules

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Introduction
The incidence of thyroid nodules is increasing. Fine-needle aspiration (FNA) of all thyroid nodules is unnecessary, but it is necessary to provide a more precise identification of those nodules that are potentially malignant in nature. In the literature there are several suggested systems for assessing malignancy of nodules in the thyroid gland.
Objective
To determine the differences between EU and ACR TIRADS recommendation for fine-needle aspiration in patients with thyroid nodules in our center.
Methods and material
The study involved 127 patients, with 132 nodes referring to FNA. An ultrasound examination was performed before the FNA, and according to its ultrasonic properties, the nodes was classified according to the EU and ACR TI-RADS classification. After the cytopathological result was obtained, differences in FNA indications, which were determined according to these two classifications, were analyzed.
Results
The analysis found that there is a statistically significant difference in relation to the classification of a node in certain TI-RADS categories when compared to the EU and ACR system ($\chi^2 = 11.105$, $P = 0.0254$). In 23.5% of the nodules, a different category was obtained. FNA was indicated in 76.5% of nodules according to ACR TI-RADS criteria, and in 81.8% of nodules according to EU TI-RADS criteria. In one case, FNA was indicated only according to EU TI-RADS, and the cytopathological finding corresponded to the Bethesda IV category. In other cases, when the indication for FNA was different, the cytopathological finding indicated a benign nodule.
Conclusion
The EU and ACR TI-RADS is a useful tool in assessing malignancy of thyroid nodules. If EU TI-RADS is used, FNA is indicated in a slightly larger number of cases.

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P752

Atypical hürthle cell adenoma: be aware

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Introduction
Among all thyroid nodules 3 to 10% are Hürthle cell (HC) neoplasms classified as either HC adenomas or carcinomas. The presence of capsular or vascular invasion is indicative of a HC carcinoma whose incidence has been found to be 5 to 35%. Hürthle cell carcinoma could also lead to distant metastases and its decreased ability to uptake radioiodine worsens the prognosis. There are reports of histologically characterized HC adenomas with unpredictable clinical course. Here, we present a case of a HC 'adenoma' proved to be malignant 11 years post-thyroidectomy.
Case Presentation
A 73-year-old male presented at our department with a history of total thyroidectomy 11 years ago due to goiter with an 8.5 cm nodule on the left thyroid lobe. The histological examination revealed an atypical Hürthle cell adenoma. Consequently, he has been receiving levothyroxine substitution therapy but never pursued follow up by a specialized Endocrinologist. On October 2018 a chest CT was performed due to a pulmonary infection that revealed a 3.5 cm nodular lesion on the left lung. The FDG-PET CT scan that followed showed additional hypermetabolic loci on the left side of the neck. Biopsy was taken from the latter as well as from transbronchial needle aspiration and both displayed neoplastic infiltration with morphological and immunohistochemical characteristics of Hürthle cell thyroid carcinoma. Thyroglobulin levels exceeded 6000 ng/mL. Brain CT was negative. The following whole-body scan with radioiodine I-131 after recombinant thyrotropin stimulation showed radionucleotide uptake on thyroid tissue remnants, on the upper mediastinum and on the upper lobe of the left lung. The patient has been evaluated by a thoracic surgeon who characterized the condition as inoperable. Therefore, he received 150 mCi I-131. The post ablation WBS showed the majority of I-131uptake on the neck area and minor uptake on the lung. Hence, additional therapeutic strategies will be followed.
Conclusion
Even though histologically characterized Hürthle cell adenomas could be reassuring, long term follow up by a specialized Endocrinologist is essential in the context of occasional recurrence or metastases, leading in a final diagnosis of a Hürthle cell carcinoma as in our case.

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P753

Falsely high serum calcitonin levels

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Calcitonin is a polypeptide hormone synthesized and secreted by the parafollicular cells of the thyroid gland, and has been considered as a good

marker for medullary thyroid carcinoma. But several physiologic and pathologic conditions other than medullary thyroid carcinoma have been associated with increased levels of calcitonin. A 39-year old woman was admitted to our hospital for further testing due to high calcitonin level (467 ng/L) measured by immunochemiluminometric assay (ICMA). She had a history of multinodular goiter in past eight years, and calcitonin level was measured for the first time one month before the admission. She had no history of any other disease, and she did not take any medication. On admission, her calcium and phosphate levels, as well as PTH were with in normal range. She had mild hypovitaminosis D (Ca 2.21 mmol/L; PO4 1.15 mmol/L; PTH 30.15 pg/mL; 25OHD3 44.4 nmol/L). Her calcitonin levels were still high measured repeatedly by ICMA (244 ng/L; 220; 229 ng/L), while in normal range (5.3 ng/L) measured by immunoradiometric assay (IRMA). CEA (0.7 ng/mL) and chromogranin A (29.9 ng/mL) were in normal reference range. An ultrasound examination showed multinodular goiter with four heteroechoic, solid nodules in both lobes, size 19 mm, 15 mm, 12 mm and 11 mm, with no suspicious characteristics. An ultrasound guided fine needle biopsy was performed and cytopathologic result was benign (colloid nodules). Dilution of patient's serum 1:3, 1:5, 1:10 showed lost of linearity of calcitonin values measured by ICMA (1240; 85; 61 ng/L). Calcium stimulation test (2 mg/kg of elemental Ca, iv inf. during 5 minutes) showed persistently elevated levels of calcitonin, with absence of calcitonin response and domed calcitonin curve measured by ICMA (258.0; 268.0; 263.0; 252.0; 241.0 ng/L), while normal stimulation curve of calcitonin measured by IRMA (5,9; 9,0; 15,7; 9,2; 6,6 ng/L). We concluded that the calcitonin levels measured by ICMA were falsely elevated, probably due to presence of heterophilic antibodies, and that calcitonin measured by IRMA was her true calcitonin level. We followed patient annually for the next four years with ultrasound scan and measuring calcitonin by IRMA. Her calcitonin levels were with in normal range (4.4; 4.2; 2.5 ng/L). Due to nodular growth, patient was sent on thyroidectomy in december 2018. Patohistological diagnosis was: struma colloides cystica partim hyperplastica.

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P754

Hyperthyroidism revealed by pulmonary embolism: a case report

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Introduction
Pre-thrombotic states may be primary, related to a hereditary coagulation disorder or secondary (venous stasis or drug intake). We report a case of hyperthyroidism revealed by pulmonary embolism.
Observation
A 82-year-old woman, with a forty years history of type 2 diabetes mellitus, was admitted to the emergency room in a respiratory distress condition. The clinical examination found a dyspnoeic patient with tachycardia, hypertension, and a systolic murmur at the mitral focus, and the resting ECG showed atrial fibrillation. Pulmonary embolism was suspected, then confirmed by thoracic angioscan, which showed the presence of thrombus in the right middle lobe bronchus, and the segmental and sub segmental branch of the left lower lobe bronchus. Transthoracic ultrasound showed a normal size ventricle, a 50% ejection fraction, and a pulmonary arterial hypertension at 58 mmHg. The patient was put on anticoagulants and antihypertensive drugs. Obvious causes of pulmonary embolism have ben eliminated, the remaining suspected cause was hyperthyroidism, since the patient showed signs of thyrotoxicosis that have been evolving for 6 months. Moreover, the cervical examination revealed a medium sized and homogenous goiter. The diagnosis was confirmed: suppressed TSH at 0.02 mIU/ml, elevated FT4 at 73 ng/dl, and cervical ultrasound showed a multi-heteronodular goiter. The patient was put on synthetic antithyroid drugs (Carbimazole). The patient showed signs of clinical, biological and ECG improvement.
Discussion
This association is rare. The advanced hypothesis is the disorders of hemostasis encountered in hyperthyroidism, especially the elevation of Von Willbrand factor and factor X activity.

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P755

Indicators of hormones before and after the operation of the goiter root of the tongue

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Actuality
Goitre of the tongue root malformation of the thyroid gland is a violation of the process of migration from the tongue root to the definitive position at the level of the 2nd - 4th rings of the trachea, when the thyroid gland remains in whole or in part in the area of the blind opening of the tongue.
The aim
To evaluate the results after operative complications, to determine the main changes in TTH and T4 after surgery in the debut of the disease and in the dynamics on the background of treatment.
Materials and methods
Twenty-eight patients examined for goiter of the root of the tongue in the endocrine surgery department. The level of TTH and T4 was determined in all patients before and after the operation.
Results
Initially, 67.8% (19 people) had symptoms of hypothyroidism, euthyroidism was detected in 8 patients (14.2%), thyrotoxicosis in 1 patient (3.57%). Clinically, in the debut of the disease in 19 patients (67.8%), disturbed swallowing disturbed, breathing difficulty - 15 patients (53.5%), nasal humility and hoarseness of the voice — 25 patients (89.2%), foreign body sensation in the throat - 13 patient (46.4%). The condition of patients after surgery in patients with euthyroidism level of TTH is 2.6 ± -1.2 (mIU/l), T4 of st. (pmol/l), and in patients with hypothyroidism the level of TTH is 7.6 ± -2.2 (mIU/l), T4 of St. 7.5 ± -3.1 (pmol/l). And in patients with thyrotoxicosis, the level of TTH is 0.40 (mIU/l), T4 of St. 23.5 (pmol/l).
Conclusion
Given the propensity for malignancy, patients with an established diagnosis of 'Goiter of the root of the tongue' are subject only to surgical treatment. Scintigraphy of the 'Crab of the tongue root' is necessary before the operation - diagnosis, after the operation - quality control or the presence of a relapse.

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P756

Systematic review and meta-analysis of occurrence of other autoimmune diseases in autoimmune polyglandular syndrome type II and type III

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Introduction
The autoimmune polyglandular syndrome (APS) is a complex, heterogeneous condition in which autoimmune diseases (AIs) of endocrine and non-endocrine organs can occur. There are four subgroups. The majority of patients are categorized as having APS II or APS III. In APS II, patients have Addison's disease (AD) and autoimmune thyroid diseases (AITDs) or type I. diabetes mellitus (T1DM), while in the APS III, AITDs are combined with other autoimmune illnesses except AD.
Aim of the study
The main goal of this meta-analysis was to identify the frequency of different AIs in APS II and III in order to provide details for a possible screening protocol.
Method
In Pubmed and Embase databases 479 studies were found with the keywords of APS II and APS III. Among these, 118 records fulfilled the criteria of the study (original reports containing the combination of other AIs). Excluding case-reports, 18 articles containing a total of 1277 (2–254/papers) patients were selected for further analysis. Forrest plot was used for statistical analysis.

Results
The mean age of patients at the time of diagnoses was 34.7 years (95% CI: 22.75 – 46.64). Females were more often affected by APS than males (75% (95% CI: 68% – 81%) vs 25% (95% CI = 19% – 32%), $P < 0.001$). Distinction between APS II and APS III was made in 842 cases, of which 177 and 665 were APS II and III (21.1% vs 78.9%), respectively. The prevalence of Hashimoto's thyroiditis was significantly higher than of Graves's disease (39% (95% CI: 17% – 65%) vs 4% (95% CI: 0% – 10%), $P = 0.001$). Two other AIs occurred more often in combination with Hashimoto's thyroiditis than with Graves's disease (81% (95% CI: 37% – 100%) vs 3% (95% CI: 0% – 18%), $P = 0.001$). Interestingly, Graves's disease was never diagnosed in association with more than two other AIs. In APS II, AD coexisted with AITDs, T1DM or the combination of these conditions in 114, 32 and 18 cases, respectively. Above these, 1 other endocrine and 5 non-endocrine organ-specific AIs were reported. In APS III, 2 autoimmune endocrinopathies, 6 non-endocrine organ-specific and 4 systemic AIs were detected in combination with AITDs.
Conclusion
Based on this meta-analysis, AITDs, AD and T1DM are the most common combinations occurring in APS, thus screening for these conditions seems to be reasonable. The association of other AIs is more common in Hashimoto's thyroiditis compared to Graves's disease.

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P757

Hypo-coagulated patients and ultrasound guided fine-needle aspiration of thyroid nodules: a worry?

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Introduction
Ultrasound guided Fine-Needle Aspiration (USFNA) of Thyroid is the gold standard for diagnosis of thyroid nodules. Nowadays, many patients are under anticoagulation and antiplatelet medication. Some of the rare complications of USFNA are haemorrhage therefore it's not clear if performing thyroid USFNA in hypo-coagulated patients increase that risk of complications or if this medication should be stopped before the procedure. Additionally the influence that the hypo-coagulated state may have on the number of non-diagnostic cytological results is unknown. It is our purpose to assess the haemorrhagic risk and impact on non-diagnostic results of thyroid USFNA performed in patients under anticoagulation/antiplatelet therapy.
Methods
Retrospective study of 223 patients that performed 278 thyroid USFNA between January of 2017 and July of 2018. Patients were divided into two groups according to whether doing or not anticoagulation/antiplatelet medication (including novel oral anticoagulant agents (NOAC)). None of patients stopped anticoagulation/antiplatelet medication before the procedure. In each group was evaluated the prevalence of haemorrhagic and non-haemorrhagic complications and the number of non-diagnostic results. All statistical analysis, was performed by using SPSS with significance index $P < 0.05$.
Results
A total of 278 thyroid USFNA were analysed. The majority of the patients were female (55.5%) with a medium of age of 66.8 years. 71.7% of the patients were included on Control Group (without medication) and 28.3% on the Hypo-coagulated Group (under anticoagulation/antiplatelet medication). This last group comprise 67.5% of patients doing antiplatelet medication (20% under aspirin (AAS), 1.35% under AAS and clopidogrel, 41.9% under clopidogrel, 2.7% with triflusal and 1.35% under ticlopidine), 25.6% of patients undergoing NOAC (14.9% under rivaroxaban, 9.5% under dabigatran and 1.35% under edoxaban) and 6.7% of patients on vitamin K inhibitors (warfarin). Comparing with Control Group (0%), the prevalence of haemorrhagic complications on the Hypo-coagulated Group was 1.35% ($P = 0.11$). Non-haemorrhagic complications such as local pain and discomfort, were reported in 1.96% on control group and in 2.7% on hypo-coagulated group ($P = 0.71$). Relatively to the number of non-diagnostic cytological results, was found in 2.5% of the total US-FNA performed, 1.47% on the control group and 5.4% on hypo-coagulated group ($P = 0.07$).
Conclusion
Haemorrhagic complications after thyroid USFNA are minimal and usually without severity. Taking into account the results obtained and the existing bibliography, it is concluded that the haemorrhagic risk of hypo-coagulated patients is not significantly increased. It seems wise to recommend the non-cessation of anticoagulation/antiplatelet medication prior to the thyroid USFNA.

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P758

Nivolumab-induced hypothyroidism in young male without prior antithyroid autoimmunity

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Introduction
Nivolumab, an anti–programmed cell death-1 (PD-1) monoclonal antibody, is a promising treatment of variety advanced malignancies. Immune checkpoint inhibitors can cause immune-related adverse events, including endocrine pathology. Destructive thyroiditis is one of the most frequently observed nivolumab-induced endocrine irAEs which associated with the presence of anti–thyroid peroxidase antibodies (TPO-Abs) and anti-thyroglobulin antibodies (Tg-Abs) prior to treatment. In this case we have described occurrence frank hypothyroidism during nivolumab treatment in young male without antithyroid autoimmunity at baseline.
Case
A 19-year-old male patient has presented with history of refractory classic Hodgkin lymphoma (stage III). It was decided to conduct nivolumab treatment after failure of several polychemotherapy courses (ABVD, BEACOPP). There was no history of endocrine diseases. Thyroid-stimulating hormone (TSH) levels was 2.4 mIU/l (reference range 0.4–4.0 IU/l) and TPO-Abs/Tg-Abs was absent at the time of therapy initiation. ^{18}F-FDG PET/CT scan performed after four cycles of nivolumab (3 mg/kg once every two weeks) was revealed positive response to treatment and signs of increased ^{18}F-FDG uptake in thyroid. Moreover, the patient developed symptoms of progressive fatigue and dizziness. Thyroid tests were performed: TSH level was 56.4 mIU/l (reference range 0.4–4.0 mIU/l), free T4 – 5.2 pmol/l (reference range 9.0–19.0 pmol/l), free T3 – 1.5 pmol/l (reference range 2.6–5.7 pmol/l), TPOAbs – 1.0 IU/l (reference range 0.0–5.6 IU/l), TgAbs – 0.4 IU/l (reference range 0.0–4.0 IU/l). Thyroid colour flow Doppler sonography demonstrated markedly decreased parenchymal blood flow within thyroid. Thus, the diagnosis of nivolumab-induced primary hypothyroidism was established due to destructive thyroiditis. The patient was commenced on gradually increasing doses of levothyroxine up to total dose 1.6 μg/kg without discontinuation of nivolumab therapy. Two weeks later, patient noted relief of symptoms and free T4 level was 14.4 pmol/l (reference range 9.0–19.0 pmol/l). Six weeks later, TSH level was 14.3 mIU/l (reference range 0.4–4.0 mIU/l) and subsequent values were within normal range.
Conclusion
Our observation implies that treatment with anti-PD-1 antibody could lead to frank primary hypothyroidism even in patients without prior antithyroid autoimmunity and emphasizes the importance of thyroid function monitoring during nivolumab treatment.

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Correlations between thyroperoxidase antibody titers and Levothyroxine dose in patients with primary hypothyroidism

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Introduction
The main objective in the management of primary hypothyroidism is to normalize thyrotropin (TSH) level with Levothyroxine replacement therapy. The optimal dose of Levothyroxine may be affected by several factors such as age, gender, body weight, some medical disorders and drugs intake. The aim of this study was to assess the relationship between thyroid antibody titers and Levothyroxine dose in patients with primary hypothyroidism secondary to Hashimoto thyroiditis.
Patients and methods
In a cross sectional study, we enrolled 40 women with primary hypothyroidism secondary to Hashimoto thyroiditis. All patients were put on Levothyroxine replacement therapy for at least one year. Patients with liver dysfunction, renal failure, malabsorption diseases and pregnancy and those taking drugs affecting lévothyroxine absorption or metabolism were excluded. Anti-thyroid peroxidase antibodies (TPOAb) were measured in all participants.
Results
The study population consisted of 40 patients, all women with a mean age of 53.08 ± 11.46 years. The mean duration of treatment with Levothyroxine was 5.15 ± 4.35 years. TPOAb were positive in all participants. Euthyroidism was achieved in 33 patients (83% of cases). TSH level was 2.66 ± 1.58 µIU/ml in euthyroid group vs 9.72 ± 4.58 µIU/ml in non-euthyroid group ($P < 0.001$). Mean TPOAb levels in euthyroid group and non-euthyroid group were 564.42 ± 349.84 IU/ml and 1533.33 ± 1497.98 IU/ml, respectively ($P = 0.007$). TPOAb titers were positively correlated with Levothyroxine dose ($r = 0.338$, $P = 0.03$). However no correlations were found between Levothyroxine dose and age, body weight, body mass index and the severity of hypothyroidism at the diagnosis.
Conclusion
Our results revealed a positive correlation between TPOAb titers and Levothyroxine dose in patients with primary autoimmune hypothyroidism. Therefore, a higher dose is necessary to achieve euthyroidism in patients with higher TPOAb titers.

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NMR-measured subfractions of HDL-cholesterol through thyroid function spectrum

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Thyroid dysfunction has been traditionally related to several lipid abnormalities. Indeed, even within the normal range of thyroid-stimulating hormone (TSH) values, a linear increase in total cholesterol, low-density lipoprotein cholesterol and triglycerides and a linear decrease in high-density lipoprotein cholesterol (HDL-C) levels has been observed with increasing TSH. With respect to serum high-density lipoprotein (HDL) cholesterol concentrations, high, normal, or low values have been reported in different series. The aim of this report is to evaluate HDL-cholesterol subfractions analysed through nuclear magnetic resonance (NMR) through thyroid function spectrum in a Brazilian population.
Methods
We included 15,093 individuals that had serum TSH measured in the baseline evaluation of the ELSA-Brasil study. Disregarding those using levothyroxine, metimazole or statins, we analysed 12,245 individuals. These individuals were divided in quintiles of TSH (Q1: 0.0002–0.95 – median 0.74 (0.58–0.85); Q2: 0.955–1.33 – median 1.14 (1.05–1.23); Q3: 1.34–1.78 – median 1.54 (1.43–1.65); Q4: 1.79–2.58 – median 2.14 (1.97–2.33); Q5: 2.59–260 – median 3.39 (2.91–4.31)). Nuclear magnetic resonance (NMR) spectroscopy (LabCorp) measured the methyl terminal of lipoprotein subclasses and size of HDL particles using a targeted metabolomics platform (NMR LipoProfile analysis by the LP3 algorithm). This platform comprises concentrations of very large, large, medium, small, and very small HDL particles. We analysed the quantity of small, medium and large particles of HDL-cholesterol by TSH quintiles using Kruskal-Wallis test. We used the Spearman correlation in order to analyse the subfractions though TSH levels as a continuous variable (log-transformed TSH).
Results
We evaluated 12,245 patients (52.5% female, Age 50.9 ± 8.7 years-old). The groups were very similar concerning age, gender-distribution, blood pressure and prevalence of diabetes and hypertension. There were significant differences concerning triglycerides levels ($P < 0.01$), body mass index ($P = 0.0014$), HbA1c ($P = 0.0032$), total cholesterol levels ($P = 0.0004$) and smoking ($P < 0.001$). Glucose ($P = 0.0935$), LDL-cholesterol ($P = 0.1079$) and HDL-cholesterol ($P = 0.0933$) levels were not statistically different between the 5 groups. When evaluating the subfractions of HDL-cholesterol as small, medium and large, there were also no differences between the groups - small particles ($P = 0.60$), medium particles ($P = 0.56$) and large particles ($P = 0.53$). Considering TSH-log transformed as a continuous variable, the results remained non-statistically significant (small particles – $P = 0.42$, medium particles – $P = 0.19$, large particles – $P = 0.58$).
Conclusion
In this large cohort of Brazilian population, there was no significant difference concerning HDL subfractions through the spectrum of thyroid function.

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Two cases of hypothyroidism induced by tuberculosis drug

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Introduction
Adverse events among patients treated for tuberculosis are under-researched and underreported. Two cases of hypothyroidism induced by tuberculosis drug were reported in two older women.
Observations
Case 1: A 69-year-old male, complaining of asthenia and weight gain. He had been treated for his pulmonary tuberculosis during the past 6 months with a quadritherapy antituberculous regimen consisting of Rifampicin, isoniazid, ethambutol, pyrazinamide. A thyroid profile performed when he was admitted to our hospital showed several marked abnormalities: serum thyroid stimulating hormone (TSH) was elevated (40 microIU/ml), free thyroxine level (T4) (7 pmol/l). A thyroid profile, after one month and a half, that was repeated after the exclusion of tuberculosis drug since il is the end of this treatment showed the following results: the TSH level was decreased (6 mIU/ml), the free T4 (12 pmol/l) were normal. During treatment with tuberculosis drug, he had never received thyroid replacement therapy.
Case 2: A 66-year-old female, complaining of asthenia and myalgia. She had been treated for her osteoarticular tuberculosis during the past 12 months with a quadritherapy antituberculous regimen. A thryoid profile performed when she was admitted to our hospital showed several marked abnormalities: elevated serum TSH (60 mIU/ml), and low T4 (5 pmol/l). She received a progressive L-thyoxine therapy. A thyroid profile that was repeated after the exclusion of tuberculosis drug at end of his treatment showed the decrease in needs of L-thyroxine therapy and the following results: the TSH level was normalized (3.1 mIU/ml) without any L-thyroxine replacement.
Discussion
Drug-induced hypothyroidism is an infrequent side effect of tuberculosis therapy, and only a few cases of Rifampicin (RFP) induced hypothyroidism have been reported so far. In this report, we describe patients with hypothyroidism who were receiving therapy for tuberculosis. Rifampicin would be the most incremental in this condition. Early hypothyroidism screening was recommanded in treated tuberculosis to avoid severe and complicated forms especially in the elderly.

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Thyroid ecostructural implications of antinuclear antibodies in patients with chronic autoimmune thyroiditis and hypovitaminosis D

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Aims
Presence of antinuclear antibodies (ANA) is correlated to tissue involutive lesions by microvascular alterations. The possible involvement of hypovitaminosis D as a negative immunomodulatory factor along with the presence of ANA and the

incidence of chronic autoimmune thyroiditis (CAT) atrophic form is a complex mechanism with multiple pathological intercorrelations.
Material and method
Inclusion criteria: patients - new cases diagnosed with CAT without other associated autoimmune diseases and without specific thyroid therapy. Variables studied: serum pathological ANA level. Serum level 25-OH-vitamin D (normal and moderate/severe low); incidence of atrophic CAT/absence of intrathyroid vascular Doppler signal. Group 1: $n=56$; 25-OH-vit D: 20–29 ng/ml; Group 2: $n=41$; 25-OH-vit D <19 ng/ml; Group 3: $n=43$; 25-OH-vit-D $>$ 30 ng/ml.
Results
Incidence of pathological serum ANA level: Lot 1: 31 (55.3%); Lot 2: 22 (53.7%); Lot 3: 12 (28%). Incidence of atrophic form of CAT: Lot 1: 28 (50%); Lot 2: 37 (90%); Lot 3: 4 (9.3%).
Discussion
The presence of ANA ($P<0.05$) was not significant between group 1/group 2 and significant ($P<0.001$) for both versus group 3. Incidence of atrophic form of CAT between group 1/group 2 ($P<0.001$) versus group 3 ($P<0.001$) – with a minimal incidence. The presence of ANA in patients with CAT may have a thyroid involutive effect. The low serum level of vitamin D is directly proportional to the incidence of atrophic CAT in positive ANA patients. Hypovitaminosis D appears to be involved depending on the severity of the deficiency without excluding its duration.
Conclusions
The role of ANA in the thyroid involutive process seems possible and the early correction of hypovitaminosis D in patients with CAT could have an effective therapeutic method.

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Antinuclear antibodies, chronic autoimmune thyroiditis, periodontal disease – pathological correlations

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Aims
To evaluate the prevalence of antinuclear antibodies (ANA) in patients with chronic autoimmune thyroiditis (CAT) associated with periodontal disease (P.D).
Material and methods
42 patients with TCA and BP were tested for ANA (Group 1) and 50 patients with TCA without BP (Group 2). Inclusion criterias – absence of other autoimmune diseases associated with positive ANA patients. Thyroid hormone deficiency has established thyroid function. Patients with B.P were differentiated: initial lesion - gingivitis, aggravated lesion - loss of dental attachment/endodontic lesions.
Results
Incidence of ANA: Group 1–36 (85.7%), Group 2–15 (30%). ANA/PD distribution – initial lesions – 10 (23.8%), advanced lesions – 26 (32%). ANA distribution/thyroid function: hypothyroidism – 21 (50%); normothyroid – 4 (9.5%), thyrotoxicosis – 11 (27%). Hypothyroidism associated to PD: inward lesions – 3 (30%); advanced lesions – 17 (5.3%).
Conclusions
There may be common pathogenic mechanisms for TCA and PD. Hypothyroidism produces an intensified lesional effect at periodontal level.

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Experience in treating patients with endocrine ophthalmopathy

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The results of treatment of 72 patients with endocrine ophthalmopathy in the Clinical Hospital No. 10 in Minsk during 2 years are presented. Thyroid pathology was detected in 63 patients (87.5%): in 39 (54.2%) - Graves disease, in 24 (33.3%) - autoimmune thyroiditis. All patients with Graves' disease received thyrostatic therapy; 10 persons developed ophthalmopathy after thyroidectomy. 11 patients with autoimmune thyroiditis had hypothyroidism and received levothyroxine, the rest had thyrotoxicosis. In 26 patients (36.1%) the process was one-sided. The average age of patients was 34 ± 8 years; (men: women – 32:40). The following ophthalmologic examinations were performed: visual acuity test, computer perimetry, CT of the orbits, the study of intraocular pressure. The ophthalmopathy activity assessment was measured according to the CAS scale. Ophthalmic hypertension was detected in 24 patients (33.3%). According to the EUGOGO classification, 68 patients (94.4%) had a moderate severity of the disease, 4 (5.6%) had a severe degree with the development of optic neuropathy and a decrease in visual acuity. Patients with moderate severity received methylprednisolone pulse therapy of 500 mg intravenous No. 3 every other day, in total 3 courses with an interval of 7–10 days. It was followed by intravenous administration of methylprednisolone 250–500 mg once in 7–10 day No. 6, depending on the activity of the process. The total dosage of methylprednisolone was 8 g, in some cases a prolongation of treatment was required. Due to therapy the signs of ophthalmopathy activity significantly decreased, patients' quality of life improved. No significant adverse events including hepatic failure were reported. In 10 cases transient hyperglycemia was observed. Blood pressure increased slightly. The main complaints of patients on the day of administration were hot flashes, heart palpitations, anxiety and insomnia. The patients with severe ophthalmopathy received 750 mg of methylprednisolone intravenous daily for 3 days in a row and then at intervals of one week 500 mg daily for 3 days; in total 2 courses. Subsequent therapy included weekly administrations of 500 mg for 6 weeks. The patients also received nootropic, neurometabolic and diuretic drugs. Improvement in visual acuity was noted after 3 weeks of treatment. By the end of treatment in two patients the visual acuity recovered completely, in others it remained slightly reduced. Therapie complications with large doses of corticosteroids have not been identified. Conclusion: the treatment of endocrine ophthalmopathy using the method of high-dose corticosteroid pulse therapy in form of series of intravenous injections is effective and safe.

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Thyroid disfunction during treatment with Nivolumab: nuances in clinical presentation

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Context
Monoclonal antibodies to Immune Check Point inhibitors (ICPis) are powerful anti-cancer drugs. They trigger the immune system against cancer cells, blocking inhibitory signals of T-Cells. However, ICPi therapy can also stimulate autoimmune reactions, inducing the so-called immune-related adverse events (irAEs). Endocrinopathies are common iRAEs and thyroid disfunction is the most common endocrinopathy during ICP therapy. We report three cases of thyroid disfunction during Nivolumab (Anti-PD1) therapy.
Case 1
A 65 year old male that undergoing Nivolumab treatment for metastatic non-small cell lung cancer. At baseline, FT4, FT3 and TSH were in the normal range, while thyroid autoantibodies (TgAb and TPOAb) were slightly positive. Neck ultrasonography showed a hypoechoic normal size thyroid with no nodules. Eight weeks later, thyroid function test demonstrated an overt hyperthyroidism. TRAb were undetectable and thyroid scintigraphy showed low uptake. During follow-up, FT4, FT3 and TSH normalized spontaneously within 3 months and remained in the normal range during Nivolumab treatment.
Case 2
A 67 year old female came to our observation because of recent onset of fatigue and hair loss. She was administered the third infusion of Nivolumab because of a metastatic non-smal cell lung cancer. Thyroid function tests revealed an overt hypothyroidism (FT4: 0.5 ng/dl (normal range 0.7–1.7); TSH: 38 mcUI/ml (normal range 0.4–4)). At baseline, thyroid function test was in the normal range and thyroid autoantibodies were highly positive. Neck ultrasonography showed a markedly hypoechoic thyroid of small size. Levothyroixe treatment was started. Euthyroidism was restored in 2 months with improvement of symptoms.
Case 3
A 51 year old male came to observation because of palpitations, heat intolerance and insomnia. He was at the sixth infusion of Nivolumab for a metastatic melanoma. Before the immune therapy thyroid function tests were in the normal range; autoantibodies were undetectable. An increased heart rate and sweaty skin were found at physical examination. Thyroid function tests showed an overt

hyperthyroidism (FT4: 2.28 ng/dl; FT3: 7.82 pg/ml (normal range 2.7–5.7) TSH: < 0.004 mcUI/ml). Thyroid autoantibodies remained undetectable. Neck ultrasonography showed an enlarged hypoechoic thyroid with a hypervascular pattern. Tc99 thyroid scintigraphy showed an increased uptake. Methymazole therapy was started and a normal thyroid function was restored within a few days.
Conclusions
Thyroid dysfunction during immunotherapy is a common irAE that may have variable presentation and impact negatively on patient's general conditions. When thyroid dysfunction is managed properly, immunotherapy does not usually need to be discontinued.

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Is the determination of rTSH estimulated thyroglobulin necessary for long term management in patients with differentiated thyroid carcinoma?

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Introduction
In clinical practice guidelines for differentiated thyroid cancer (DTC) it has been proposed to perform thyroglobulin (Tg) stimulated by rTSH determination 6–12 months after initial therapy in patients with low or intermediate risk, in order to establish the absence of disease. The use of ultrasensitive Tg assays could avoid the need of stimulation to establish the absence of disease.
Objectives
To evaluate the usefulness of the determination of rTSH-stimulated Tg in patients with low and intermediate risk CDT treated with I131 and with undetectable ultrasensitive Tg (<0.04 ng/ml) under levotiroxine suppressive therapy.
Material and methods
The values of stimulated Tg after rTSH were evaluated in patients diagnosed of low and intermediate risk CDT treated with I 131, that presented undetectable Tg and negative anti-thyroglobulin antibodies (AbTg) after 6 months of initial treatment. From October 2016 to December 2017 an ultrasensitive Tg assay was used, in which it was considered undetectable <0.04 ng/ml (Group A) compared to a control group (Group B) from July 2015 to September 2016, in which the determination of Tg was made by a lower functional sensitivity test (considering Tg <0.20 ng/ml undetectable). High-risk CDT or positive AbTg patients were excluded.
Results

	Group A (Ultrasensitive Tg) p NS	Group B (Control group) p NS
Total patients	35 (47.9%)	38 (52.1%)
Women/men	24 (68.6%)/ 11 (31.4%)	33 (86.8%)/ 5 (13.2%)
Age at diagnosis	48.8±14.4 years	44.5±13.2 years
Type of tumor Papillary/ Follicular	32 (91.4%)/ 3 (8.6%)	34 (89.5%)/ 4 (10.5%)
Extrathyroid extension	4 (11.4%)	1 (2.6%)
Presence of adenopathies	4 (11.4%)	1 (2.6%)
Size		
T1	13 (37.2%)	15 (39.5%)
T2	19 (54.3%)	17 (44.7%)
T3	3 (8.6%)	6 (15.8%)
Normal / altered ultrasound	34 (97.1%)/1 (2.9%) ganglion	38 (100%)/0
Estimulated Tg after rTSH		
< 1 ng/ml	35 (100%)	36 (94.7%)
>1 ng/ml	0	2 (5.3%)
Response to treatment		
Excellent	33 (94.3%)	36 (94.7%)
Undetermined	1 (2.9%)	2 (5.3%)
Pending classification	1 (2.9%)	0
Follow-up time	23.7±9.3 months.	36.7±6.8 months.

Conclusions
- The determination of ultrasensitive Tg stimulated with rTSH in patients with low and intermediate risk CDT provides little additional information, so in this group of patients the determination of ultrasensitive Tg in suppressive treatment could be an adequate method to establish absence of disease.
- There were no statistically significant differences between both groups regarding the distribution of stimulated Tg greater than 1.

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Endocrine malignancies and systemic lupus erythematosus: case report

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Introduction
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, which pathogenesis remains elusive. Patients with SLE have a higher overall risk of malignancy than the general population. Herein, we report an original association of SLE with ovarian and thyroid malignancies.
Case report
A 52-year-old woman was followed-up for 13 years in the dermatology department for SLE. Her disease remained stable under hydroxychloroquin with SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) score less than 5. She was diagnosed 2 years earlier with ovarian cancer and treated with total hysterectomy and bilateral adnexectomy followed by chemotherapy. Her last magnetic resonance imaging showed complete remission 6 months earlier. She reported a history of ovarian cancer in her sister, who also had thyroidectomy for hyperthyroidism. On her last medical visit, physical examination revealed enlarged bilateral cervical nodes. Biological tests showed normal levels of thyroid hormone and thyroid stimulating hormone and positivity of anti-nuclear and anti-dsDNA antibodies (respectively 1/800 and 1/37). Thyroid ultrasound revealed a hypoechoic 3×4 mm thyroid nodule with irregular margins located in the middle right pole, graded EU-TIRADS 5. The diagnosis of thyroid cancer associated with SLE was raised. The patient was referred to the department of otolaryngology to undergo thyroidectomy.
Discussion
SLE patients especially females have an increased risk of developing overall malignancies. Immunological abnormality and cumulative exposure to immunosuppressive drugs are possible causes. Chemotherapy for ovarian cancer may have triggered thyroid cancer in our patient, as she was only taking hydroxychloroquin for her SLE. While we did not have histological confirmation of the thyroid cancer, a score of EU-TIRADS 5 indicated that the nodule was very probably malignant (risk >95%). Based on systematic reviews and meta-analysis, SLE has been correlated with increased risk for thyroid cancer. However, low rates of breast cancer susceptibility gene II (BRCA2)-associated malignancies, including ovarian and breast cancers, were observed among SLE patients. To explain this finding, Hansen et al. suggested the possible role of lupus autoantibodies. They even demonstrated the therapeutic potential of cell-penetrating lupus autoantibodies for BRCA2-deficient human cancers. Therefore, a lack of these antibodies in the present case (SLEDAI score <5) may have been related to the onset of ovarian cancer. BRCA2 mutations were not investigated in our patient, but their presence is very probable given the familial history of ovarian cancer.

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Assessment of thyroid functions and thyroid volume in normal pregnant Egyptian females

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Background and aim
The normal range of thyroid functions during pregnancy differs between ethnic groups**.** The aim of this work was to assess the thyroid functions in normal pregnant Egyptian females in order to establish a population-specific reference range. Thyroid peroxidase antibodies (TPO Abs) and thyroid volume were also assessed.
Methods
The study included 150 normal pregnant Egyptian females (with no history suggestive of thyroid disease), recruited from Cairo university hospital antenatal care clinic (50 in each trimester), with 40 age-matched non-pregnant females, as a

control group. Serum TSH and TPO Abs were measured. Thyroid volume was assessed in both groups by ultrasonography.
Results
TSH ranges were 0.21–1.7, 0.52–3.2 and 0.72–2.6 mIU/l during first, second and third trimesters respectively. The mean TSH level in pregnant females was significantly lower than that of non-pregnant women (1.2 ± 0.7 vs 2.7 ± 0.9 mIU/l, $P < 0.001$). The mean TPO Ab level was significantly higher in the first trimester compared to both second and third trimesters ($P < 0.001$ for both). Thyroid volume of pregnant females was non-significantly higher than that of non-pregnant control subjects ($P = 0.126$). A significant positive correlation was found between thyroid volume and BMI in pregnant females ($P < 0.001$).
Conclusion
Our study established trimester-specific reference ranges for thyroid functions in normal pregnant Egyptian females. A larger population-based study would help to confirm those ranges. Thyroid volume was non-significantly higher than that of non-pregnant control subjects.

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The evaluation of peripheral vestibular system in Hashimoto's thyroiditis

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Introduction
The aim of this study is to investigate association between Hashimoto's thyroiditis (HT) and vestibular function and the possible effect of levothyroxine (LT4) treatment on vestibular function
Patients and methods
We recruited 61 patients with HT and 30 age and gender matched healthy individuals for the study. Of 30 patients with HT were on LT4 treatment (group I) and 31 patients were treatment naive (group II). None of the patients had vestibulary and hearing complaints. Each subject was submitted to complete vestibular evaluation [Vestibular evoked myogenic potentials (VEMPs), and video head impulse test (vHIT)].
Results
There was no differences between groups for the frequencies of altered cervical and ocular VEMP tests (cervical VEMP for right ear $P = 0.161$; for left ear $P = 0.357$; ocular VEMP for right ear 0.895, for left ear $P = 0.379$). The frequency of altered vHİT tests were similar for all groups ($P > 0.05$). As we compared the hypothyroid and euthyroid patients there were significant differences between groups for left ear cVEMP ($P = 0.042$) and in vHIT tests in right ear's lateral semicircular canal ($P = 0.018$).
Discussion
In contrast to most studies concerning the relationship between HT and vestibular function, in our study, there were no differences between patients with HT and control group. We evaluated all participants with more detailed compared with the studies in the literature. Since HT is an autoimmune disease restricted to he thyroid, there may not be any systemic effects of autoantibodies in other organ systems. However the altered tests of vHIT for lateral canal for both ears in hypothyroid patients needs to evaluated with further studies.

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Voluminous multinodular goiter revealing an isolated thyrotropin deficiency

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Introduction
The goiter represents the most common of all the disorders of the thyroid gland. Many Factors may be involved in the evolution of multinodular goiter. Although thyroid stimulating hormone (TSH) was described as the most important goitrogen factor, impairment of TRH-induced TSH release was reported with nodular goiter, suggesting thyroid autonomy. Herein, we report two cases of an isolated thyrotropin deficiency in patient presented with a voluminous goiter.
Observation 1
A 80-year-old man with no past medical history presented with a 6-year history of a massive multinodular goiter and inspiratory dyspnea. Physical examination showed no signs of dysthyroidism. A computed tomography (CT) scan revealed heterogeneous enhancing of an enlarged thyroid gland (10*13*12 cm) with extension into the chest and compression of the trachea and esophagus. Hormonal tests revealed an isolated central hypothyroidism with a suppressed FT4 levels of 0.69 ng/dl and 0.61 ng/dl (reference range: 0.7–1.5 ng/dl) and a normal TSH levels of 0.55 mIU/l (reference range: 0.35–4.95 mIU/l). Patient was put on Levothyroxine replacement therapy and then underwent total thyroidectomy.
Observation 2
A 38-year-old man with no past medical history was admitted to our department with a massive goiter without compressive signs. Cervical computed tomography (CT) scan revealed a multinodular goiter with chest extension. Thyroid function tests showed a low serum FT4 level of 0.45 ng/dl and a normal serum TSH level of 0.52 mIU/l controlled to many times with no other hormonal deficiency detected.
Conclusion
Among too many factors involved in the development of multinodular goiter, TSH remains the most important one. However, in our cases, the multinodular goiter was associated with a central hypothyroidism which is not a common condition.

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Functional thyroid changes in the first trimester of pregnancy in a normal iodine intake area

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Objectives
Evaluation of functional thyroid alterations in correlation with hyperemesis gravidarum (HG).
Material and method
Study performed on a group of 136 pregnant women with HG and a control group of 101 pregnant women. In both groups, cases with a known history of thyroid disease, molar pregnancy, multiple pregnancies or other systemic chronic diseases were excluded. Patients were clinically and serologically examined (TSH, FT4, ATPO, TRAb), the residence being the perimarine area of Romania.
Results/discussion
Thyroid dysfunction prevailed in pregnant women with HG (53.6% versus 38%). Functionally pregnant women with hyperemesis presented: 44.8% subclinical thyrotoxicosis; 46% - normothyroidism; 3% - subclinical hypothyroidism; 5.8% – thyrotoxicosis; 9.5% – pathologic ATPO level; 0.4% had elevated TRAb. In the control group, pathological changes were: 62% – normothyroidism, 27% - subclinical hypothyroidism, 11% – subclinical thyrotoxicosis. Pregnant subjects with HG showed lower mean TSH than control (1.22 ± 0.64 μU/ml vs 2.18 ± 1.10 μUI/ml); also elevated FT4 values in the study group compared to the control group (17 ± 1.37 pmol/l vs. 15.4 ± 0.82 pmol/l), but all values were within normal range for the first trimester range. The incidence of autoimmune thyroid disease was significantly higher in women who also had hiperemesis gravidarum compared to the control group (9.5% versus 3.9%). The mean ATPO was slightly increased in the HG group (138 ± 9.61 IU/ml) vs. control group (127 ± 11 IU/ml). There have been two cases of spontaneous abortion associated with thyrotoxicosis (1.4%) without antithyroid therapy. In the remaining cases with thyrotoxicosis, without clinical manifestations, were not established specific treatment, and between 11 and 14 weeks serum hormonal values in this group were normalized. Pregnant women with hypothyroidism have received levo-thyroxine treatment in doses between 25 and 75 μg/day with normalization of hormone serum levels.
Conclusions
Pregnant women with hyperemesis gravidarum associated thyroid autoantibodies and functional thyroid abnormalities require obstetrical follow-up and pre/-postpartum thyroid reevaluation. For expectant mothers with subclinical thyrotoxicosis, the transient character of thyroid functional disorder is often considered. Pregnancy can be a way of onset of autoimmune thyroid dysfunction.

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P772

Clinical features, diagnosis and management of hypothyroidism in the elderly at the Endocrinology-Diabetology-Nutrition Department of Oujda's University Hospital

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Introduction
Hypothyroidism affects 2 to 3% of the elderly population. Its diagnosis and management can get difficult considering the clinical and biological particularities of this age range. The aim of this study is to describe the clinical characteristics, diagnosis and management data of elderly patients suffering from hypothyroidism.
Materials and methods
This is a retrospective and descriptive study conducted in the Endocrinology-Diabetology-Nutrition Department of Mohammed VI University Hospital, Oujda, Morocco. It included 22 patients aged over 65 years with hypothyroidism.
Results
The mean age was 71.73 ± 8.72 years with extreme ages (65 years and 91 years). A female predominance was observed. Hypothyroidism was incidentally discovered on biological assessment in 54% of the cases. 31.8% of the patients showed signs of hypometabolism. The major comorbidities associated to hypothyroidism were: Hypertension (69%), diabetes mellitus type 2 (61%), heart diseases (30%) and dyslipidemia (15%). The diagnosis was confirmed in all patients using TSH and FT4 blood tests. 16% of the patients had a subclinical hypothyroidism profile. Primary hypothyroidism was found in 53% of the cases including: autoimmune thyroiditis (49%), previous thyroid surgery (16%) and Amiodarone therapy (8.3%). The etiology was unknown in 16% of the cases. 31% of the patients had a central hypothyroidism due to pituitary adenoma in most of the cases. A thyroid hormone replacement therapy with L-thyroxin was prescribed for all patients. The majority of patients needed a small initial dose, which was increased progressively with close monitoring.
Conclusion
Hypothyroidism is the most common thyroid condition in patients over 65 years, occurring most frequently in aging women. Hypothyroidism associated symptoms are very similar to those of the aging process. Thus, the screening, by measuring thyroid-stimulating hormone (TSH) blood levels, for older patients is recommended. Caution is advised when treating elderly patients with synthetic thyroid hormone, while taking into consideration the coexisting comorbidities.

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P773

Evaluation of oxidative stress parameters in subacute thyroiditis patients

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Objective
The aim of our study was to determine whether there is a relationship between oxidative stress parameters and subacute thyroiditis.
Material and methods
The study included 55 subacute thyroiditis patients and 30 healthy volunteers. Total antioxidant status (TAS), total oxidant status (TOS), paraoxonase (PON) and thiol/disulfide homeostasis parameters were measured by a novel and automated assay in the patient and control groups.
Results
TAS, TOS, oxidative stress index (OSI: TOS/TAS) and PON values were similar in both groups ($P > 0.05$). Native thiol (NT) and total thiol (TT) values were significantly higher in the control group ($P < 0.001$). Disulfide/native thiol (DS/NT) and disulfide/total thiol (DS/TT) levels were higher in the subacute thyroiditis group. Native thiol/total thiol (NT/TT) levels were significantly higher in the control group ($P = 0.02$). When the all participants were evaluated, there was a negative correlation between white blood cell (WBC), neutrophil counts and sedimentation levels and only NT and TT ($P < 0.05$). CRP levels were negative with NT, TT and NT/TT levels; there was a positive correlation with DS/NT and DS/TT levels ($P < 0.05$). In the subacute thyroiditis group, only CRP levels were correlated with TAS ($r = -0.55$, $P = 0.004$) and OSI ($r = 0.451$, $P = 0.24$) levels.
Conclusion
It was first shown that there may be a relationship between subacute thyroiditis and oxidative stress. Oxidative stress may also be the cause of pathophysiology in subacute thyroiditis.

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P774

Uncommon cause of dilated cardiomyopathy

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Thyrotoxicosis is an uncommon cause of congestive heart failure with depressed ejection fraction. However, when it presented in patients without classical cardiovascular risk factors and high heart rate, that not response to usual therapy, other conditions should be considered.
Case report
A 36-year-old male was admitted to our hospital's Coronary Critical Care Unit in acute hypertensive pulmonary oedema. He had noted weight loss, palpitations, shortness of breath and abdominal pain during the previous months. Physical exam: temperature (T) was 37.5°C, heart rate (HR) 150 beats per minute (bpm), firm grade II goiter, gynecomastia, bilateral wet rales and inferior limbs oedema. The neurologic examination demonstrated intense fine tremor of hands and proximal muscle weakness. EKG: atrial fibrillation with high ventricular rate response (HR: 165 bpm). Chest X-Ray: cardiothoracic index pulmonary congestion. The initial echocardiogram revealed left ventricular dilatation with an ejection fraction (EF) of 30%. The coronary angiogram was negative for atheromatous lesions. Laboratory: TSH was undetectable. fT3: 25.73 (2.04–4.4) pg/ml, fT4 > 7.7 (0.93–1.71) ng/dl, TSI 21.59 (0–1.75) UI/l. Laboratory findings were negative for acute myocardial ischemia. The patient received digoxine, furosemide, nitroglycerine perfusion, 40 mg/24 h thiamazole and 2 mg/6 h dexamethasone at first, and then i.v. propranolol. Initial evolution: 24 hours after initial treatment: HR was 130 bpm, T 36.8°; fT3 6.12, fT4 5.39; 48 hours later: HR was 120 bpm, T 36°; fT3 2.61, fT4 1.94, TSI 17.98. Mild dyspnea. At 4th day: fT3 1.65, fT4 1.12. HR 87 bpm. Endocrinology was consulted and advised total thyroidectomy with previously administration of potassium iodine solution. Total thyroidectomy was performed on day 12. Two months later the patient was asymptomatic, in sinus rhythm, on levothyroxine alone. Five months later, the patient was found to be euthyroid, symptoms were relieved and the echocardiogram findings for left ventricular ejection fraction were drastically improved (EF of 64%). In conclusion, an overt congestive heart failure, with left ventricular dilatation and depressed ventricular ejection fraction, is potencially reversible with restoration of the thyroid state in this case. However, other causes of myocardiopathy should be rule out previously, as coronary artery disease.

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P775

Clinical profile and treatment modalities of patients presenting with hyperthyroidism in a tertiary endocrine center in nepal

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Data regarding hyperthyroidism is lacking in Nepal. We did a retrospective analysis of clinical profile and treatment modalities of hyperthyroidism patients in our center.
Methodology
Retrospective data of 132 hyperthyroidism patients between March 2013 and April 2014 at Kathmandu Diabetes and Thyroid Center were analyzed. These patients' records were followed up for one year.

Results
Hyperthyroidism was common in females (73.5%). Graves' disease (GD) was the most common cause (60.6%), then thyroiditis (30.3%), toxic multinodular goiter (Toxic MNG) (5.3%) and autonomously functioning thyroid nodules (AFTN) (3.8%). Mean age of the patients (years) were 36.0±12.2 (GD), 38.7±10.7 (thyroiditis), 52.4±18.9 (Toxic MNG) and 52.6±17.8 (AFTN). 11 (13.8%) patients with GD had Graves' ophthalmopathy. Subacute thyroiditis was seen in 13% with thyroiditis and rest had painless thyroiditis. In GD, 80% patients were treated with antithyroid drugs (ATDs) initially. 55% patients received Radioactive Iodine ablation (RAIA) in GD ultimately. 4 patients required a second dose of RAI. The mean duration to become hypothyroid after RAIA was 4.1±1.7 months. The hypothyroid patients required mean dose of 68.7±18.4 μg of thyroxine. All seven patients of toxic MNG were treated with ATDs. Of 5 AFTN patients, 2 had RAIA, 1 had hemithyroidectomy and rest treated with ATDs.
Conclusion
Hyperthyroidism was found to be most common in females. GD was the most common cause. Most patients with GD were treated with ATDs initially but 55% had RAIA done ultimately. ATDs were also commonly used in toxic MNG and AFTN.

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P776

Community based study of thyroid disorder prevalence in Nepal

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Nepal seems to have high thyroid disorder prevalence but there has been no prevalence studies done so far in general population. We do have a few hospital based prevalence studies of hypothyroidism in Nepal. Our study aims to find the prevalence of thyroid disorders in general population in Nepal.
Methods
We did thyroid function tests of the general population through screening camps in different parts of Nepal. We screened people from 7 places in 5 districts of Nepal. 7 places were Taudaha, Kirtipur and Chabahil (Kathmandu), Lubhu (lalitpur), Gaindakot (Nawalparasi), Lokanthali (Bhaktapur) and Jutpani (Chitwan). Total 671 people were screened. We excluded patients already diagnosed with thyroid disorders. Their blood samples were collected and transported to our center's laboratory. The tests were carried out next day by Roche ECLIA.
Results
Of 671 people screened, 29 people (4.32%) were found to have thyroid disorders. 21 people (72.41%) were diagnosed as sublinical hypothyroidism, 4(13.7%) people had primary hypothyroidism and 4(13.7%) people had hyperthyroidism. Among patients diagnosed with thyroid disorders, male:female ratio was 1:2, mean age was 42.6±13 years, mean weight was 64.3±12 kg, 12 out of 29 patients (41.37%) had family history of thyroid disorders.
Conclusion
We found the prevalence of thyroid disorders in general population in Nepal to be 4.32%. Thyroid disorders were more prevalent in females than in males (2:1). Among people diagnosed with thyroid disorders, 72.41% were diagnosed as sublinical hypothyroidism, 13.7% people had primary hypothyroidism and 13.7% people had hyperthyroidism.

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P777

Lipid profile in primary hypothyroidism: a comparative study between genders in the Endocrinology-Diabetology-Nutrition Department of Oujda's University Hospital in Morocco

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Introduction
Hypothyroidism can be responsible for lipid abnormalities, which increases the risk of cardiovascular diseases and even morbi-mortality. The aim of this study is to analyze the lipid profile in patients with primary hypothyroidism while comparing between genders.
Materials and methods
It is a retrospective and comparative study conducted on 57 patients with primary hypothyroidism in the Department of Endocrinology-Diabetology-Nutrition of Oujda's Mohammed VI University Hospital in Morocco.
Results
The mean age was 51.26 years (extreme ages: 7months and 91 years), with a neat female predominance (80% of women). 82.6% of the patients, with newly diagnosed hypothyroidism, had altered lipid parameters. In general, dyslipidemia was more frequent in females (F): 73.9% F versus 75% of males (M). Decreased HDL-cholesterol was the most common abnormality (73.9% of the patients): 76.3% F versus 62.5% M. 42.8% of the patients had high triglyceride levels: 51% F versus 50% M. Elevated LDL-cholesterol was the least common disorder (31%), found in female patients only. Female patients had a higher mean body mass index (BMI) than male patients: 29.6% kg/m^2 F versus 21.6% kg/m^2 M. Moreover, women had a higher mean thyroid-stimulating hormone (TSH) value, at the moment of diagnosis, compared to men: 33.3mUI/l F versus 30 mUI/l M.
Conclusion
Thyroid hormones are known to have an effect on lipoprotein metabolism. Overall, measurement of blood TSH levels should be included in the screening of patiets with dyslipidemia. There is a significant correlation between the high rate of dyslipidemia in women and elevated BMI and TSH value in women compared to men ($P=0.04$). Management of hypothyroidism with thyroxin substitution therapy (L-thyroxin) can effectively improve lipid levels.

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P778

Graves' disease: woman or man, is there a difference in clinical presentation or evolution?

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Grave's disease (GD), like all autoimmune diseases, is predominantly female, with sex ratio to 3 women for one man. The treatment of first intension is based on antithyroid drugs (ATD). Our objective is to compare the clinical presentation and the evolution of GD by gender. It's a retrospective study. We studied patients with a first diagnosis of GD, in the department of endocrinology in Farhat Hached hospital in Susah, between Juanuary 2010 and December 2015. The patients were subdivised into two groups: G1 (42 men) and G2 contains (75 women). The clinical presentation and evolution were compared in 2 groups. The medium age was 40.6±15 years in G1 and 36.5±13.6 years in G2 with no significant statistical difference ($P=0.14$). A family history of thyroid illness was similar in men and women ($P=0.6$). Thyrotoxicosis symptoms were similirally identified in 90.5% of men and 88% of women ($P=0.35$). The most common symptoms were: weihgt loss, then palpitations and tremors with no significant difference between the groups. Ocular symptoms, especially exophtalmia, were similar in men and women ($P=0.46$). The mean value of fT4 was 59±24.2 pg/ml in G1 and 56±22.7 pg/ml in G2 with ($P=0.55$). TRAbs were positif in 88.1% of men and 89.3% of women ($P=0.2$). The ultrasound volume of thyroid was 37.5±18.6 cm^3 in G1 and 27.6±11.2 cm^3 in G2 with $P=0.05$. Methimazol (MMI) was prescribed to 12 men (28.6%) at a mean dose of 23.3±6.5 mg/day and to 28 women (37.3%) at a mean dose of 25.9±7.5 mg/day ($P=0.29$). Benzylthiouracil (BTU) was prescribed to 30 men (71.4%) at a mean dose of 257.5±64 mg/day and to 47 women (62.7%) at a mean dose of 248.4±60 mg/day with no significant difference ($P=0.53$). The mean durations of treatment with MMI and BTU were similar in both groups (respectively $P=0.3$ and $P=0.23$). Adverse effects were observed in 4 men (9.5%) and 10 women (13.3%) with no remarkable difference ($P=0.2$). ATD remission was higher in women than in men with a significant difference (47.3% vs. 32.5%, $P=0.02$). A relapse after discontinuation of ATD was noted in 10% of men and 16.2% of women, with a significant difference ($P=0.02$). The male sex is associated with a higher risk of failure of ATD during the GD. A higher thyroid volume in men may explain this difference, as a larger thyroid volume is considered a predictor of failure of medical treatment.

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P779

Medical treatment of Gaves' disease in Tunisia: comparison of Methimazole and Benzylthiouracil

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Background
Antithyroid drugs (ATD) are indicated as first intension in the treatment of Graves'disease (GD). Only two molecules are marketed in Tunisia: Benzylthiouracil (BTU) and Methimazole (MMI). There is still no clear conclusion about the choice of appropriate drug. Our objective was to compare the MMI treatment with the BTU in terms of efficacy and adverse effects (AEs).
Methods
It's a retrospective study. We studied patients with a first diagnosis of GD, in the department of endocrinology in Farhat Hached hospital in Susah, between Juanuary 2010 and December 2015. Patients were divided into two groups: G1(patients treated with BTU ($n=77$)) and G2 (patients treated with MMI ($n=44$)). Percentages of patients with normal serum FT4 and frequency of adverse effects were measured at 3, 6, 12, 18, 24 and 30 months. The rates of remission and relapse after standard duration with ATD treatment (12 to 18 months) were assessed in each group.
Results
Two groups are similar as genre and clinical presentation. ATD-related AEs were more common with MMI (18.2%) than with BTU (10.4%), but with no significant difference. There was no significant difference in the frequency of occurrence of different minor AEs between the two groups. For major AEs, there was one case of agranulocytosis in the MMI group (2.3%) and one case of ANCA vasculitis in each group (1.3% in G1 and 2.3% in G2). The delay between the occurrence of AEs and the onset of ATD treatment the most frequently was at 3 months with a predilection for MMI-treated patients ($P=0.02$). The decrease in the fT4 rate was significantly greater with the MMI than with the BTU from the 3rd to the 24th month of the follow-up. The percentage of patients who normalized their fT4 levels was also greater with MMI than with BTU, with a statistically significant difference, up to the 18th month of treatment. The outcome after standard duration with ATD treatment was characterized by a higher remission rate with MMI than BTU (58.3% vs. 31.9%, $P=0.012$). The relapse rate was similar in both groups (14.5% in G1 vs. 11.1% in G2, $P=0.76$).
Conclusion
MMI seems to be more effective than BTU on fT4 normalization and remission rate of the GD. However, its accountability for the occurrence of more adverse events needs to be more studied by studies with a larger sample size.

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P780

Prognostic value of the determination of interleukin-8 in development of thyrotoxic cardiomyopathy in patients with Graves' disease

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Objective
To evaluate the prognostic value of interleukin-8 studies in the development of thyrotoxic cardiomyopathy in patients with Graves' disease.
Materials and methods
86 patients with newly diagnosed Graves' disease were examined, aged 18 to 55 years (mean age 37 years [28; 45]) without previous cardiovascular events. All patients were analyzed by interleukin-8 by immuno-enzyme analysis. To determine the threshold value for Interleukin-8, the logistic recession method (ROC analysis) is used.
Results
Of the 86 patients initially, 33 showed signs of cardiomyopathy, and the level of interleukin-8 was higher than in patients without signs of cardiomyopathy (18.6 [15.7; 19.6] vs. 13.2 [11, 4; 14, 6] ($P=0.0001$)). The area under the ROC curve (AUC), the diagnostic ability of the logistic regression model, predicts the development of thyrotoxic cardiomyopathy using the definition of IL-8 is 0.888, which corresponds to the very good predictive ability of this diagnostic parameter. According to the obtained result, the threshold value for the diagnosis of thyrotoxic cardiomyopathy in patients with Graves' disease in terms of IL-8 level can be taken as equal to more than 14.7 pg/ml, while the sensitivity is 84.8%, and the specificity is 87.1%.
Conclusions
Determination of the concentration of IL-8 in patients with Graves' disease may serve as an additional marker in the diagnosis of thyrotoxic cardiomyopathy, especially in unclear cases.

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P781

Iodine and selenium status in adult PKU

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Background
The standard, lifelong therapy of phenylketonuria (PKU) is natural protein-restricted diet completed with Phenylalanine (Phe)-free L-amino acid mixtures that provide the daily necessary micronutrients, such as iodine and selenium. Our main objective in this study was to assess the iodine and selenium status of patients with PKU, based on their adherence to the low-Phe diet, compared to a healthy control group. Secondly, we aimed to asses whether adherence to therapy has any effect on thyroid function and structure of PKU patients.
Methods
A single-center, case-control study was conducted with seventy-seven PKU patients (age 18–41 years) and 50 matched healthy controls. Thyroid hormones, serum thyroglobulin (Tg), thyroid antibodies (TgAb, TPOAb), urinary iodine (UIC) and selenium concentrations (USeC) were measured, and thyroid ultrasound was performed.
Results
Although optimal iodine status was found in the entire PKU population, by dividing the patients according to their therapy compliance significantly higher median urinary iodine concentration was found in the control and good adherence group compared to the low adherence group (control: 145 μg/l good adherence: 165 μg/L vs. low adherence: 61 μg/l, $P=0.001$, and $P<0.001$, respectively). Median urinary selenium concentration was comparable between control and good adherence groups (21 vs 21 μg/g), whereas low adherence group had significantly lower USeC levels (16 μg/g, $P=0.019$, and $P=0.017$, respectively). The incidence of thyroid dysfunction in the PKU group was infrequent (5%). Median serum TSH was significantly higher in the control the ($P=0.018$) and good adherence ($P<0.001$) groups compared to low adherence group, without any free thyroid hormones changes. TSH levels in PKU group showed a negative correlation with Phe levels (rs $=-0.34$, $P=0.005$). Thyroid antibody (TgAb and/or TPOAb) positivity was found to be similar to those detected in the control group and the general population. No significant difference in thyroid volume and nodularity has been observed between the good adherence, low adherence and control group.
Conclusions
The results of this study suggest that iodine status is strongly influenced by the adherence to therapy in early-treated adult PKU patients. Protein-restricted diet combined with Phe-free L-amino acid mixtures provide adequate iodine intake. No or not enough medical food consumption combined with a low-Phe diet can lead to subclinical iodine deficiency, but it does not influence thyroid function.

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P782

Polymorphisms G691S/S904S of RET proto-oncogene in a patient with sporadic medullary microcarcinoma

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Introduction
Previous studies have shown that the G691S and S904S variants of *RET* proto-oncogene are associated with Multiple Endocrine Neoplasia (MEN) 2A syndrome and have a modifier effect on the age of onset. They are also associated with Papillary Thyroid Carcinoma and with Pheochromocytoma without Medullary Thyroid Carcinoma (MTC). Nevertheless, the influence of these polymorphisms on cases of sporadic MTC is still unclear. We present a patient with sporadic Medullary Microcarcinoma with polymorphisms in RET proto-oncogene.
Methods
A 56 year-old-male with a mild increase of Calcitonin levels (CT:26.3 pg/ml <10) was admitted to the outpatient Endocrinological Clinic for further evaluation. TPO and Tg antibodies were negative and CEA was within normal range. He had a history of congenital cryptorchidism and hypercholesterolemia. Family history for MTC was negative. A Calcium stimulation test was performed, which showed an increase of CT levels up to 637 pg/ml in 2 minutes. Thyroid sonography was normal (without Hashimoto thyroiditis or any nodules). Total thyroidectomy was performed.
Results
The histology of the thyroid gland showed a Micro-Medullary Carcinoma, 1 mm diameter with positive Chromogranin and Synaptophysin staining along with bilobar diffuse and nodular C-cell hyperplasia. RET oncogene analysis was performed and showed two polymorphisms, in exon 11 G691S and in exon 15 S904S of RET proto-oncogene.
Conclusion
Polymorphisms in RET proto-oncogene are rare. Further studies are needed in order to confirm a possible association of polymorphisms of RET proto-oncogene in sporadic MTC.

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P783

Paradoxical first manifestation of papillary thyroid carcinoma in a young male patient

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Introduction
Most thyroid neoplasms arise from follicular cells and are well differentiated. We present an interesting case of a rare first manifestation of Papillary Thyroid Carcinoma (PTC) as a cervical cystic mass, as well as the therapeutic approach.
Material-method
A 29 year-old-male, without personal or family history for PTC and no history of neck radiation referred to our department because of a slow growing right lateral cervical mass in the last 18 months. Sonography and CT imaging showed a mass with the characteristics of a lymphangioma. The patient was submitted to surgical excision. The mass contained *straw-colored* fluid and the histology revealed a follicular thyroid carcinoma with cystic lesions. Thick lymphatic tissue in the cystic wall posed the suspicion for lymphatic metastasis. Postoperatively, the patient underwent a thyroid ultrasound and the result revealed the presence of two suspicious nodes of the thyroid gland, as well as the presence of pathological lymph nodes of the central neck and the lateral compartments, between 2–4. A total thyroidectomy with radical central and right neck dissection was performed.
Results
Histology of the thyroid gland showed the presence of multiple foci of follicular cancer of the right lobe with focal invasion of the surrounding fat tissue and metastatic invasion of 4 out of the 37 excised lymph nodes.
Conclusions
The presentation of this case has the intention to stress out the high suspicion for malignancy that every physician must have, when examining a cervical mass, despite the possible negative imaging report. We would also like to annotate that the neck ultrasound, performed by an expert radiologist, is the gold standard examination on differentiating various pathologies of the thyroid gland.

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P784

The association between the levels of the TSI antibodies and thyroid cancer among patients with Graves' disease who have undergone total thyroidectomy

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Introduction
TSI (Thyroid Stimulating Immunoglobulin) antibodies are a form of immunoglobulin G (IgG) that can bind to thyrotropin receptors on the thyroid gland causing over-production of thyroid hormones and hyperthyroidism. The presence of positive TSI is considered pathognomonic for Graves' disease. Although the association between Graves' disease and thyroid cancer (TC) has been reported in previous studies, the association between the levels of TSI antibodies and TC has not been investigated.
Methods
We included patients with Graves' disease (with elevated TSI >1.75 iu/l) who had undergone total thyroidectomy. We measured TSH, anti-TPO, anti-TG and TSI antibodies. Patients were divided in two groups: patients with TC and patients whose pathology exam was negative.
Results
115 patients (73 females) with mean age 51.47 years and mean TSI levels 8.83 IU/L were included. Eleven patients had TC. Among those patients, the mean TSI antibodies levels were 4.14 IU/L compared with patients who had not developed cancer, whose mean TSI antibodies levels were 9.26 IU/L ($P=0.31$).
Conclusions
Patients with Graves' disease and TC had lower mean levels of TSI antibodies, though statistically not significant, in comparison with patients without TC.

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P785

Never too late for a papillary thyroid carcinoma recurrence

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Introduction
We report a case of papillary thyroid carcinoma recurrence. According to most of the guidelines, patients with PTC have recurrences in the first 5 years after diagnosis and the most rigorous follow-up is indicated in this time; however metastasis are reported beyond this period and are associated mostly with lack of adherence to follow-up.
Case report
A 76-year-old female was admitted in our department for the evaluation of a 5 cm laterocervical lymphadenopathy, which appeared in the last year. She was referred by an ENT doctor who didn't find a cause for her lymphadenopathy. From her medical history: papillary thyroid carcinoma treated with surgery 10 years ago, and afterwards she underwent 3 radioiodine therapy sessions, with normal TSH stimulated thyroglobulin in the first year and normal unstimulated thyroglobulin in the last 10 years. The thyroglobulin value in 2017 was normal (9.66 ng/ dl). Clinical features: Normal BMI, BP, right laterocervical mass of 5 cm, hard at palpation, fixed to the underlying tissues causing a slight dysphagia. Laboratory: thyroglobulin of 199.4 ng/ml, negative thyroglobulin antibodies (10IU/ml), TSH of 2.98, negative calcitonin. Cervical ultrasound: left hypoechoic mass, with a glandular aspect, with micro calcifications, intense vascularization,

but also infiltration into the surrounding muscles. Cervical CT: left laterocervical lymphadenopathy which measured 5 cm, with calcifications, compressive with the adjacent structures and infiltrating the left intern jugular vein. We performed FNAB which showed thyroid tissue with cell atypia and the suspicion of papillary carcinoma (Bethesda V), so we referred her to surgery.
Conclusion
The typical papillary thyroid carcinoma follow-up period is 5 years post radioiodine as the most recurrences appear in this time. A large part of the patients who pass this point without relapse, consider themselves cured and are not as compliant in the thyroid monitoring even though in some cases metastasis occur after 20 years. As the thyroid cancer is forgotten as a possibility, the diagnosis and management of these masses are delayed.

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P786

Long-term efficacy of percutaneous ethanol injection in symptomatic thyroid cysts: Results and protocol proposal

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Aim
To evaluate the long-term efficacy of percutaneous ethanol injection treatment (PEIT) as an alternative to thyroid surgery in symptomatic thyroid cysts with a structured protocol.
Methods
Seventy five subjects (48 ± 12 years; 58% women) with symptomatic benign thyroid cysts relapsed after drainage were included. PEIT was conducted using the established procedure in our hospital, and the initial cyst volume, pain perceived by the patient and symptoms were assessed. In our procedure, a 21G needle was used and the volume of instilled alcohol was <2 ml without re-extraction in all cases. After >1 year follow-up, final cyst volume and symptoms improvement were evaluated.
Results
Symptoms were mainly compressive (91%). Mean maximum cyst diameter before drainage was 3.1 ± 1.2 cm. A single session of PEIT was required to complete the procedure in 38% of patients, two in 33% and three or more in 29%. Mean maximum cyst initial volume was 17.4 ± 15.7 ml before the first drainage and mean total volume extracted from the cysts in all procedures performed was 33.8 ± 47.8 ml. After a mean follow-up period of 42 ± 16 months, 98% of patients reported absence of symptoms. The final volume in the whole group was 1.7 ± 2.6 ml with a mean volume percentage reduction of $88 \pm 13\%$ (53–100%). A final volume reduction greater than 65% was observed in 90% of the cases. Reported pain during the procedure was virtually absent in 20.9%, mild in 54.2 and moderate in the 23.6% of the cases.
Conclusions
Our protocol is proposed as a long-term effective, safe and well-tolerated first-line treatment for symptomatic thyroid cysts.

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P787

Cervical lymph node metastasis in thyroid microcarcinoma

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Introduction
Thyroid microcarcinoma with palpable cervical node metastasis is a rare clinical situation. Through this work, we aim to study its clinical, therapeutic and evolutionary features.
Material and methods
We conducted a retrospective study over 14 cases of thyroid microcarcinoma presenting with a palpable cervical lymph node metastasis collected on the ENT department of Farhat Hached hospital over 28 years (1990–2017).
Results
The mean age of our patients was 47 years. The Sex-ratio was 0.14. The mean lymph node size was 3 cm. There was no palpable tumor in the thyroid gland in 10 cases. All our patients underwent an exploratory cervicotomy. Histological examination revealed a lymph node metastasis of a thyroid carcinoma (papillary in 13 cases and follicular in 1 case). All our patients had a total thyroidectomy. Twelve patients had a central neck dissection with a lateral dissection in one case. Bilateral lymph node dissection was performed in one case. Thirteen patients had a radioactive iodine treatment. We had no case of death or recurrence. The follow-up period was 58 months.
Conclusion
The diagnosis of cervical lymph node metastases in thyroid microcarcinoma should be considered especially with young patients. Their treatment includes total thyroidectomy, lymph node dissection and complementary radioiodine treatment. Long-term follow up is necessary. Their prognosis remains excellent.

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P788

Riedl thyroiditis associated with intense cervical pain

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Introduction
Riedl thyroiditis is a rare thyroid disorder of unknown etiology (autoimmune assumed), in which the gland is invaded by dense fibrous tissue, that extends in the vicinity. Goiter is usually painless and can be accompanied by other fibrous affections (retroperitoneal fibrosis, sclerosing cholangitis, mediastinal fibrosis).
Case presentation
Patient, 39 years old, smoker, from nonendemic area, initially presents in 2011 with voluminous polynodular goiter, spontaneously painful associated with primary myxedema. The painful symptomatology was responsive to glucocorticoids, but relapses severely when trying to stop the administration. In this context, it was performed total thyroidectomy and postoperative histopathological examination revealed thyroiditis scleroatrophic Riedl. Postoperative, she developed severe hypoparathyroidism, corrected with calcitriol(alphacalcidol later) and calcium. Early postoperative cervical ultrasound showed hypodense area of 6 mm in bilateral thyroid box. 5 years later, the patient returns accusing anterior neck pain, anorexia and growth of the thyroid lodge. Investigations carried out show euthyroidism (under substitution therapy), severe persistent hypoparathyroidism, corrected with treatment. A cervico-thoracic CT scan reveals replacement process of the thyroid space bilaterally extended to the posterior vertebral bodies adjacent, that displaces the esophagus posteriorly and the internal carotid arteries and internal jugular veins laterally. Due to the extension of the fibrotic process in the upper mediastinum it was decided to temporize the surgical reintervention and corticosteroid therapy was initiated. The therapy was maintained for 8 months and stopped by patient's initiative, accusing depression and lack of appetite. Thus, hormonal therapy was recommended, with selective estrogen receptor modulator (SERM)- that has shown partial efficiency in Riedl disease. The therapy is relatively better tolerated, but with no signs of improvement. Moreover, she presents in 2019 with recurrence of the disease locally.
Conclusion
Riedl thyroiditis may present with atypical forms, dominated by intense pain in the neck region. Severe recurrence of the disease is present even after the initial quasi-total excision of the affected thyroid tissue and the patient's life quality is gravely affected.

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P789

Is repeat fine needle aspiration required in thyroid nodules with initial benign cytology?

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Background
Fine needle aspiration (FNA) is the preferred method for assessing thyroid nodules but concern remains about false negative results. The primary aim of this study was to investigate the malignancy rate in nodules which were initially classified as benign (BTA classification Thy 2). The secondary aim was to look at the distribution of different cytological categories in a large cohort of patients.

Methods
We retrospectively examined 719 nodules in 714 patients between 2013 to 2017. All FNAs were performed under US guidance. Nodules were cytologically classified according to the BTA guidelines. 53% of nodules were either followed up by ultrasonography or repeat FNA and rest were followed up clinically. Decision regarding follow up was done at a multidisciplinary meeting (MDM). Patients were followed for a median of 48 months.
Results
604(84.5%) patients were female.558 nodules (77.6%) were classified as benign (thy2), 82 (11.1%) were thy1,52 (7.2%) were Thy3.6 (0.8%) were Thy4 and 15 (2.0%) were Thy5. Five Thy 2 nodules (0.89%) were later diagnosed with thyroid cancer of which one had low initial cellularity, one was a co-incidental microcarcinoma in a colloid nodule and one was a cystic papillary carcinoma. All 5 were in remission following treatment with surgery ± radioiodine therapy.
Conclusion
The false negative rate of initial benign FNA is very low in our cohort so routine second FNA is not required in these patients. MDM is useful in informing decision making in those patients

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P790

The prevalence of macro TSH in patients with subclinical hypothyroidism: experience of a single centre

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Background
Subclinical hypothyroidism (SH) is a frequent clinical condition with a prevalence of 3–15% in general population. It is defined by elevated TSH levels with normal thyroid hormones [free thyroxine (FT4) and free triiodothyronine (FT3)]. Similar to prolactin, high TSH levels may be caused by macroTSH, a large molecular sized TSH with a low bioactivity. The aim of the study was to assess the prevalence of macroTSH in patients with subclinical hypothyroidism.
Subjects and methods
Blood samples were obtained from 500 adult patients with subclinical hypothyroidism (TSH > 5 mUI/ml and FT4 within the reference interval: 8–17 ng/l) between September 2017 and September 2018. The presence of macroTSH was assessed by precipitating 250 µl of serum treated with 250 µl of 25% polyethylene glycol (PEG). The precipitable TSH (%) was calculated using the formula: [1-(2* post-PEG TSH/pre-PEG TSH)*100]. Samples with a precipitable TSH > 75% were considered as macroTSH positives.
Results
Of 500 patients (mean age 53 ± 18 years), 366 (73%) were females. The median of pre-PEG TSH was 6.5 mUI/ml (IQR: 5.5-8.5) with a mean FT4 of 11.6 ± 1.85 ng/l. The median post-PEG TSH was 3.1 mUI/ml (IQR: 2.4-4.2) with a mean precipitable TSH of 53 ± 12%. Three patients (0.6%) had macroTSH and 26 (5.2%) a borderline precipitable TSH between 70 and 74%. MacroTSH positive patients were all young females, aged between 31 and 41 years with negative antithyroid antibodies [antithyroglobulin (AbTg) and antithyroidperoxidase (AbTPO)] and not receiving any related thyroid therapy. Pre-PEG TSH levels ranged between 5.7 and 12.9 mUI/ml, whereas the post-PEG TSH ranged between 0.98 and 3 mUI/ml. Regarding 26 patients with borderline precipitable TSH, 20 (77%) were females with a mean age of 58 ± 16.3 years. Evaluation of AbTg and AbTPO was available in 13 patients: 12 out of them (92%) had at least one positive antibody and 11/13 was receiving thyroid substitutive therapy. The median pre-PEG TSH was 6.2 mUI/ml g(IQR: 5.4-7.9), while the median post-PEG TSH was 1.77 mUI/ml (IQR: 1.5-2.3).
Conclusion and discussion
The prevalence of macroTSH in our cohort of patients with SH was 0.6%. This result is in line with other previous studies that reported a prevalence between 0.6 and 1.62%. Despite the low prevalence, the assessment of macroTSH could be useful in patients with subclinical hypothyroidism and negative antithyroid antibodies in order to better evaluate the need of a chronic substitutive therapy.

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P791

Transient thyrotoxicosis in chronic thyroiditis unrelated to a pregnancy

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Abstract
A transient thyrotoxicosis followed by a phase of hypothyroidism, sometimes transient and preceding full recovery, is a usual presentation of postpartum thyroiditis, a form of autoimmune thyroiditis occuring after a pregnancy with a worldwide prevalence averaging 5%. Far less commonly, the same presentation may be observed in various circumstances unrelated to pregnancy. We have observed this condition in 6 patients, 4 women, aged 30 to 44 years, and 2 men, 48 and 68 years. They were seen for a thyrotoxicosis, which was clinically mild in 2 cases, and associated in one of them by a painful neck, and more intense in 4 cases. The thyroid was normal or slightly enlarged.. In all of them, the TSH was suppressed, the free T4 elevated and the TSH receptor antibody negative. The diagnosis of autoimmunity was confirmed in 4 of them by high levels of thyroid antibodies, (both anti-TPO and anti-Tg) and in the 2 other cases, was suspected on an echography consistent with this diagnosis. The duration of the thyrotoxic phase was estimated between 4 and 8 weeks, It was followed in 5 of them by a phase of hypothyroidism, which was only transient in 2 cases and persisted in 3 cases. In only 1 case, the thyrotoxicosis was directly followed by full recovery. In one of these patients, the auto-immune thyroiditis was associated with a Systemic Lupus erythematosis, and in a other case it occured in a patienf treated for chronic myeloid leukemia by Nilotinib, a tyrosine kinase inhibitor.
Discussion and conclusion
We have described 6 patients with a transient thyrotoxicosis in the course of a chronic thyroiditis unrelated to pregnancy. This condition is usually described under the terms of 'silent thyroiditis' or 'painless thyroîditis' (which wouldn't be appropriate to one of our patients).It may be considered as a rare variant of autoimmune thyroiditis. The occurence of a transient thyrotoxicosis is believed to be due to the release of thyroid hormones, caused by the disruption of thyroid follicles. The factor triggering the transitory destructive process is not known. The thyrotoxic phase must not be confused with Graves' disease: the most important of the criteria is the absence of thyroid receptor antibody. It must also be differentiated from other causes of transient thyrotoxicosis such as subacute thyroîditis, associated with a painful neck (but pain was also observed in one of our patients), and iodine-induced thyrotoxicosis

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Clinical staging of well differentiated thyroid cancer patients according to american thyrid association risk calculator version 7 and 8 models

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Aim
The aim of the present study was to compare version 7 of ATA risk calculating tool, developed for the staging of well differentiated thyroid cancers,and is used commonly in the clinical practice with its version 8 developed in 2018 with respect to clinical staging.
Material and method
295 patients followed with the diagnosis of well differentiated thyroid cancer were included in the present study. According to pathology reports and clinical data, their stages were calculated using risk calculator tool AJCC(American-JointCommittee on Cancer) of ATA Version 7(Ver7) and Version8(Ver8). Age, sex, age of diagnosis, duration of disease, pathology reports, the presence of metastasis and radioactive iodine ablation (RAI) were evaluated retrospectively.
Results
Of 295 cases included in the study, (F/M:242/53) 191 was classified as Stage 1, 9 as Stage 2, 83 as Stage 3, and 12 as Stage 4 by Ver7. When the same patients were evaluated with Ver8, 268 was classified as Stage 1, 26 as Stage 2, 1 as Stage 4, without any patients in Stage 3.All patients classified as Stage 1 in Ver7 remained in Stage 1 with Ver8. It was also established that higher number of Stage 1 patients were classified as high risk in Ver8 and that MACIS and AMES scores did not change for the same patient between Ver7 and Ver8 and AGES value was not given in Ver8. However, it was also found that of 83 patients classified as Stage 3 in Ver7, 68 were classified as Stage 1 and 15 as Stage 2 in Ver8. In addition, of 12 patients classified as Stage 4 in Ver7, 6 were classified as Stage 1, 5 as Stage 2 and 1 as Stage 4 in Ver8. Of patients classified as Stage 1 both in Ver7 and Ver8, age, age of diagnosis, and MACIS values were found to be signficantly higher in the latter version. There was significant difference between patients who

were classified as Stage 3 in Ver7 and as Stage 1 and 2 in Ver8 in terms of the age of diagnosis, maximum tumor size and MACIS values.
Conclusion
ATA staging calculator Ver8 classifies the patients into lower stages but to higher risk groups compared to previous version. It is thought that multicentricity and invasion criteria in addition to new age and tumor size limit may have been influential in this result.

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P793

Follicular lesion of undetermined thyroid significance: therapeutic approach to the diagnosis of bethesda 3

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Introduction
Thyroid nodules are very common in the general population (20–75% ultrasound) . There are clinical management criteria established by international societies and standardized cytological diagnostic criteria (Bethesda). However, there is still uncertainty in the management of category 3 (follicular lesion of undetermined significance). Objectives: To evaluate the clinical attitude to the cytological diagnosis of Bethesda category 3 (B3) in thyroid fine-needle aspiration cytology (FNA).
Material and methods
Retrospective study of thyroid nodules classified as B3 after FNA referred to our hospital between 2012 and 2018. Statistical analysis: SPSS vs 22.0 (Student's t-test to compare means and Chi-square/Fisher's test for proportions).
Results
Two hundred two patients (80.7% female); mean (s.d.) age, 53.5 (13.7) years. 151 nodules underwent a second FNA, with diagnosis B1 12.4%, B2 24.2%, B3 45.8%, B4 (13.1%), B5 (2%) and B6 (1.3%), 4 are pending a second FNA. Forty (40) patients underwent surgery. The remaining 7 were managed (in accordance with patient preferences) with active surveillance alone. After the second FNA, 71.6% patients underwent surgery and 2 (1.3%) were waiting for a third FNA. In 41 cases (27.2%) surgery was ruled out because the 2nd FNA was B2 or by patient preference (B3 in both FNA). Eigteen (8.9%) lesions met the reference-standard criteria for malignancy: 13 papillary thyroid cancers, 4 follicular thyroid cancer, 1 thyroid metastases from other malignancies. The rest: 45.8% (60) follicular adenoma, 11.5% (15) multinodular goiter, 8.1% (11) non-invasive follicular neoplasm with nuclear alterations of papillary carcinoma, 3.1% (4) well-differentiated follicular tumor, 2.3% (3) papillary thyroid microcarcinoma.
Conclusions
The percentage of patients with malignant processes of our series corresponds to the bibliography. Although the use of this category seems correct, the clinical attitude is erratic and surgical over-treatment of hyperplasias occurs. In our series, the second FNA, only recodes 24.2% of the cases as benign, being in practically half of the cases (45.8%) B3 again.

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P794

The minimal effective dose of thyroxine is increased in hypothyroid patients with ulcerative colitis

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Abstract
Gastrointestinal disorders may impair oral thyroxine (T4) absorption by either affecting the tablet dissolution or adsorbing the hormone in the first tract of intestinal lumen. Ulcerative colitis (UC) is an inflammatory disease whose interference with oral T4 treatment has been suggested but no evidence have been presented so far. This study was aimed at examining the presence of UC and its possible interference in the pharmacologic thyroid homeostasis, in a large cohort of patients with thyroid disorders. Among 8573 outpatients with thyroid disorders we recruited 34 patients with a definite diagnosis of UC. We selected them using these inclusions criteria: a) hypothyroidism due to Hashimoto's thyroiditis (HT); b) at least two years of thyroxine treatment using the same dose and brand; c) TSH values between 0.8 and 2.5 mU/l in at least three subsequent control visit; d) ulcerative colitis in a stable remission phase. According with the policy of our Centre, all patients enrolled in the study have pledged to take T4 in a tightly controlled fashion and we checked their compliance with the treatment by interviewing them. Patients non compliant or treated with drugs interfering with thyroid homeostasis and/or bearing chronic, infectious, inflammatory or neoplastic diseases had been also excluded. Overall, only 13 of them (12F/1M; median age = 53years) met the criteria and were included in the study group. To calculate the possible excess of T4 required, we compared the minimal effective dose of T4 the UC patients to the one observed in 51 similarly treated age- and weight-matched HT patients, clearly devoid from gastrointestinal and/or pharmacological interference. Twelve out of 13 patients (92%) with HT and UC, required a dose of T4 higher than in the control patients to reach target TSH. Therefore even the median T4 dose required by UC patients was 26% higher (1.54 vs 1.23 μg/kg weight/day; $P = 0.0002$). Since half of our study group consisted of patients aged over 60 years and elderly patients usually require a reduced T4 dose, we reanalyzed our data after their subdivision in two classes of age. Six out of seven (86%) adult patients (<60 years) required a higher T4 dose (1.61 vs 1.27 μg/kg weight/day; +27%, $P < 0.0001$) than the one in the control group. Similarly, all senior patients showed an increased need for thyroxine but to a lesser extent (1.25 vs 1.07 μg/kg weight/day; +17%, $P = 0.0026$). Ulcerative colitis, even during clinical remission, may represent a novel cause of increased need for oral thyroxine.

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P795

Effect of vitamin D supplementation on cardiovascular indices in Graves' disease. A randomized clinical trial

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Background
Risk of cardiovascular disease (CVD) and mortality is increased in Graves' disease (GD) even years after initial diagnosis and treatment. The mechanisms are incompletely understood. Vitamin D insufficiency is associated with an increased risk of CVD and has been reported to occur frequently in GD. Pulse wave velocity (PWV) and blood pressure (BP) are important predictors of CVD. We performed a clinical trial, testing whether vitamin D supplementation affects PWV and BP in GD.
Methods
Using a double-blinded design, 86 hyperthyroid patients with a first time diagnosis of GD were randomized to vitamin D 70 mcg/day or matching placebo as add on to standard antithyroid medication (ATD). At baseline and after three and nine months of intervention, we measured PWV, augmentation index (Aix), brachial and central BP in both office (SphygmoCor Xcel) and 24h setting (Arteriograph). Differences in change between groups were analysed using linear mixed modelling. In subanalysis, interaction between intervention and presence of baseline vitamin D insufficiency (25(OH)D < 50 nmol/L) was tested. (The DAGMAR study clinicaltrials.gov ID NCT02384668).
Results
Nine months of vitamin D supplementation did not affect PWV or Aix. Office central systolic BP declined by −3.9 (95%CI: −7.5; −0.3) mmHg and office brachial mean arterial BP declined by −3.3 (95%CI: −6.5; −0.3) mmHg in response to vitamin D supplementation. However, supplementation had no effect on 24h BPs. Compared to patients with a replete vitamin D status, PWV decreased significantly by −1.2 (95%CI: −2.3; −0.1) m/s in the group of patients with 25(OH)D levels <50 nmol/l ($n = 28$). The reduction of PWV was partly mediated by a decrease in central systolic BP. There were non-significant differences in baseline characteristics in this subanalysis, and the observed response might reflect regression towards the mean.
Conclusion.
Overall, nine months on vitamin D supplementation as add on the standard ATD did not affect PWV and BP in patients newly diagnosed with GD. Whether vitamin D supplementation is of benefit to PWV in GD patients with vitamin D insufficiency needs further investigation.

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Dystrophin and titin – the new markers of muscle dysfunction in thyroid disorders?

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Introduction
Severe thyroid disorders are usually associated with myopathy. Muscle weakness may occur in both hypothyroidism and hyperthyroidism. However, only hypothyroid patients experience increase in creatine kinase levels, depicting destruction of muscle fibers. There were recently some reports showing the lowering in serum concentrations of large sarcomere proteins – titin (TTN) and dystrophin (DMD) in patients with hypo- and hyperthyroidism.
Aim
The aim of the study is to preliminarily evaluate the changes in serum levels of TTN and DMD in patients with severe thyroid disorders and after restoration of euthyroidism.
Methods
The study enrolled 21 patients, newly diagnosed with overt thyroid dysfunction (11 with hypothyroidism and 10 with hyperthyroidism) and 12 healthy control subjects. All subjects underwent laboratory tests (TTN, DMD and thyrometabolic state) at baseline and patients were reevaluated after restoration of euthyroidism.
Results
The median serum TNT and DMD levels were lower in patients affected by thyroid disorders than in control group ($P<0.05$). After restoration of euthyroidism hypothyroid patients showed increase in DMD levels ($P=0.0009$), with no difference compering to controls ($P=0.1768$), while their TTN levels remain low ($P=0.2787$). In hyperthyroid patients there were no statistically significant changes in DMD and TTN concentrations ($P>0.05$), that were still lower comparing with controls ($P=0.02817$; 0.0049, respectively).
Conclusions
Obtained results suggest that even after restoration of biochemical and clinical euthyroidism, these disorders might still negatively affect muscle tissue metabolism. That might be reflected by decreased levels of large sarcomere proteins. However, this preliminary study needs following evaluations on larger groups to confirm this promising results.

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Gender-specific variations of clinical outcomes after thyroidectomy

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Background
Incidence of thyroidectomies and awareness to postoperative quality measures have both increased in the last decade. Gender-specific indications and variations in clinical outcomes of patients undergoing thyroidectomy in Switzerland are of interest.
Methods
We cross-sectionally compared administrative nationwide patient-level data for length of hospital stay (LOS), intensive care unit (ICU) admission, 30-day readmissions rates, and other quality measures among hospitalized female and male patients from January 2011 through December 2015. Multivariate regression models were used to determine gender-specific variations.
Results
A total of 17,410 patients were included whereof 8,629 underwent a unilateral thyroidectomy and 8,721 a total thyroidectomy. 13,732 (78.9%) were female and the median age was 52 (IQR 41–63) and 54 (IQR 44–65) for females and males, respectively. The overall mean LOS was lower in female compared to male patients (3.3 [SD 2.8] vs 3.6 [SD 4.0] days, $P<0.001$). Male patients had a higher risk for postoperative ICU admission compared with female patients (4.8% vs 7.9%; OR, 1.59 [95%CI, 1.38–1.84], $P<0.001$). 30-day overall readmission rate was increased by about 40% in male patients compared to females (5.5% vs 9.3%; OR, 1.42 [95%CI, 1.23–1.63], $P<0.001$). In contrast, less postoperative hypocalcemia were documented in male patients (6.0% vs 8.5%; OR, 0.66 [95%CI, 0.57–0.76], $P<0.001$). The rate of recurrent laryngeal nerve palsy was similar between females and males (2.1% vs 2.4%; OR, 1.05 [95%CI, 0.84–1.33], $P=0.67$).
Conclusions
In Switzerland, the rate of thyroidectomies is more than four times higher in females than in males. Female patients undergoing unilateral- or total thyroidectomy had more favourable clinical outcomes compared with male patients. Importantly, these findings are not explained by the common complications of thyroidectomy (i.e. hypoparathyroidism and laryngeal nerve palsy). The underlying reasons remain to be elucidated.

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P798

Value and limitation of serum MMP-9 in thyroid nodular disease

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Background
Matrix metalloproteinase-9 (MMP-9) is overexpressed in almost all human cancers (including thyroid). High serum levels are generally associated with an adverse prognosis, although the evidence related to thyroid cancer is still controversial.
Aim
We aimed to evaluate pre- and post-surgical serum MMP-9 levels for its diagnostic and prognostic value in a series of patients with benign thyroid disease (BD) or differentiated thyroid carcinoma (DTC).
Patients and methods
We evaluated 306 patients referred for thyroidectomy, aged 49.55 ± 13.76 years, divided in 2 groups according to pathology: BD ($N=173$) and DTC ($N=133$). Sera were collected before surgery in all patients and 1-2 months after surgery in a subset of 66 patients (41 BD, 25 DTC). All sera were stored at -80^0C until MMP-9 was measured, after a median storage of 24 (range 7-45) months. MMP-9 was measured by Elisa (R&D Systems).
Results
Low MMP-9 values were detected in older samples of both BD and DTC patients, and a significant correlation was found between MMP-9 levels and storage duration ($r=-0.449$, $P<0.001$), suggesting that continuous MMP-9 degradation occurs in frozen samples. Median pre-op MMP-9 did not differ significantly between BD and DTC patients (630 ng/ml vs 581 ng/ml), even after correcting for storage duration in multiple regression analysis. After stratifying by storage duration, no MMP-9 difference was noted in cancer patients, irrespective of multifocality, invasiveness, pathological stage or histological subtype. After surgery, median MMP-9 decreased significantly in both BD (from 977 to 833 ng/ml, $P=0.02$) and DTC patients (from 931 to 718 ng/ml, $P=0.02$), suggesting that both benign and neoplastic nodules contribute to serum secretion. Post-op serum MMP-9 was significantly lower in DTC vs BD patients ($P=0.019$), possibly reflecting a more complete thyroidectomy in oncologic patients. In 5 DTC patients (20%) MMP-9 levels increased post-surgery by $>20\%$, and 2 of them had high stimulated thyroglobulin on follow-up, so a more careful follow-up might be warranted for these patients; however 11 BD patients (26.8%) also presented with unexplained higher post-op MMP-9 levels.
Conclusion
Serum MMP-9 cannot distinguish benign from malignant thyroid disease. The MMP-9 dynamic after surgery remains incompletely explained, but postop MMP-9 may be useful in selecting cancer patients who require additional therapy. Because of sample instability during storage, careful protocols need to be established for standardisation of MMP-9 measurement. Since most published studies are conducted on bio-bank samples, comparison between studies must be conducted with care.

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P799

Cut-off values for basal and calcium stimulated calcitonin for the diagnosis of precocious medullary thyroid carcinoma

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Introduction
Thresholds of basal (bCT) or stimulated serum calcitonin (sCT) levels for the diagnosis of medullary thyroid carcinoma (MTC) aren't specified in current revised MTC guidelines.
Objective
We aim to setfemale (F) specific thresholds for bCT and sCT for MTC diagnosis.
Methods
CT samples were measured during calcium-stimulation test (25 mg/kg BW adapted to ideal body mass index) before and at 2, 5 and 10 minutes after administration of calcium gluconate in 34F with thyroid nodules before thyroidectomy. The analysis involved2 1F with abnormal bCT (>9.82 pg/ml) and a control group of 13F with normal bCT (<9.82 pg/ml). Median age was 45.5 years (23–69). CT was measured by immunochemiluminescence. bCT and sCT were correlated to histological results.
Results
The test had minimum side-effects and was well-tolerated. In the control group, the mean bCT was 2.35 ± 2.71 pg/ml (range: <1-9.23) and the mean peak-sCT was 38.83 ± 54.46 pg/ml (range:1.02-167). We identified 1-MTC (sCT = 42.66 pg/ml), 1-macro-papillary thyroid carcinoma (PTC), 3 micro-PTC and 8-benign lesions. For the 21 patients with abnormal bCT, the mean bCT and mean peak-sCT were: 27.54 ± 27.42 pg/ml (range: 9.85–104.4), and respectively 371.24 ± 225 pg/ml (range: 33.16–881.6). We identified: 9-MTC (associated with PTC in 3 cases), 2-macro-PTC, 6-micro-PTC, 1-C-cell hyperplasia (CCH), 3-benign lesions. The best thresholds to discriminate MTC or CCH from the other pathologies and normal subjects were: 13.15 pg/ml for bCT (sensitivity 82%; specificity 70%), AUC 0.85 (CI:0.71-1), $P = 0.001$, and 208.2 pg/ml for sCT (sensitivity 80%; specificity 74%), AUC 0.82 (CI:0.67-0.98), $P = 0.004$. Interestingly enough, the cut-off of 208 remains if we also want to discriminate patients with either MTC, CCH or macro-CPT from other cases. Other pathology results are awaited. Sex specific differences and genetic data are the subject of future reports.
Conclusions
Our study identified bCT and sCT thresholds for distinguishing MTC or CCH for female subjects. The calcium stimulation test is safe to use. Larger groups studies are needed to enhance diagnosis of early stages of MTC, and interestingly enough, maybe also of macro-PTC.

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P800

Pulmonary embolism: a rare complication of hyperthyroidism Report of a case

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Introduction
Venous thrombotic disease is a multicausal disease with many powerful risk factors (genetic, hormonal, environmental …). In recent years, several reports suggest possible relationships between hyperthyroidism and risk of venous thrombosis. We report the case of a patient with hyperthyroidism complicated by pulmonary embolism.
Case report
A 43-year-old female patient, who's under treatment for a relapse of Grave's disease, she was put on Dimazol 30 mg/day with poor adherence; the medication was discontinued 2 months ago. The patient was admitted for a proximal deep venous thrombosis in the left lower limb, complicated two days later by chest pain, dyspnea and hemoptysis. The diagnosis of pulmonary embolism was made, the patient still showed signs of hyperthyroidism: tachycardia with palpitation, weight loss, asthenia, diarrhea with tremor. The patient was hospitalized in cardiology intensive care unit. On examination the patient was: tachycardia at 138 bat/min, polypneic at 48c /min, BP: 14/08 with homogeneous flapping goiter and protruding eyes. Laboratory investigation reported: T4: 100 pmol/l, T3: 34pmol / l. The patient was put on Dimazol 80 mg/day, anticoagulant therapy and Beta blockers with good clinical and biological improvement.
Conclusion
Hyperthyroidism is a potentially serious disorder, but absolutely curable; it is widely associated with increased risk of prothrombotic and hypofibrinolytic states. This observation emphasizes the importance of determining the place of this disorder within the various known risk factors of the thrombotic disease, thus the need to put in place appropriate preventive measures, especially when the usually effective treatment of hyperthyroidism is in default.

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P801

Autoimmune polyendocrine syndrome in patients with Graves' disease

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Introduction
Graves' disease is an autoimmune disease, it is considered to be the most common cause of hyperthyroidism. Autoimmune pluriendocrine syndromes include a diverse group of diseases characterized by functional impairment of at least two endocrine glands due to autoimmune events.
Material and methods
This is a retrospective hospital record-based study of patients with Graves' disease followed up in the day hospital of the department of endocrinology of the CHU Mohamed VI of Marrakech.
Results
A total of 22 patients were analyzed, of which the majority were female, the mean age of presentation in years was 27 years. In addition to Graves'disease, 9 patients (36.6%) showed other autoimmune disorders: 5 cases of Type 1 diabetes, a case of Sjogren's *syndrome*, a case of primary ovarian insufficiency, a case of rheumatoid arthritis and a case of Hodgkin's lymphoma.
Discussion
Hashimoto's thyroiditis is *often* observed together with *other autoimmune* diseases unlike Graves' disease; it is an organ-specific autoimmune thyroiditis that can be associated with other non-organ specific autoimmune diseases, which can lead to states of cross-immunity as to widening the range of multiple autoimmune syndromes. Therefore in view of any autoimmune disease, clinical and biological monitoring especially thyroid biological assessment are highly recommended.

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P802

Carbimazole-induced agranulocytosis: A case report

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Introduction
Hematological toxicity is considered as the main risk of synthetic antithyroid drugs; its major form consists of acute agranulocytosis which can be lethal and requires urgent and adequate management. We report the case of a patient who developed acute agranulocytosis within 1 month of therapy.
Observation
A 24-year-old patient with no particular medical history was admitted for management of hyperthyroidism, with a history of weight loss, palpitation, diarrhea, anxiety and asthenia. On examination: BMI at 20 kg/m^2, heart rate: 100 beats/min, homogeneous goiter. Laboratory investigation reported: TSH: 0.01 Ui/l, T4: 44.8 pmol/l, T3: 15 pmol/l, Absolute neutrophil count (ANC): 2000, Cervical ultrasound showed a thyroid increased in size without nodule; the patient was put on carbimazol 40 mg/day. The patient did not get to do the NFS at the 10th day of the follow-up. A month later, she presented a fever with dysphagia and thrill, the NFS showed agranulocytosis with ANC = 0.00, White globule = 2440, CRP: 199. Carbimazol was withheld and she was started on double antibiotherapy, the evolution was marked by the control of the infection and increase of the PNN at 1300 after 1 week of treatment.
Conclusion
Although rare, the severity of carbimazole-iduced agranulocytosis imposes a good education of the patients as well as a through monitoring of both clinical state and blood count, in particular during the first two months of treatment.

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P803

Genome wide linkage scan for autoimmune thyroid disease susceptibility loci in multiplex Tunisian family.

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The autoimmune thyroid disease (AITDs) comprises two clinical phenotype, Graves' disease (GD) and autoimmune hypothyroidism (AIH), which include goitrous [Hashimoto thyroiditis (HT)] and non goitrous forms [Primary idiopathic myxoedema (PIM)]. These disorders are characterized by loss of immunological self tolerance including the presence of a thyroid lymphocytic infiltrate and autoantibodies to thyroglobulin (Tg) and thyroid peroxidase (TPO). Inheritance of AITDs is complex and, most likely, due to the occurrence of multiple susceptibility genes and the existence of environmental factors modulating their effect. Genetic factors associated with AITDs have been tentatively identified by candidate gene and genome scanning approaches. We enrolled 12 members from multiplex Tunisian family, with high prevalence of AITDs. Nine members were affected with AITDs. Genome wide linkage scan was performed using 395 highly polymorphic markers with an average spacing of 10 cM. Statistical analysis was performed using the non parametric Lod score (NPL) test of Merlin software. Three regions were identified on chromosomes 5q13, 12q24 and 18q21 with a non parametric lod score (NPL) above 2.0. The most significant NPL in this pedigree, was obtained at marker D12S79 (NPL = 3.68, $P = 0.0001$). However, no linkage was found with microsatellite markers spanning the HLA system as well as candidate genes (*CTLA-4*, PTPN22, *Tg, TCR Cβ* and *Ig VH*) and AITDs. the analysis of 20 additional microsatellite markers flanking D12S79, gives significant NPL for seven markers (D12S1341, D12S354, D12S1718, D12S1612, D12S340, D12S1639 and D12S1675) (NPL > 3.0, $P = 0.0001$). Ours findings provide evidence for susceptibility locus for AITDs on chromosome 12q21-24 by use of a genome wide approach and support the existence of genetic heterogeneity in AITDs.

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P804

The manifestation of graves' disease in women with hypopituitarism as a result of radiosurgical treatment of acromegaly

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Cases of hyperthyroidism manifestation associated with previous secondary hypothyroidism are extremely rare. The article presents a rare clinical case of Graves' disease manifestation in a patient with secondary hypothyroidism after radiosurgical treatment of acromegaly. A 38-year old woman with acromegaly and endo-supra-laterosellar pituitary adenoma had transsphenoidal non-radical surgery and subsequent radiosurgical treatment. After 2 years of radiation treatment, she developed secondary hypothyroidism, adrenal insufficiency, hypogonadism, growth hormone deficiency. However, 1.5 years after the diagnosed hypopituitarism the manifestation of Graves' disease was noted, which required thyrostatic and radioactive iodine treatment. Diagnostic criteria for secondary hypothyroidism include low levels of freeT4, freeT3 with reduced, normal or slightly elevated levels of TSH. The criterion for the development of thyrotoxicosis in patients with secondary hypothyroidism was persistent increase of freeT4 and T3 levels in an adequate therapy with levothyroxine. The detection of high level of thyrotrophin receptor antibody in the described case has confirmed Graves' disease manifestation.

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P805

Predisposition to autoimmune thyroid diseases within a Tunisian multiplex family

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Autoimmune thyroid disease (AITD), including Graves' disease (GD) and Hashimoto's thyroiditis (HT), is caused by multiple genetic and environmental factors. The clinical and immunological features of GD and HT are distinct; however, there are multiplex families with both GD and HT. In order to study the genetic susceptibility factors to AITDs, we have followed up 115 control members belonging to a large Tunisian family with a high prevalence of AITDs (Akr family) during 15 years between 1990 to 2005. The follow-up of these control members have showed that 13 subjects (11.3%) developed AITDs. HT was the most frequently seen in 77% of the cases, whereas GD was present in 23% of the cases. One hundred and two members remained controls. High female predominance was noted in the two groups. The mean age of the control subjects group was slightly higher than patients group. The prevalence of positive antithyroglobulin antibody (TgAb) and antithyroperoxydase antibody (TPOAb) was more frequent in patient group ($P = 0.27$ and $P = 0.23$) respectively. The HLA haplotypes was realized in 42% of control members. The most frequent HLA haplotypes that were found were B37, DRB11 and A1. HLA B37 and DRB11 were significantly more frequent for patients ($P = 0.0001$ and $P = 0.034$) respectively. Our study confirms the contribution of the genetic factors in the development of AITDs in 'Akr' family and suggested that the members of this family share the same genetic inheritance.

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P806

The relation of thyroid autoimmunity and parameters of cardiac function

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Introduction and aims
Autoimmune thyroiditis represent a state predisposed for the development of hypothyroidism. It is known that subclinical and overt hypothyroidism are important risk factors associated with the development and progression of heart failure. These effects are due to the changes in the structure and function of the cardiac muscle, as well as the overall cardiac mechanics. The aim of our study was to examine the influence of autoimmune thyroiditis (Hashimoto thyroiditis-HT) on the risk of developing a heart failure.
Methods
We analyzed 56 patients with HT, thereof 31 patients were considered sub-/clinically hypothyroid and on substitution therapy with l-thyroxine. Control group consisted of 25 sex-, age- and BMI- matched healthy individuals. We determined values of thyroid hormones (triiodothyronine T3 and thyroxine T4) and thyroid antibodies (anti-TPO and anti-Tg), as well as serum lipid levels [cholesterol, HDL, LDL and triglycerides (Tg)]. Ultrasonographic evaluation of cardiac cavities [left atrium (LA) area, LA volume, right ventricle (RV), end systolic diameter left ventricle (ESDLV), end diastolic diameter left ventricle (EDDLV), heart wall thickness (posterior left ventricle wall -PLVW, interventricular septum- IVS, systolic function (ejection fraction-EF), diastolic function (E/A) and decelerating time (DT) were evaluated. Statistical analysis was done using the SPSS software.
Results
Patients with HT had significantly higher values of TSH ($P = 0.002$), cholesterol ($P = 0.02$) and LDL ($P = 0.009$). They also had significantly higher parameters of the size of the LA ($P = 0.005$ for LP area, $P = 0.03$ for LP vol) and DT ($P = 0.007$), while the values of other cardiac parameters did not differ significantly among groups ($P > 0.05$ for all). Thyroid hormone and antibody values were not correlated with echocardiographic parameters in patient with HT ($P > 0.05$), except that T3 levels significantly correlated with DT ($P = 0.031$). A significant correlation was confirmed between the values of cholesterol and RV ($P = 0.041$),

IVS ($P=0.041$), IVS ($P=0.16$), ESDLV ($P=0.005$), LAarea ($P=0.025$) and LAvol ($P=0.013$) in patients with HT. Also, the value of Tg was significantly correlated with RV ($P=0.005$), LAarea ($P=0.002$) and LAvol ($P=0.008$), and LDL with PLVW ($P=0.047$) and ESDLV ($P=0.018$). In patient with previous hypothyroidism duration of treatment was significantly correlated with IVS ($P=0.05$), LAarea ($P=0.003$) and LAvol ($P=0.011$) and the dose of l-thyroxine with IVS (0.039), ESDLV ($P=0.002$), LAarea ($P=0.013$) and LAvol ($P=0.028$).
Conclusion
Overt hypothyroidism leads to structural changes of the myocardium, which is only partially reversible after adequate substitution, indicating the need for timely diagnosis of hypothyroidism in patients with autoimmune thyroiditis.

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P807

Breast cancer mimicking metastasis on iodine-131 imaging in thyroid carcinoma

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Introduction
Radioiodine ablation with a whole-body scan is a well known therapeutic regimen for differentiated thyroid cancer. I-131 uptake in the breast has been described with a variety of normal and pathologic conditions such as gynecomastia, supernumerary breasts, fibroadenoma and lactational duct cyst or galactocele. Here we report a case with an incidental radioiodine uptake in breast who turned out to be breast cancer.
Case report
A 70 years old woman presented to our institution with 5 cm hypoechoic thyroid nodule. Since fine needle aspiration was suspicious for malignancy, she underwent total thyroidectomy. Postoperative pathologic examination revealed bilateral papillary carcinoma with capsular invasion and central lymph node metastasis (T1bN1aM0). The patient treated with 100 mci of radioactive iodine I-131 after levothroxine withdrawal for remnant ablation. Posttreatment scan showed an increased focal uptake in the upper-inner quadrant of her left breast. Digital mammography of left breast showed a 10 mm irregular contoured, peripherally spiculated lesion with internal pleomorphic calcifications which was assumed to be malignant.
Discussion
To the best of our knowledge this is the first case in the literature showing a malignant lesion of breast with increased raidoiodine uptake. Sodium/iodide symporter (NIS) is the route of access for iodine to the thyroidal follicular cells for normal thyroid hormone synthesis. The sodium iodide symporter (NIS) mediates the active transport of iodide in the thyroid gland, as well as several nonthyroidal tissues such as breast. Although the functional capacity of NIS seems to be variable, an expression of NIS both in benign and malign breast lesions has been reported. In conclusion the anatomical site of a persistent positive finding should be further characterized with other imaging tests.

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P808

Clinical presentation of hypothyroidism caused by TSH-receptor antibody

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Introduction
Anti-thyrotropin receptor antibodies (TSHR-Abs) stimulating the thyroid (TSAb) are responsible for Graves' disease. In some patients, the TSHR-Abs can block thyrotropin action (TBAb) and cause hypothyroidism, the switch between stimulating and blocking activity in Graves' disease being well. This reports aims to describe clinical presentation of patients affected directly by hypothyroidism.
Material and methods
Retrospective clinical data collection and literature review.
Results
Between 2010 and 2017 in our center, a functional bioassay assessing TSHR-Abs activity was carried out on 9 patients who did not have prior history of hyperthyroidism or ophthalmopathy. These 9 patients were diagnosed with severe hypothyroidism including a major increase in TSH [median: 125.6 µIU/ml (82–132)]. Myxoedema were present in 8 patients and complicated by a cardiac tamponade in one patient. The only patient without myxedema was diagnosed and quickly treated after the onset of hypothyroidism, with a TSH level rising from 0.71 to 46 µIU/ml in two weeks. All patients had a normotrophic gland on ultrasound with features of thyroiditis in 8 patients. Interestingly, three patients had a history of BMT. Series of AITD assessing TRAbs aimed to determinate their frequency, then clinical data are lacking. In case reports describing TBAb-related hypothyroidism, we also observed patients with severe hypothyroidism.
Conclusion
Hypothyroidism induced by TSHR-Abs seems to present often with a severe hypothyroidism. Diagnosing this form could be interesting regarding the risks of switching to hyperthyroidism, orbitopathy and neonatal hypothyroidism in case of pregnancy. Prospective studies are also needed to determinate the prevalence of TBAb in severe hypothyroidism and after BMT and their clinical utility.

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P809

Bone metastasis revealing thyroid micro-carcinoma

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Introduction
Occult carcinoma of the thyroid is defined as a microcancer less than 1 cm in size, clinically undetectable. Discovered accidentally during routine radiological examination, cervical surgery of a benign thyroid tumor, varies from 0.01% to 35.6%. Mostly it is papillary type. Occult cancers revealed by bone metastasis have rarely been reported. We report two patient observations presenting bone localizations of occult thyroid carcinoma.
Observation 1
A 72-year-old woman with a history of right lobustomyectomy for a benign thyroid nodule 15 years ago had three thoracic parietal masses on the right and one on the left. A thoracic CT revealed solid and lytic cost masses: a posterior left centered on the 8th dimension of 70×81 mm and two on the right centered on the 10th posterior dimensions of 84×49 and 67×46 mm. A CT biopsy performed concluded a metastasis of vesicular carcinoma of the thyroid. Thyroglobulin+ and TTF1+. A cervical ultrasound showed two micro nodules of 6x 8 mm and 9×6 mm. She was summed left lobar thyroid with histopathological examination an aspect of a remodeled goitre without histological sign of malignancy. On the post-I131therapeutic whole-body scan, metastases intensively fixed radioactive iodine. A blood test of thyroglobulin, showing high levels at 500 ng/ml.
Observation 2
A 15-year-old patient consulted in neurosurgery for non-painful cranial parietal swelling of fortuitous discovery. A cerebral MRI performed revealed an aggressive solido-cystic osteolytic process of the right parietal vault with endocranial development. The patient underwent complete excision and cranioplasty. Pathological examination concluded bone metastasis of vesicular thyroid carcinoma thyroglobulin+ and TTF1+. The cervical ultrasound found two micro nodules TIRADS4b. Histological examination of the total thyroid-ectomy specimen found favor for a papillary micro carcinoma p T1m N0 M1. Thyroglobuline=38 ng/ml.
Discussion - Conclusion
The term occult thyroid carcinoma, as used by Woolner or thyroid micro-cancer, refers to a cancer whose diameter is one to a few millimeters. In the majority of cases, these micro-carcinomas are imperceptible and histological discovery per or post-operative, their incidence is variable. On the other hand, the micro carcinomas revealed by a bone metastasis, relatively more rare, must be considered as true cancers which have already given metastases and must be treated as such. Boucek et al divided it into four groups distinguished by their initial clinical presentation and the mode of discovery of the primary tumor. Our various reported cases highlight this entity with its diagnostic and clinical features.

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P810

Outcomes of treatment for severe and active Graves' ophthalmopathy

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Introduction
Graves' ophthalmopathy (GO) is an orbital autoimmune disorder closely linked to thyroid autoimmunity, mainly Graves' disease. After an initial progressive inflammatory period (active phase), GO stabilizes and eventually subsides (inactive phase). Treatment should rely on a thorough assessment of the activity and severity of GO and its impact on the patient's quality of life. Patients with active, mild disease generally benefit from local therapies and selenium, while patients with moderate to severe active disease usually require the addition of intravenous glucocorticoid (GCs) therapy. If there is an inadequate response to GC therapy, several second line therapies have been used, including orbital radiotherapy and biological agents.
Method
We performed a retrospective review of patients assessed in the thyroid GO clinical board of the Parc Taulí Hospital between 2016 and 2018; we selected those with moderate and severe active GO that received treatment with intravenous GCs and, in the absence of response, other second or third line therapies. The activity of the disease was assessed according to the clinical activity score (CAS).
Results
Of 53 patients assessed, 17 had moderate to severe active GO (CAS ≥ 3) and were considered candidates for receiving treatment with intravenous GCs. The underlying thyroid disorder was Graves' disease in 16 patients and Hashimoto thyroiditis in 1 patient; thyroid stimulating immunoglobulin was positive in all patients. The age range of the patients was 41–72: 10 women and 7 men. A satisfactory CAS reduction was observed with GCs in 11 patients, but 6 patients did not respond, so we initiated a second and third line therapy. 5 patients received radiotherapy, being effective in 3; 3 patients received rituximab, being effective in 2; 1 patient received tocilizumab, obtaining remission. It is important to note that the treatments carried out were only effective in controlling the inflammatory symptoms (assessed according to the CAS), but the outcomes in terms of improvement of diplopia and proptosis were poor, with 6 patients undergoing strabismus surgery and 4 patients undergoing not emergent orbital decompression.
Conclusion
In our cohort the rate of response of the different treatments was 64.7% with intravenous GCs, 60% with radiotherapy, 66% with rituximab and 1 of 1 with tocilizumab.

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P811

Malignant lentigo melanoma in patient with agressive thyroid folicular carcinoma

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Lentigo malign melanoma corresponds to the main histological type of melanomas 'in situ', particularly affecting Caucasian elderly exposed chronically to the ultraviolet rays. The therapeutic course should be surgical, with careful resection of the tumor, allowing free and wide margins. Follicular thyroid carcinoma corresponds to the second most common histological type characterized as a well differentiated neoplasm. It presents markedly vascular dissemination, being rare lymph node involvemen. The degree of vascular extension determines the severity of the tumor, as well as if the variant is from Hurthle cells, which confers a higher risk prognosis. Both tumors have congruent mutations, especially BRAF, RAS family (K-RAS, N-RAS and H-RAS) and TERT as carcinogenesis mechanisms. Although rare in lentigo maligna melanoma, the presence of these markers should be suspected in patients who evolve with other malignant neoplasms, with similar genetic pathophysiology.
Case
A 62 years old female, caucasian, with no known comorbidities, sought medical assistance due to the growth of blackened macular lesion on the lower left lip. He had goiter on physical examination. The labial lesion was suspected of melanoma, being surgically resected. The anatomopathological result was compatible with lentigo maligno melanoma in situ, measuring $3.4 \times 2.3 \times 1.2$ cm, with free lateral and deep surgical margins. Patient was submitted to total thyroidectomy with cervical emptying in November 2018, whose anatomopathological result was: granular follicular thyroid carcinoma variant of widely invasive, multifocal, right lobe, measuring 5 cm and 3.8 cm in the right lobe axis, with angiolymphatic infiltration and focally compromised surgical margins. Dermal and subcutaneous metastasis of the carcinoma, with the same histopathological characteristics.
Discussion
- This is an uncommon case with extensively invasive follicular carcinoma, with very aggressive behavior, diffusely affecting the lungs, and presenting metastases to the dermis and subcutaneous, these latter two sites being infrequent for metastatic involvement by thyroid tumors. The association with lentigo maligna melanoma, whose pathophysiology involves mutations in BRAF and RAS genes, may not be merely sporadic but associated with mutations in the same genes. The association of thyroid cancers with other malignant tumors has been described in the literature, being the breast, kidneys and skin the most common. In view of the aggressiveness of the patient's thyroid tumor and the association with lentigo malign melanoma, the case report is important, allowing new lines of study between thyroid carcinomas and other related malignancies.

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Adrenal and Neuroendocrine Tumours 3

P812

Robotic-assisted interaortocaval dissection of an extra-adrenal paraganglioma in supine position via a trans-peritoneal approach

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Introduction
Pheochromocytoma and paraganglioma (PPGLs) are rare neuroendocrine tumors. Some of them are catecholamine-secreting tumors responsible for hypertension or adrenergic symptoms. Among 10% are malignant with a higher rate of malignancy in the inherited syndromes. Management of patients with hereditary pheochromocytoma and PPGLs is well defined and standard treatment is surgical resection.
Case report
We report the case of a 53-year-old man who had been discovered a SDHB gene mutation (c.594C>A) through a familial genetic screening. An interaortocaval mass of 8mm corresponding to a non-secreting PPGL was highlighted by [18F]-fluorodeoxyglucose PET and ^{68}Ga-DOTATATE. Tumor did not appear on ^{23}I-metaiodobenzylguanidine (mIBG) scintigraphy. After two years follow-up, tumor was growing from 8mm to 12 mm and patient decided to undergo surgical resection. In order to reduce surgical morbidity, robotic-assisted interaortocaval dissection of the PPGL in supine position via a trans-peritoneal approach was proposed. Surgical method: Under general anesthesia, the patient was placed in a supine position. An 8 mm robotic optic port was positioned below the umbilicus, at the level of the right umbilical ligament. Three operative 8 mm port were positioned then in a linear configuration, along with an assistant 12 mm port in the right iliac fossa. The DaVinci Xi robot was docked and directed cephalad. The dissection began by mobilization of the caecum and incision of the posterior peritoneum overlying the right common iliac artery, in order to expose the inferior vena cava and the aorta. The dissection was then advanced cranially, taking care to ligate any perforating vessel, until the renal bifurcation was encountered. The mass was identified in the inter aortocaval region and fully dissected. The operative time was 130 minutes and estimated blood loss was <50 ml. No drain was positioned and no opioid analgesics were required in the post-operative setting. The patient was discharged on POD 1. Final pathology revealed a sympathetic extra-adrenal paraganglioma, $20 \times 13 \times 10$ mm and negative margins: pT1R0.
Conclusion
Robotic-assisted interaortocaval dissection is safe and feasible with great reduction of surgical morbidity and minimal blood loss. This approach can be efficiently be implemented to address tumors or malignant lymph node pathology of this surgical region. Large prospective studies are required to define the role of robotic assisted surgery in the field of retroperitoneal neuroendocrine tumors.

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P813

Pituitary metastasis of Neuroendocrine Carcinoma – a rare case report

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The authors report the clinical case of a 59-year old female who had vague complaints of impaired vision, fatigue and diffuse pain for more than a year before medical evaluation at our hospital. At the ophthalmology appointment, bitemporal hemianopsia was evident. Brain MRI was the diagnostic test of choice and revealed a mass involving de sellar and suprassellar space, causing compression of the optic chiasm, as well as osteolytic lesions in cranial vault. The patient was then referred to the endocrinology department where hypopituitarism was detected in blood work-up; hormone replacement therapy ensued. Whole-body CT screening identified pulmonary, pancreatic and hepatic nodules and multiple bone metastasis on axial skeleton were evident on skeletal scintigraphy. Surgical removal of the suprassellar mass and a bone biopsy of the cranial osteolytic lesions were scheduled, and histological findings confirmed both lesions as metastasis of a neuroendocrine carcinoma with a Ki 67 between 5 and 10%. Visual impairment improved after surgery, but *de novo*polyuria and polydipsia required therapy with desmopressin. Octreotide scan showed increased tracer uptake in the sella turcica, thorax, liver and right iliac fossa. The patient started monthly injections of long-acting octreotide, but follow-up scintigraphy revealed progression of pulmonary and bone lesions six months after surgery, with concurrent deterioration of the patient performance status and increased pain complaints. Further follow-up studies were performed at the patient's local hospital. This clinical setting is particularly rare since most pituitary metastases are clinically silent. Moreover, the rarity of a pituitary metastasis of a neuroendocrine carcinoma is also to be noted. Guarded prognosis of such malignant disease was evident, considering therapeutic resistance, even though it is typically a slow-growing tumor.

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P814

Abnormal serotonin regulatory loop in adrenals of patients with Cushing's syndrome and 21-hydroxylase deficiency

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In the human adrenal gland, serotonin (5-HT), released by subcapsular mast cells stimulates corticosteroid secretion through activation of type 4 serotonin receptors (5-HT4R) positively coupled to cAMP/proteine kinase A (PKA) signaling pathway and calcium influx. The 5-HT4R is principally expressed in zona glomerulosa cells explaining why 5-HT strongly stimulates aldosterone production but only exerts a modest stimulatory action on cortisol. Interestingly, in primary pigmented nodular adrenocortical disease (PPNAD) cells, activation of the cAMP/PKA pathway by *PRKAR1A* mutations triggers upregulation of the 5-HT synthesizing enzyme tryptophan hydroxylase (TPH) together with the 5-HT4, 5-HT6 and 5-HT7 receptors. 5-HT strongly stimulated cortisol production and inhibition of TPH reduced corticosteroidogenesis in cultured PPNAD cells. ACTH stimulates cortisol secretion through binding to the melanocortin receptor type 2 (MC2R) and activation of PKA. We have thus investigated the 5-HT signaling pathway in adrenal tissues removed from patients suffering from diseases associated with chronically high plasma ACTH levels, such as Cushing's disease (CD), ectopic secretion of ACTH, and 21-hydroxylase deficiency (21-OHD), in comparison with normal adrenals. Like in PPNAD tissues, TPH and 5-HT4/6/7 receptors were overexpressed in the different types of tissues studied. In one adrenal tissue removed from a patient with paraneoplastic Cushing's syndrome, the cortisol response to 5-HT *in vitro* was exaggerated *vs* normal adrenals and the stimulatory action of 5-HT was reduced by 5-HT4R antagonist. Finally, 5-HT was found to dose-dependently stimulate dehydroepiandrosterone secretion from cultured normal adrenocortical cells, suggesting that enhancement of the adrenal 5-HT tone in 21-OHD tissues may favor androgen hypersecretion together with ACTH. Collectively, our results indicate that activation of the cAMP/PKA pathway in adrenocortical cells resulting either from *PRKAR1A* mutations or activation of the MC2R by sustained increase in plasma ACTH levels induces an aberrant serotonergic stimulatory loop in zona fasciculata. Potentiation of the intraadrenal 5-HT signaling pathway may participate in the pathophysiology of hypercortisolism and could represent an adaptive mechanism to increase glucocorticoid synthesis in 21-hydroxylase deficiency.

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P815

Insulinoma: Diagnosis and surgical management retrospective analysis of 9 cases

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Introduction
Inslinomas are the most common cause of hypoglycemia resulting from endogenous hyperinsulinism. Although rare, they have the potential to produce metabolic derangements, necessitating early diagnosis. The aim of our study was to determine the clinical manifestations, diagnostic methods, treatments used and results of patients with insulinoma.
Patients and methods
It's a retrospective study including 9 patients with insulinoma, diagnosed between 1991 and 2016, at the department of endocrinology at Hedi Chaker-hospital Sfax-Tunisia.
Results
No sex predilection was apparent: 5 males and 4 females, with a mean age of 44.2 years (range, 18–68). Average duration of symptoms was 18, 25 months (6 months–6years). Frequency of hypoglycemic episodes ranged from daily to 7 times a week. Approximately 88.5% of patients consulted for neuroglycopenia symptoms: loss of consciousness (6 cases), convulsions (4 cases), abnormal behavior (2 cases) and headache (4 cases). Weakness and weigh gain was observed in 8 patients each. 66.5% of patients experienced late postprandial hypoglycemia. Therefore, fasting hypoglycemia were observed in 88.8%. The mean fasting blood sugar level was 2, 91 mmol/l. Six (66.5%) patients had spontaneous hypoglycemia during hospitalization and 44.5% required a prolonged fast to induce hypoglycemia, with a mean duration of fast of 22.75 hours. The mean blood glucose level at the time of hypoglycemia was 0.39 g/l and concomitant mean plasma insulin was 20.2 µUI/ml (range 10.6–45.6). Concomitant pro-insulin level was estimated in 2 patients with a mean level of 45.13 pmol/l. Multiple endocrine neoplasia type 1(MEN1) was objected in one patient. Preoperative localization identification was accomplished in eight cases, using a combination of radiological techniques including: transabdominal ultrasonography (9 cases), endoscopic ultrasound (6 cases) and MRI (2 cases). The tumor was located in the body and tail regions in 4 patients each and in the head region in only one case. Multiple adenomas were observed in only one case. 8 patients underwent surgery. The tumor size ranged from 9 mm to 40 mm. Death occurred in 2 cases. Five subjects had no recurrence of hypoglycemia and are considered cured on follow-up. In addition, one patient developed transient post operative diabetes and glucose intolerance was observed in only one case.
Conclusion
Insulinoma may occur at any age and the diagnosis must be established as soon as the first manifestations occur to preserve prognosis.

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P816

A case of pheochromocytoma diagnosed with maternal lung edema and fetal mortality

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Aim
Pregnancy and pheochromocytoma are an important clinical picture in which the mother and fetus are under threat. Herein, we present a case diagnosed with pheochromocytoma in the follow-up of fetal mortality and maternal pulmonary edema after emergency postnatal caesarean section.
Case Report
Our case was a 32-year-old female, fetal distress was determined after hypertension and maternal hypoxemia in 26 weeks of gestation and emergency caesarean section was performed. The baby did not alive due to postpartum arrest and the mother could not be extubated because of hypoxemia. When the blood pressure and pulmonary edema were examined for the etiology, two masses of 3 cm and 5.5 cm were detected in the left surrenal gland. Blood catecholamines were found to be high and the patient was diagnosed as pheochromocytoma, and prepared to operation with alpha blocker, calcium channel blocker and beta blocker. Laparoscopic excision of the masses in the left adrenal region was completed without complication. Additionally, fine needle aspiration due to multinodular goiter and calcitonin elevation was followed up for multiple endocrine neoplasia.
Discussion
An unrecognized pheochromocytoma can result in loss of mother and / or infant during pregnancy. Pheochromocytoma should be suspected at any stage of pregnancy, especially in all pregnancies with paroxistic hypertension and / or familial history. Maternal and fetal complications should be prevented with proper preparation and surgery.

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P817

A case of bilateral pheochromocytoma presenting with peritoneal metastasis after 12 years of primary diagnosis

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Introduction
Ten per cent of pheochromocytomas are malignant. Malign pheochromocytoma could cause metastasis, relapse and local invasion. The most common sites of metastasis for pheochromocytoma or extra-adrenal paraganglioma are lymph nodes, bones, lungs, and liver. Here, we present a case who had pheochromocytoma relapse and unusual peritoneal metastasis after 12 years of left adrenalectomy.
Case presentation
A 38 year-old woman, who had left adrenalectomy due to malignant pheochromocytoma in 2006, was admitted to outpatient clinic for routine visit. Her physical examination was normal. In the blood tests, ACTH level was 29,1 pg/ml and cortisol level was 14 ug/dl. In 24-hour urine tests, the hormone levels were as defined: free cortisol: 60 nmol/g (N: 38–208), metanephrine: 3469 µg (N: 276–341), normetanephrine 8199 µg (N: 88–444). In the abdominal MRI, there was a solid mass of 50×86×55 mm in the right adrenal gland on and left adrenal gland region findings were compatible with adrenalectomy. An operation was offered, but she came for the operation after 5 months. Pre-operative CT showed a relapse or residual mass of 25×20 mm, suspicious features for renal capsular invasion and multiple nodules suspicious for malignant implants in the adipose tissues of subhepatic, right paracolic, bilateral pelvic and left retroperitoneal regions. There was also a solid mass of 85×53×53 mm in the right adrenal gland region. Cortex sparing adrenalectomy on the right side, left adrenal glandresidual mass excision, omentectomy and appendectomy were performed. Multiple tumor implants scattered in the abdomen were also resected. The pathological findings of all surgery materials exhibited metastatic pheochromocytoma. Postoperative ACTH stimulation test indicated adrenal gland IN sufficiency. Hence, hydrocortisone was added to the treatment. Genetic tests demonstrated heterozygous RET mutation c.1891G>T(p.Asp631Tyr).
Conclusion
Pheochromocytomas may occur in large sizes and metastasize. The standard treatment of malignant pheochromocytoma is excision of the tumor. Despite to radical excision, relapse in chromaffin tumors and metasynchronous tumor development may evolve. Close follow up of the patient is mandatory.

Keywords: bilateral, pheochromocytoma, peritoneal metastasis
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P818

Adrenal oncocytic pheochromocytoma with probable malignant potential: a case report

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Introduction
Adrenal tumors present with clinical features and signs unique to their specific hormonal hypersecretion. Among adrenal tumors, oncocytic pheochromocytomas are exceedingly rare tumours. We report an unusual clinical presentation of an adrenal cortical tumor with histologic features of an oncocytic pheochromocytoma.
Case Report
We present a case of a 64-year-old man with moderate hypertension, type 2 diabetes and an incidental adrenal mass on radiological investigations. The patient had high levels of 24-hour urine metanephrines and normetanephrines: 13 (normal: <0.9 nmol/l). A CT scan of the abdomen revealed a 76 × 64 mm hypodense solid lesion in the right adrenal gland. The tumour was subsequently excised. Macroscopic examination revealed a yellow-buff mass of the adrenal gland measuring 100×70×55 mm and 151 g. Histologically, the tumour cells showed oncocytic appearance with high-grade nuclear abnormalities (nécrosis) and foci of extension into the peri-adrenal fat. Immunohistochemical studies revealed that the tumour was positive for chromogranin and synaptophysin and negative for cytokeratin. The malignant potential of pheochromocytoma is known to be difficult to predict. scoring system used was PASS (phaeochromocytoma of adrenal scaled score) by Thompson, which schowed that the tumour had a malignant potential.
Conclusion/Discussion
Oncocytic phaeochromocytoma should be in the differential diagnoses of oncocytic tumours of the adrenal gland. The majority of neoplasms are benign and should not be misdiagnosed as carcinoma...

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P819

A novel pathogenic mutation in neurofibromatosis type 1

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Introduction
Neurofibromatosis type 1 (NF1) is one of the most frequent genetic dominant syndrom in men with a prevalence of 1 in 2600 to 3000 individuals worldwide.

NIH NF1 diagnostic criteria are driven by the most frequent manifestations of the disease ('café au lait' macules (CAL), neurofibromas, freckling, optic glioma, Lisch nodules and bone lesions). There are many clinical manifestations of NF1 (neurological, cardiovascular, gastrointestinal, endocrine and orthopedic features). Phechromocytoma is one of them, occurring in approximately 0.7% of cases. The protein encoded by NF1 gene, neurofibromin, is a RAS GTPase-activating protein. NF1 belongs to the group of RASopathies which are syndromes predisposing to benign and malignant tumors. There are more than 1400 indentified mutations of NF1 gene of which 50% are singular mutation. NF1 is sporadic in approximately 50% of cases. The penetrance is complete but there is lack of genotype-phenotype correlation, except in some cases, probably because of the existence of modifier genes.
Case report
We report the case of a 23-year-old men who complained for recent discomfort characterized by paroxysmal headache, palpitations with unusual fatigue, epistaxis and severe hypertension. He didn't take any medication or drug. He had no medical history except the removal of an unsightly frontal skin lesion. Clinical examination showed CAL spots and a lesion suspected for neurofibroma on the right forearm. Repeated 24-hours urine fractionated metanephrine and catecholamine measurements showed elevation of catecholamine and (nor) metanephrine levels between 7- and 10-fold the upper limit of reference range. Abdominal CT revealed a voluminous mass of 50×30mm of >40 HU density in left adrenal gland. Patient underwent adrenalectomy and excision of the forearm lesion. Histopathology confirmed the suspected diagnosis of pheochromocytoma and neurofibromatosis. Genetic testing showed an heterozygote variant of NF1 (c.5791T>A(p.TRP1931Arg). No other genetic variant was identified with cDNA sequencing and MLPA. This variant had previously been reported in an adult man with CAL spots and freckling but without neurofibromas. In the LOVD database this variant is reported as a variant of unknown clinical significance. We decided to perform segregation analysis within his family in order to reveal whether this variant is present in the unaffected parents. Target mutation analysis showed the absence of the tested NF1 variant in both parents, revealing a *de novo* event in the patient and a new deleterious effect of the NF1 variant c.5791T>A (p.TRP1931Arg).
Conclusion
We report a novel pathogenic NF1 mutation responsible for pheochromocytoma.
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P820

Clinical, hormonal and histopathological evaluation of adrenal incidentalomas: About 45 cases

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Introduction
Given their prevalence of up to 5% of the general population, A discovery of an asymptomatic adrenal mass (incidentaloma) during the investigation of an unrelated condition is relatively common. The issue of crucial importance is the histopathological differentiation between benign lesions and malignant tumours of the adrenal gland.
Objective
To evaluate the secretory or non-secretory profile and the benign and malignant nature of incidentalomas.
Patients and Methods
Retrospective study of 45 cases of CT-confirmed adrenal incidentalomas followed between 2010–2019 in the endocrinology department. Their clinical, radiologic, and histopathological evaluation were reported.
Results
The average age was 51.8 years with female predominance (Ratio H/F: 0.68). Eleven patients had masses in the adrenal gland discovered by abdominal ultrasonography (24.5%), 33 patients by abdominal CT (73,4%) and one patient by MRI (2.1%). The most common clinical abnormalities were abdominal pain (10 cases), chronic diarrhea (6 cases), weight loss with deterioration of the general state (6 cases), an unexplained ketosis in a type 2 diabetic (1 case), a chronic renal failure assessment (1 case). Incidentalomas were unilateral in 33 patients and bilateral in 12 patients. The size of the tumours ranged between 0.8 and 16.0 cm. The diagnosis was pheochromocytoma in 12 patients, metastasis in 5, adrenal carcinoma in 2, 2 lymphomas, 2 Conn adenomas, one adrenal cyst, 2 myelolipomas, and cortical adenomas in 19 patients. Management reposed on an adrenalectomy in 22 patients, followed up in 15 patients, 4 abstentions and 4 patients died before surgery (metastatic neoplasia).
Conclusion
In our series, 40% of the lesions were secreting and 20% malignant. In the vast majority of cases, the adrenal incidentaloma was a non-secreting benign adenoma. However, it is imperative to ensure the absence of malignancy requiring specific management.
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P821

The malignant potential of oncocytic adrenal tumours should not be underestimated

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Background
Oncocytic neoplasms are rare adrenal tumours usually considered as benign and non-functional. Conversely, in recent large nationwide study from COMETE network over 50% of the oncocytic adrenocortical tumours were diagnosed as carcinoma according to Lin Weiss-Bisceglia-score. However, until now only 11 cases of metastatic oncocytoma were reported in English literature.
Case report
A 54-year-old man with history of abdominal pain and weight loss (18 kg in 12 month) was diagnosed with left adrenal mass in 2014. In March 2016, hormonal evaluation showed that the tumour was non-functional. Left adrenalectomy with simultaneous nephrectomy were performed in another centre. The pathological examination revealed a 23×13×9 cm tumour. Initial histological analysis was in favour of a benign oncocytic adenoma with no Weiss criteria for malignancy, without kidney invasion. There was no further follow-up, no thoracic imaging. Postoperatively, the patient developed end-stage renal failure because right kidney was non-functional (which unfortunately had not been checked preoperatively) and required haemodialysis. Hydrocortisone supplementation was stopped in June 2016. In June 2018, the patient was referred to our centre (Felix Guyon University Hospital). Abdominal and thoracic CT-scan showed two pulmonary nodules (2.8 cm and 0.8 cm, in left and right lower lobes, respectively). 18F-FDG PET/CT imaging showed intense 18F-FDG uptake of pulmonary lesions. Pathologic examination of the CT-guided percutaneous needle biopsy showed large tumour cells with eosinophilic granular cytoplasm, diffuse architecture and nuclear atypia. There was no mitosis; central zone of necrosis was noted. Immunohistochemistry confirmed the adrenocortical origin with positivity for synaptophysin, cytokeratin-8/18, melan-A, MART1 and α-Inhibin-A and no expression of chromogranin-A. Adrenal tumour samples from 2016 were reviewed by two independent pathologists (one of them belonging to a national reference centre) who concluded to malignant adrenal oncocytoma with two major criteria of malignancy (mitotic rate 6/40 high power field, atypical mitoses) and at least 1 minor criteria (size >10 cm) according to Lin–Weiss–Bisceglia score. Ki67 was 8%. Immunohistochemistry showed positivity for synaptophysine, cytokeratin-8/18, melan-A and MART1 but no expression of α-Inhibin-A, chromogranin-A. The patient underwent radiofrequency ablation of metastatic pulmonary lesions (Paris). A low dose of mitotane treatment (1500 mg/d) was introduced due to renal impairment. Mitotane dose was progressively increased to 3000 mg/d. Mitotane serum level was stable before and after haemodialysis which suggests that it is not dialyzable. Short-term evolution was eventless.
Conclusion
Oncocytic adrenocortical carcinoma are rare tumours with potent metastatic evolution. They should be managed by a multidisciplinary expert team.
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P822

Melasma as a sign of Addison's disease: case report

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Introduction
Addison's disease was first described in 1855 by Thomas Addison as a result of adrenal insufficiency. It is most common in females aged 30–50 years. Symptoms are often non specific.Weakness and weight loss are universal features of Addison's disease. It can present to a dermatologist in different ways. We present a case of a young female who reported to dermatology outdoor with a typical melasma-like eruption over her face.
Case report
A 23-year-old young woman presented to our clinic with 5 months history of progressive facial pigmentation, gradually worsened. She noted a weight loss of 8 kg during this period. She also reported that previous Ramadan fasting was a challenge for her. On examination she was found to be weak with marked pallor. Dermatological examination revealed typical melasma-like pigmentation over bridge of the nose and prominence of the cheeks. There was no pigmentation in palmar creases, flexures, nipples, knuckles, genitalia or oral mucosa. Systemic examination was unremarkable. Our major diagnostic doubt was between diagnosing classic melasma or Addison's disease. Therefore, we requested laboratory tests. Blood chemistry tests revealed low plasma cortisol associated to hyponatraemia and hyperkalaemia. Furthermore, a short synacthen tes was requested to confirm adrenal insufficiency, in which impaired response to adrenocorticothropin hormone was found. MRI of the adrenal glands showed absence of any masses or swellings that could mimic a neoplasm producing ACTH. On the basis of the above findings, a diagnosis of Addison's disease was made.
Discussion
Addison's disease is a primary adrenal failure caused by infiltrative or autoimmune processes. Hyperpigmentation of the skin is considered a hallmark of Addison's disease, related to ACTH melanogenesis action. It may involve skin, oral cavity, conjunctiva and genitalia. It is more evident in areas exposed to the sun and under mechanical stimulation: palmar creases, knuckles, flexural areas, areolas of nipples, scars and genital mucosa. Melasma-like pigmentation without involving any other area of the body is an uncommon finding in Addison's disease. Our patient initially presented with only melasma like hyperpigmentation and Addison's disease were never thought of at that time, but when it was soon followed by other suggestive manifestations we correlated it and considered it to be one of dematological presentation of the disease.
Conclusion
Every melasma-like pigmentation is not always melasma. We, dermatologists, should have a high index of suspicion for a rare and potentially dangerous medical illness i.e. Addison's disease.

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P823

Pheochromocytoma affecting Pregnancy: still searching the needle in the haystack?

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Introduction
Pheochromocytoma associated with pregnancy carries a great risk for adverse fetal and maternal outcome, especially when the diagnosis is missed. Symptoms can present in a wide variety regarding intensity and duration, making it difficult for the treating midwife or obstetrician to draw correct conclusions.
Clinical Case
We present a case of a 29 years old patient whose third pregnancy was complicated by short, but frequent and intense spells of unbearable headaches and excessive vomiting up to 10 times a day. She began to experience these symptoms, accompanied by occasionally shortness of breath and a feeling of paraesthesia in her face about 6 months prior to this current pregnancy. The patient was referred to several specialists, but no abnormalities of the eyes, head and neck were found. Symptoms were treated with intravenous fluids, dimenhydrinat, metoclopramide and ranitidine. Routine antenatal care revealed no abnormalities, all routine testing including blood pressure measurements, urine and blood glucose testing remained within normal limits. Fetal growth was always satisfactory. After an especially severe episode at term the woman referred herself to the local obstetric unit. Initially her blood pressure was normal and the cardiotocogram (CTG) showed a reassuring trace, but after 2 more episodes of extreme headaches, vomiting and hypertension (blood pressure up to 256/130 mmHg) within few hours after admission and signs of fetal compromise the pregnancy was terminated by emergency caesarean section under spinal anaesthesia. A healthy male newborn was delivered. Postoperatively, extremely fluctuating blood pressure with peaks up to 245/137 mmHg (mean daytime value 163/95) combined with persisting nausea and vomiting led to the suspicion of an underlying catecholamine excess. MRI scanning revealed a tumor measuring 3.3 cm$\times$4.3 cm$\times$2.7 cm in the left adrenal, plasma and urinary normetanephrine were elevated to 944.4 pg/ml (normal $<$118.3) and 7913 nmol/24h (normal $<$1950 nmol/L) respectively. Histopathological examination after tumor removal confirmed a pheochromocytoma. In the context of a research protocol, which the patient gave written consent for, very high rates of fumerate were measured in the tumor tissue.The strongly suspected germline FH mutation (associated with renal cell carcinomas, leiomyomas and metastatic disease) was confirmed by genetic testing.
Discussion
This case clearly mirrors the ongoing difficulties in the timely diagnosis of a pheochromocytoma during pregnancy. In the presented case, symptoms appeared frequent, but with a short duration only. This explains why it was possible to miss the symptomatic spells completely during routine antenatal care.

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P824

Laparoscopic adrenalectomy for adrenocortical carcinoma is not inferior to open adrenalectomy

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Background
Laparoscopic adrenalectomy (LA) is the standard treatment for benign adrenal tumours but its role in the surgical management of adrenocortical carcinoma (ACC) is controversial. Therefore, the aim of this study was to compare long-term outcome between open adrenalectomy (OA) and LA in the treatment of primary ACC.
Methods
This retrospective cohort study included patients with ACC ENSAT stage I-III referred to the Croatian referral centre for adrenal gland disorders from 2004 to 2018. Main outcomes analyzed in the study were: recurrence free survival (RFS) and disease-specific survival (DSS).
Results
Among 57 consecutive patients, 44 met the inclusion criteria for the study (ACC stage I-III). The patients who underwent LA ($n=22$) had significantly smaller tumours compared to those who underwent OA (70.5 (26–110) mm vs 120 (70–250) mm, $P<0.001$). There were no differences between the groups regarding gender, age, tumour functional status, Ki-67 labelling index and Weiss score. Median follow-up for patients who underwent LA and OA was 36.5 (3–133) and 64 (9–163) months respectively ($P=0.12$). Five patients in OA group (22.7%) and three patients in LA group (13.6%) had tumour recurrence ($P=0.698$). Three patients died during follow-up. One death in OA group was related to ACC, whereas two deaths in LA group were not related to ACC. The 5-year RFS and DSS calculated by Kaplan-Meier method was 86.4% and 90.9% for LA and 77.3% and 86.4% for OA with respective P values of 0.664 and 0.495.
Conclusions
There is no difference between LA and OA in the long-term outcome of patients with ACC treated in an expert centre. These results imply that LA could represent a suitable surgical approach in a number of patients with non-metastatic ACC.

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P825

Prevalence of adrenal glands lesions and correlation with radiological findings

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Objectives
To evaluate the prevalence in our work center of pathology of adrenal glands and to assess the efficacy of the radiology imaging in the detection of especific features and to exclude malignancy lessions.
Material and Methods
We included patients who presented some adrenal lesion with histological study after surgerie between January 2010 and December 2015 in the hospitals of Albacete, Almansa and Villarrobledo. We use the Pathological Anatomy database and retrospectively review the clinical histories and radiological findings. We exclude fine needle puncture procedures and those cases without pathology after histological analysis. We describe the radiological findings in CT and/or MRI of these lesions, emphasizing the malignant and less frequent ones.
Results
We present a total of 83 patients. 59 patients had benign adrenal pathology: 29 adenomas, 12 pheochromocytomas, 7 myelolipomas (1 xanthogranulomatous), 1 endothelial cyst, 1 ganglioneuroma, 2 hemorrhages, 1 congenital adrenal hyperplasia, 3 cortical nodular hyperplasias, 1 tuberculous granulomatous adrenalitis and 2 collision tumors (adenoma and pheochromocytoma, pheochromocytoma and ganglioneuroblastoma). Malignant adrenal pathology was observed in 24 patients: 20 metastases, 3 cortical carcinomas and 1 type B non-Hodgkin lymphoma. The radiological findings were diagnostic of adenoma in 25 of 29 patients. The three cases of feocromocitoma were ONLY considered in the list of the radiological differential diagnosis (one in association to MEN2). 5 mielolipomas and endotelial cyst had a specific feature and were diagnosed by radiology imaging. Two of the three adrenal carcinoma and 90% of metástasis had a high suspicious diagnostic by radiology imaging. Ganglioneuroma, tuberculous granulomatous adrenalitis, hemorrhage, collision tumors and lymphoma had inespecific radiologic findings.
Conclusion
- Most adrenal lesions are benign.
- The adenomas, followed by the metastases, are the most frequent adrenal lesions.
- There are some typical radiological signs that allows the diagnosis of the lesions, as in the case of adenomas cyst or in myelolipomas.
- Even the size greater than 4 cm is a criteria that suggests malignancy, in our series many benign lesions such as myelolipomas and hemorrhages were larger than 4 cm.
- The metastases were solid tumors in the context of a known neoplasm (carcinoma). The most frequent primary tumor were the lung and kidney.
- Pheochromocytomas are inespecific but most are hypervascular and hyperintense in T2.
- To consider that the clinical context of the patient can help us to diagnose nonspecific lesions such as pheochromocytoma or tuberculosis infection.

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P826

The French COMETE-Cancer network for adrenal cancer: 10 years of activity as part of a national plan for clinical care of rare cancers

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Introduction
The French National Institute of Cancer (INCa) launched supported by the Ministry of Health in 2008 a program for the recognition of national networks for the management of rare cancers. Among the 23 selected networks COMETE-Cancer was recognized by INCa in 2009 for Adrenocortical carcinoma (ACC) and malignant pheochromocytoma/paraganglioma (MPP). At that time 60–120 new ACC/year and 30 new MPP/year were expected at the national level.
Aim
To describe the general activities of COMETE-cancer after 10-years of activity.
Materials and methods
INCa list 7 tasks for the national rare cancer networks: 1) Expertise: double reading of tumor samples, Referral National Multisciplinary Staff (RNMS); 2) Care practice: national best practice guidelines release; 3) Referral: patient access to highly specialized/innovative treatments (clinical trial); 4) Observation: exhaustive recording of national cases in registries; 5) Clinical and translational research; 6) Healthcare professional training; 7) Role of patient associations. The French COMETE-K network is coordinated by two-sites Centers (Cochin and Gustave Roussy). Ten Regional Experts Centers have been recognized for a national geographical coverage.
Results
A double reading is done in about 200 cases of ACC/MPP tumor samples/year. A RNMS is organized twice a month (web based system): about 170 ACC and MPP patients/year are discussed. The coverage rate of 'new' patients reviewed in RNMS/'estimated' total number cases was 68%. The consistency between treatment proposed in RNMS and treatment administered was of 84%. Since 2010, 958 ACC and 384 MPP have been entered in the ENSAT database. Two National best practice guidelines for ACC/MPP were released. About 70 ACC/MPP have been referred to the COMETE-Cancer centers for highly specialized and innovative treatment (phase II-III trial, radiofrequency/cryotherapy, liver chimioembolisation). COMETE-Cancer participated in two international trials (ADIUVO in ACC and FIRSTMAPP in MPP) and more than 20 translational studies. Every year more than 500 healthcare professional (student, endocrinologists, surgeons, pathologist, oncologists) are trained. Moreover, it strongly collaborates with the patients 'Association Surrénale' by writing specific documents on the clinical ACC/MPP management.
Conclusions
COMETE-cancer has led to a homogenous national organization for clinical care of ACC and MPP. The RNMS proved to be very efficient for that. Links with the ENSAT, ENDO-ERN and EURACAN networks will allow further progress at the European level.

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P827

Congenital adrenal hyperplasia: clinical and hormonal presentation about a Tunisian serie

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Introduction
Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders that result from the deficiency of one of several enzymes involved in the steroidogenic pathway for cortisol biosynthesis. The most common cause of CAH, accounting for 90% of cases, is 21-hydroxylase deficiency. The symptoms of disease very depending on the nature and severity of the enzyme deficiency as well as the sex of the individual. Non-classical CAH is generally late onset. However, treatment in the form of replacement hormone therapy corrects the hormone deficiencies. Life-long medication is required to prevent the return of symptoms.
Patients and methods
This is a retrospective descriptive study, which included patients with congenital adrenal hyperplasia, followed at the endocrinology department of the CHU Farhat Hached Hospital of Sousse between 1996 and 2018. Patients were evaluated on the clinical and biological plan.
Results
26 cases of congenital adrenal hyperplasia were included: 23.1% were males and 73.7% were females. This study found that median age of patients was 30 years ranging from 11 to 49 years whilst median age at diagnosis of CAH was 14 years, ranging from 0 to 28 years. Positive consanguinity was found in 10 cases (36.5%). Positive history of similar cases in the family was found in 10 cases (36.5%). There were 22 (84.6%) patients with congenital adrenal hyperplasia due to 21-a-hydroxylase deficiency and 4 (15.4%) due to 11β-hydroxylase deficiency. Salt losing type of CAH was found in 5 cases (19.2%) and simple virilizing type was found in 4 cases (15.4%). A late revelation type was found in 10 cases (65.4%). Almost all patients were having elevated pre-treated 17-hydroxy progesterone (17-OHP)serum.The median level of pre-treated 17-OHP was 50 ng/ml.The mean doses of hydrocortisone was 28.08 mg/day.

Conclusion
Based on the clinical and laboratory findings, the majority of CAH patients were likely to have 21-OH deficiency, the most common form of classic CAH. Thus, genetic studies should be done. Considering that the age at diagnosis is delayed in the study population, more effort is also required to educate the public regarding the disease presentation. The introduction of a neonatal screening programmeis essential so that CAH can be diagnosed early.

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P828

Nonfunctioning adrenal incidentaloma associated with diabetes: about 40 cases

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Introduction
Adrenal incidentalomas are frequent, their prevalence reaches 5% of the general population, incidental diagnosis from an imaging examination motivated by an extra-adrenal sign is common. Diabetes may be present in patients with adrenal incidentaloma, it is often diabetes secondary to secretion of cathecholamines, mineralocorticoids and cortisol.
Objective
To evaluate the clinical-biological profile of adrenal incidentalomas, as well as their association with diabetes.
Methods
Retrospective study of 40 cases of adrenal incidentaloma hospitalized between 2010–2018 in the endocrinology department. The epidemiological and clinico-biological profile of incidentalomas has been studied. Patients were compared in 2 groups according to presence ($n=9$) or no diabetes ($n=31$). Statistical analysis was univariate for all variables using SPSS software version 22.0.0.
Results
The prevalence of diabetes mellitus in patients with adrenal incidentalomas was found to be 22.5%. Diabetic patients followed were older than non-diabetics with an average age of 65 versus 52.9 years (P: 0.028) with female predominance. The majority of diabetics were at a very high cardiovascular risk with a hypertension significantly more frequent in the diabetic group (92% versus 44%) (P: 0.014) and dyslipidemia in 89% of cases versus 35% (P: 0.02). The metabolic syndrome was more common in diabetics: 84% versus 15% with an average BMI of 38.4 versus 23.6 kg/m^2 (P: 0.015). It was a unilateral lesion in 30 patients and bilateral in 9 patients. The most common etiologies found in diabetics were: pheochromocytomas in 4 patients, metastasis in 1, adrenal carcinoma in 1, lymphoma in 1, one adrenal cyst and one myelolipoma. While in the control group the most frequent were benign adenomas in 18 cases, 8 pheochromocytomas, 2 Conn adenomas, 2 adrenal cysts and 1 myelolipoma.
Discussion
Our findings demonstrate a significantly higher risk of developing incident diabetes in individuals with adrenal incidentalomas.Their association is explained by a reduction in insulin sensitivity and the presence of other cardiovascular risk factors. The subclinical cushing syndrome is the most incriminated hence the interest of a cortisone dosage.

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P829

Multiple endocrine neoplasia type 2 family case in Belarussian population

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Multiple endocrine neoplasia type 2 (MEN2) is a rare hereditary autosomal dominant syndrome, caused by activating germline mutations in the RET proto-oncogene. Medullary thyroid carcinoma (MTC) remains the most common and aggressive manifestation of MEN2. The family case of MEN 2 syndrome in Belarussian population is analyzed. During the analysis of the records of clinical case of patient's death in the reginal hospital because of thrombosis of mesenteric vessels and acute abdominal surgery of previously undiagnosed pheochromocytoma - additional anamnesis data were revealed. It appeared that in the past the women got total thyroidectomy because of MTC. According to this information the decision to do screening for MEN 2 in family members was done. Medullary carcinoma with reginal metastasis was diagnosed in her son 28 years old. Total thyroidectomy was fulfilled. Subclinical hyperparathyroidism was diagnosed in her nephews 15 and 4 years old. The family members refused from genotyping. Ultrasound investigation was done. There were no thyroid nodules and serum calcitonin levels were in normal range. Parathyroid hormone concentrations were slightly increased in both nephews, ionized calcium levels were on upper border of reference rage. The 46 years old brother of deceased women refused to have clinical examination. There were difficulties in monitoring members of this family. In 4 years regional endocrinologist succeeded to invited the family members of the deceased earlier women with MEN 2 for clinical exam. By this moment medullary carcinoma took place in both nephews, single adrenal pheochromocytoma was diagnosed in her son. Surgical treatment was done in all of them. Pheochromocytoma screening was recommended for the nephews as they were at the highest risk group. Education of members of families with the history of MEN syndromes is obligatory in clinical practice. Screening for MEN syndromes in all cases of medullary carcinoma is worth doing for the purposes of differential diagnosis, proper monitoring and treatment.

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P830

An uncommon case of a large adrenal cyst

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Introduction
Adrenal cystic lesions are rare. Differential diagnoses include pseudocysts, echinococcal cysts, hemangiomas, cystic pheochromocytomas, adrenal hematomas and lymphangiomas. We present here a rare case of an adrenal lymphangioma.
Case report
A 35-year old man was referred to our department for investigation of a right adrenal cystic mass, incidentally found during an abdominal ultrasound. The patient was completely asymptomatic and had a medical history of chronic hepatitis C, recently treated with a combination of sofosbuvir and velpatasvir. Physical examination was unremarkable and hormonal evaluation revealed that the mass was non functional. Adrenal CT imaging demonstrated a large multilocular, with low attenuation (2 ± 24 Hounsfield units on non-contrast scan) and non-enhancing cystic lesion of approximately 5 cm diameter with peripheral calcifications. The mass was excised laparoscopically and histopathological examination revealed the presence of a dual-chamber lymphangioma of the adrenal. Immunohistochemical staining was positive for ERG, CD31, CD34 and D2-40, confirming the diagnosis.
Conclusion
Adrenal lymphangiomas are extremely rare. Just around 60 cases have been reported in the literature so far. They are usually large, unilateral, benign, non-secreting masses presenting mainly with pain and showing greater prevalence in young female subjects. Differential diagnosis of adrenal lymphangiomas is challenging due to their rarity. Laboratory evaluation is essential in order to exclude hormonal hypersecretion. In case of large masses over 4 cm surgical excision represents the gold standard of treatment, while it also offers definite diagnosis.

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P831

Catecholamine-secreting tumor and pancreatic tumor fibrosis – a coincidence?

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Introduction
Cells of the neuroendocrine system are spread throughout the body, and they can give rise to various neuroendocrine tumors with unpredictable evolution. It has been observed that they are often associated with the development of fibrosis, both local and distant.

Case presentation
We present the case of an 81 year-old, normal-weight woman, who firstly presented in our clinic in 2014 for multinodular goiter (normal calcitonin). Fine needle aspiration biopsy from a mixed thyroid nodule (measuring 22.2/13.1 mm) indicated a well-differentiated follicular adenoma. Patient associated stage 3 hypertension and asthma. Also, routine abdominal ultrasound revealed a tumor in the right adrenal lodge. Consequent native computed tomography (CT) only described a well-defined dense mass measuring 5/3.6/2.6 cm in the right adrenal lodge. Further testing dismissed a secreting adrenal adenoma and catecholamines were normal at that time. In 2015, the patient underwent emergency biliary decompression surgery for mechanical jaundice due to a pancreatic tumor of the head and body. On-site evaluation rendered the tumor as unresectable, thus a side-to-side bilio-gastric anastomosis and an Omega loop gastro-enteric anastomosis were performed. Pancreatic tumor biopsy showed fibrous tissue and chronic inflammatory cell infiltrate (immunohistochemistry unavailable). 1-year follow-up magnetic resonance imaging showed the pancreatic solid tumor of the head, measuring 2/1.7/1.5 cm, and a stationary retro-caval solid tumor, without a clear demarcation from the right adrenal gland. In 2017, the patient returned with paroxysmal hypertension, partially responsive to treatment, flush, diaphoresis and fatigue. Contrast CT described the retro-caval tumor as a hypodense, iodophile, slightly unhomogenous nodule, measuring 5.6/3.5/2.2 cm, not well delimited from the right adrenal gland, which started to compress the posterior-medial side of the intrahepatic portion of the inferior vena cava. She also developed diabetes mellitus. Further testing identified elevated Chromogranin A (366 μg/l) and catecholamines (metanephrines = 445.3 pg/ml; normetanephrines = 1018.6 pg/ml), thus patient was diagnosed with a catecholamine-secreting tumor (either pheochromocytoma or paraganglioma). Currently, patient is under observation and antihypertensive treatment, as she refuses another surgical intervention.
Conclusion
Although the tumor in the right adrenal lodge was initially non-functional, catecholamines and symptoms became evident 3 years later. Also, the pancreatic tumor could be a 'sclerosing variant' of pancreatic neuroendocrine tumor, in which the associated fibrotic reaction usually involves the main pancreatic duct, resulting in ductal stenosis and upstream duct dilatation and/or pancreatic atrophy. Yet, immunohistochemistry is required for accurate diagnosis. Comorbidities, age and patient's unwillingness represent a challenge in the diagnostic process and management of neuroendocrine tumors, especially pheochromocytoma.

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P832

Addison disease in a patient with familial mediterranean fever

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Introduction
Familial Mediterranean Fever (FMF) is an autosomal recessive hereditary disease characterized by fever and inflammation of serous membranes. The most important complication of FMF is amyloidosis which has significant role in the prognosis. It is unclear how endocrine system hormones are affected in FMF. We present adrenal insufficiency in a an FMF patient without amyloidosis.
Case
A 39 years old male patient who had been diagnosed with FMF at the age of 14 years admitted to the emergency department with the weeklong complaints of cough, fatigue, fainting and abdominal pain. He had started colchicine treatment at the diagnosis but was not using it regularly. He had a personal history of hospitalization in the intensive care unit with the diagnosis of pericardial effusion and FMF attack 6 years ago. His blood pressure was 80/50 mm/hg, body temperature was 36.8°C. In laboratory examination, his blood glucose was 40 mg/dl, sodium was 133 mmol/l, potassium was 6.1 mmol/l, calcium was 8.2 mg/dl, phosphorus was 3.0 mg/dl and albümin was 4.0 g/dl. Cortisol and adrenocorticotrophic hormone were 0.326 ug/dl and 324.4 pg/ml, respectively. He was hospitalized with the diagnosis of adrenal insufficiency and glucocorticoid and mineralocorticoid therapies were started. 24 hour urine protein excretion was 265.1 mg/day which was suggestive for lack of renal amyloidosis. The size of the kidneys was normal in the abdominal ultrasonography. Abdominal magnetic resonance imaging showed aplastic/hypoplastic right adrenal gland that could not be distinguished and a small left adrenal gland. His complaints regressed with hydrocortisone, fludrocortisone and colchicine treatments.
Conclusion
The most common cause of adrenal insufficiency in developing countries is tuberculosis while its most common cause in developed countries is autoimmune adrenalitis. Lack of proteinuria and presence of hypoplastic adrenal glands were suggestive for the absence of amyloidosis in our patient. Coexistent FMF and Addison's disease in a patient might be associated with the immunopathogenic mechanisms or just a coincidence rather than amyloid involvement of adrenal glands.

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P833

The role of somatostatin analogs in the control of carcinoid syndrome: systematic review and meta-analysis

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Introduction
Somatostatin analogues (SSAs) are the mainstay of treatment for carcinoid syndrome (CS)-related symptoms. Controversy still exists regarding the extent of the efficacy of this intervention. The purpose of the systematic review and meta-analysis was to evaluate the percentage of patients achieving partial (PR) or complete response (CR) with the use of SSAs (lanreotide, octreotide, pasireotide) in patients with CS. Due to lack of uniformity and established criteria for defining the response to treatment, definition of PR and CR was based on ad hoc criteria provided in individual studies.
Methods
A systematic electronic literature search was conducted in major healthcare databases to identify eligible studies complemented by an ancillary search in the references of the retrieved studies. Any clinical trial reporting data on the efficacy of SSAs in at least 10 adult participants with minimum follow-up of three months were considered eligible for the meta-analysis. A subset of studies, in which outcomes were reported as PR or CR were considered for meta-analysis of binomial data.
Results
A total of 25 studies (published between 1994–2018 involving a total sample size of 1517 patients with CS) finally fulfilled the inclusion criteria of the systematic review and 11 studies reported extractable outcomes (PR or CR) were considered for quantitative synthesis. Significant heterogeneity was noted with regards to study design, definition of the primary outcome, follow-up, specific formulation, total dose administration, location of the primary tumour and extent of the disease. The pooled percentage of patients with PR or CR for diarrhoea was estimated 0.40 (11 studies, 95% confidence interval (CI): 0.23–0.58, I^2 test-for-heterogeneity = 97.5%). Subgroup analyses on the basis of specific drug provided no evidence of a differential response. For lanreotide and octreotide, the pooled percentage of patients with PR or CR was calculated 0.38 (95CI%: 0.23–0.53) and 0.51 (95CI%: 0.19–0.83), respectively. The pooled percentage of patients for flushing with PR or CR was estimated 0.40 (11 studies 95%CI: 0.25–0.55, I^2 = 93.4%). No evidence of a significant differential response in the control of flushing was noted (pooled percentage of patients with PR or CR for lanreotide was 0.35 (0.15–0.54) and for octreotide 0.52 (0.39–64)). Relative paucity of data prevented the calculation of pasireotide-specific outcomes.
Conclusion
This systematic review and meta-analysis provides preliminary estimate of a 40% overall reduction of symptoms of CS associated with SSAs administration. However, significant heterogeneity was detected, possibly reflecting differences in clinical course and manifestation of the disease as well as in outcome definition.

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P834

Familial multiple endocrine neoplasia type 1 revealed by a maxillary swelling

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disorder caused by mutations in the MEN1 tumor suppressor gene and is characterized clinically by tumors in two or more endocrine glands, such as the pituitary gland, parathyroid glands or pancreatic islets. We describe an atypical presentation of familial hyperparathyroidism evoking the diagnosis of MEN1 in the first place.
Observations
We report a three-member family. First, a 31 year-old female presented a maxillary swelling. A pituitary incidentaloma was revealed by a CT scan. After biological investigations and imaging, a primary hyperparathyroidism due to a parathyroid adenoma and a macroprolactinoma were revealed. Second, her 43 year-old brother presented a history of recurrent bilateral nephrolithiasis as a complication of a primary hyperparathyroidism, having as well a multinodular goiter with hypothyroidism under hormone substitution. And finally, their 48-year-old sister had also a history of hypothyroidism and a total thyroidectomy was indicated for sonographically suspicious nodules for malignancy. Histopathological examination found adenomatous parathyroid glands with no evidence of thyroid cells and developing a hungry bone syndrome 7 days after surgery confirmed the diagnosis of asymptomatic primary hyperparathyroidism.
Conclusion
This family history illustrates the clinical polymorphism of possible MEN1 and the necessity of performing genetic and clinical screening especially to provide early treatment for hyperparathyroidism and to avoid its complications.

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P835

Bilateral adrenal masses in Addison's disease: primary tumors or tuberculosis?

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Introduction
Addison's disease is a rare disorder, described mainly in isolated cases. The two most common cause of primary adrenal insufficiency are autoimmune adrenalitis and adrenal tuberculosis, which is still the primary cause of primary adrenal insufficiency (PAI) in developing countries. Adrenal tuberculosis is difficult to diagnose, the classic presentation with non specific symptoms delay the diagnosis. In some cases, the background of tuberculosis and hyperpigmentation, which is one of the most common clinical manifestation in Addison's disease, allow early recognition.
Case 1
An 43-year-old male patient without a significant past medical history was investigated for a sudden onset of: nausea, vomiting, inappetence, and azotate retention. Examination showed remarkable hyperpigmentation of the skin, oral mucosa and nails. Biological test identified hyponatremia (129 mmol/l), hyperkalemia (5.43 mmol/l), high ACTH (>1250 pg/ml), low serum cortisol level (2.1 ug/dl), suggestive values for primary adrenal insufficiency. After glucocorticoids replacement,the electrolytes imbalances and his symptoms have improved significantly. Past exposure of the pacient to tuberculosis (2 years ago) and positive tuberculin skin test have established the etiology. Abdominal CT-scan detected two unomogenous nodular lesions (right adrenal gland – 26/30/49 mm, left adrenal gland – 36/19/54 mm), with peripheral calcifications suggestive for adrenal tuberculosis.
Case 2
An 63-year-old male patient was admitted in surgical department for important weight loss (30 kg in 12 months), weakness, nausea, fatigue and loss of appetite, mental confusion and dizziness. A chest and abdominal CT-scan revealed multiple mediastinal adenopathies and bilaterally enlarged adrenal glands with unomogenous nodular lesions (on the right – 16/13/22 mm, on the left – 50/38/47 mm) with diffuse calcifications and heterogeneous peripheral enhancement. Serum cortisol level was <1 ug/dl and serum ACTH was >1250 pg/ml, confirming primary adrenal insufficiency. Due to the suspicion of adrenal carcinoma patient underwent left adrenalectomy. Histopathological examination revealed typical granulomatous infllammation with Langhans giant cells and caseous necrosis, the tissue PCR test confirming the presence of *Mycobacterium tuberculosis*. Currently, both patients started on four-drug anti-tuberculosis therapy (isoniazid, rifampin, pyrazinamide and ethambutol) along with Hydrocortisone and Fludrocortisone supplementation.
Conclusions
Adrenal tuberculosis is rare but an important disease entity that must be identified early, requiring prompt treatment with antituberculosis drugs and appropiate steroid therapy. Sometimes the ultrasound image of the adrenal tuberculosis can cause confusion with adrenal carcinoma causing important problems of differential diagnosis and treatment.

Key words: Tuberculosis, Adrenal gland, PAI
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P836

A germline ARMC5 mutation in a patient with adrenal adenoma and multiple colonic polyps: a case report

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Background
Functional studies demonstrate that Armadillo repeat-containing 5 (ARMC5) gene, controls apoptosis and steroid synthesis. A germline mutations in ARMC5 are recently been associated with Cushing syndrome and possibly can be responsible for a broader tumor predisposition.
Case presentation
A 51-year-old woman presented with intermittent rectal bleeding. A colonoscopy revealed multiple colonic polyps, histopathological analysis showed tubular adenoma with low-grade dysplasia. A surgical treatment was advised. During the preoperative assessment, an enlargement of right adrenal gland was discovered on abdominal ultrasound and she was referred to endocrinologist. Patient's past medical history was significant for hypertension. Her mother had endometrial cancer; 7 years after she died from liver cancer. Physical examination revealed typical Cushingoid features: a fool moon face and central obesity, without hirsutism. In laboratory studies, serum potassium was 2.8 mmol/l, sodium 142 mmol/l. A normal diurnal rhythm of cortisol was omitted: 0800 h – 712 nmol/l, 0400 h – – 749 nmol/ and 0000 h – 651 nmol/l, plasma adrenocorticotropic hormone (ACTH) supressed (0.6 ng/l). Serum cortisol level remained elevated after 1 mg overnight dexamethasone test (717 nmol/l). Levels of follicle-stimulating hormone, luteinizing hormone, thyrotropin, free thyroxine, parathyroid hormone, prolactin, testosterone, dehydroepiandrosterone, insulin-like growth factor 1, aldosteron/renin activity and 24-hour urinary catecholamines were within reference range. Further evaluation showed diabetes mellitus (plasma glucose at 120 min of oral glucose tolerance test 13.6 mmol/l, insulin 112.3 μIU/ml) and osteoporosis. Computed tomography confirmed an enlarged right adrenal gland, 31×36 mm. Pituitary magnetic resonance imaging showed a 6.5 mm-sized adenoma. The patient underwent laparoscopic right adrenalectomy and histopathological examination demonstrated a cortical adenoma. After surgery, Hydrocortisone supplementation was started. Genetic testing revealed germline mutation in ARMC5 (I170V; p.Ile170Val). At 2 months follow-up, her potassium level was normal, blood pressure target values achived, serum cortisol levels 610 nmol/l at 0800 h (after a regular Hydrocortisone dose) and 48 nmol/l at 0400 h, ACTH 4.8 pmol/l. Afterwards, she was referred to abdominal surgeon who performed total colectomy with ileo-recto anastomosis.Currently, the patient is stable, a hypothalamic-pituitary-adrenal axis is recovered: morning serum cortisol of 510 nmol/l and ACTH 31 pmol/l. Screening for ARMC5 mutations in first-degree relatives is advised.
Conclusion
Genetic testing for ARMC5 mutations might result in earlier identification and better management of Cushing syndrome. A prospective follow-up will allow better insight of the possible development of multiple tumor syndromes in these patients.

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P837

Metastatic adrenal cortical carcinoma presenting with cervical mass and subclinical Cushing: a case report

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Introduction
Adrenocortical carcinoma (ACC) is a rare tumor with an aggressive prognosis of 1–2 people per million per year. They are functional tumors which mostly occur with virilization and/or Cushing syndrome. Metastatic ACC has a dismal prognosis and the most common sites of metastases are the lung, liver, lymph nodes and bones. Herein, we present metastatic ACC patient without Cushing clinic at the time of diagnosis.
Case presentation
A 48-year-old male patient was admitted to the outpatient clinic due to abdominal swelling, right side pain, and a growing mass on the left side of the neck. The patient denied relevant pathological medical history including smoking, alcohol use or drug consumption and had no previous hospital admissions and was on no regular medication. On examination, patient had abdominal fullness in the left upper quadrant with a palpable mass. There were no cushingoid appearance and hiperandrojenism. CT and MRI scan of abdomen showed malignant mass with approximately 19×10×19 cm, invading the renal cortex in the right adrenal gland region. There were also pulmonary and multiple retrocrural lymph node metastasis and significant compression findings to the inferior vena cava and posterior right lobe of the liver. The excisional biopsy of cervical D5 lymph node was consistent with ACC metastasis. Laboratory studies showed that serum ACTH <5 pg/ml (N:0–46), serum cortisol 20.1 ug/dL (N:4.6–22.8), 1-mg dexamethasone-suppressed morning serum cortisol 17.8 µg/dl (*N*: <1.8), 2-mg dexamethasone-suppressed morning serum cortisol 20.73 ug/dl (*N*: <1.8), aldosterone 363 pg/ml, renin 0.3 ng/ml/h. 24-hr-urinary cortisol, vanilmandelic acid, metanephrine and normetanephrin measurements were respectively 1742 nmol/24hr (N:38–208), 8.7 mg/24hr (N:1.6–7.3), 29 µg/24hr (*N*: 276–341) and 110g/24hr (N:88–444). The patient was considered as inoperable and chemotherapy was started.
Discussion
ACC are aggressive tumors with a very poor prognosis and *70%* of *patients* have *stage* III or IV disease at the time of diagnosis. Early diagnosis and treatment determine the life expectancy of ACC. Our patient presented with multiple organ metastasis as an ACC diagnosed with biopsy from the cervical lymph node. Although laboratory findings were compatible with Cushing's syndrome, it was not reflected in clinical findings.

Keywords: Adrenal cortical carcinoma, metastasis
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P838

(131) I-MIBG therapy in metastatic paraganglioma and phaeochromocytoma: a 4-year single centre experience

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Retrospective study of patients with metastatic/progressive pheochromocytoma (PCC) and paraganglioma (PGL) treated with (131) I MIBG in our hospital during 2015–2018 period.
Methods
There are no established criteria for establishing PCC/PGL as malignant apart from de presence of metastases at diagnosis. Radionuclide therapy (131) I-metaiodobenzylguanidine (MIBG) is frequently used in this patients when surgery is not possible. Indication of MIBG treatment was made in the Neuroendocrine Tumor Multidisciplinary Team meeting. After a (123) I-MIBG to assess tracer uptake standard 200 mCi (131) I-MIBG dose was administered in each patient until disease stabilization and then follow up was made.

Results

	Paciente A	Paciente B	Paciente C
Diagnosis	PGL stage IV	PCC stage IV	PCC stage IV
Metastases at diagnosis	liver, bone, peritoneum, mesenteric lymph nodes	Lung	Diaphragm, liver, periadrenalectomy tissue, para aortic lymph node
Age	58	58	57
Sex	Female	Female	Male
Genetic testing	Negative	Negative	Negative
Ki 67	1%	-	-
Clinically functioning tumor	Mild hypertension Flushing	Bad controlled hypertension	Bad controlled hypertension
Other treatments before I-MIBG	Surgery 2009-2013 Temodal+Capecitabine 2015 (neutropenia)	Surgery 1980	Surgery 2004
Treatment cycles	4 (Jan 2016-March 2017)	4 (Sept 2015-Jan 2017)	4 (Nov 2013-2014)+4 (Feb 2018-August 2018)
Before treatment	January 2016 -Plasma Normetanephrine (N<180 pg/ml) Urine Normetanephirne (N<444 ug/24h)	September 2015 -Plasma Normetanephrine 300 pg/ml -Urine Normetanephrine 1192ug/24 h	2013 -Plasma Normetanephrine 788 (<444)
After last MIBG treatment (hormonal response)	October 2018 -Plasma Normetanephrine 158 pg/ml -Urine Normetanephrine 614 ug/24 h	November 2018 -Plasma Normetanephrine 2 213 pg/ml -Urine Normetanephrine 631 ug/24 h	-
Clinical Response to treatment	Less frequent and intense hot flashes Well controlled hypertension	Well controlled hypertension	Better control of hypertension
Radiological response (RECIST) to treatment	Stable disease	Stable disease	Progression liver metastases in 2014 Stable disease 2018
Metabolic response to treatment	Stabilization or mild response in liver and mesentery. Metabolic response in bone	Stabilization or partial response (lung)	Partial metabolic response in liver Stabilization para aortic lymph node
Free Progression Survival	+36 months	+40 months	+45 months
Cumulative activity (MBq)	800 mCi	800 mCi	1550 mCi
Haematological toxicity	None	Neutropenia grade2	None
Renal toxicity	None	None	None

Conclusion
Therapy with (131) I-MIBG is a safe therapeutical option in patients with metastatic PCC/PGL, leading to easier control of hypertension, and mild improvement or at least stabilization of disease progression without major side effects in our 4 year centre experience.

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P839

When MAX runs in the family

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Introduction
Recent advance of genetic testing has contributed to the diagnosis of hereditary pheochromocytoma and paraganglioma (PPGL). Germline mutations in MYC associated factor X(MAX) are responsible for 1.1% of these PPGL; the median age at onset is 33 years and no reliable penetrance estimation is available for MAX-carriers. The authors present the case of a synchronous bilateral pheochromocytoma that prompted the discovery of a proband of MAX mutation and three other relatives affected. Case presentation: Male, 33 years old, healthy until May′1994 when he was diagnosed with hypertension; he was started on anti-hypertensive drugs but blood pressure (BP) remained uncontrolled. Simultaneously, he initiated paroxysms of headaches, diaphoresis and pallor that lasted less than 5 minutes and occurred at least twice daily. He was observed at our Endocrinology outpatient clinic in March′1995. Other than a BP of 170/100 mmHg he had no abnormality on physical examination. Our investigation revealed elevated 24 hour-urinary catecholamines (noradrenaline 11754 nmol [25× upper limit of normal range (ULN)], adrenaline 239 nmol [2.2ULN] and dopamine 3668 nmol [1.4ULN]) and metanephrines (normetanephrine 1.36 mg (1.36 ULN) and metanephrine0.54 mg (1.35 ULN).

Abdominal-CT revealed two round shaped adrenal lesions (one at each adrenal gland) measuring 2.5 cm in diameter with smooth and well-defined margins, no evidence of metastasis; 123I-MIBG showed bilateral trace uptake. MEN-2 was excluded and genetic testing for RET mutation was negative. He was submitted to right total adrenalectomy and left subtotal adrenalectomy on May'1995; pathological findings indicated bilateral hyperplasia. Normal urinary catecholamines and fractionated metanephrines until June'1996, when he presented with clinical and biochemical evidence of catecholamine excess and imaging compatible with a residual lesion on the left adrenal gland. Left total adrenalectomy on June'2000.This time, anatomopathological examination was consistentwith pheocromocytoma and until now he has no clinical or biochemical evidence of catecholamines excess or relapse. A multigene panel- search revealed a truncating MAX mutation affecting exon 3(c.97C>T). We evaluated all the proband's relatives and discovered the same MAX mutation with bilateral adrenal mass and evidence of catecholamine excess in all three of the proband's sons; the older son died in 2014 from malign pheocromocytomawith unresectable metastasis. The two younger sons have refused surgery and remain under surveillance.

Conclusions

In face of a patient with bilateral pheocromocytoma, hereditary aetiology must always be considered. Once a mutation is identified in the family, molecular testing of the relatives must be offered.

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P840

Adrenal incidentalomas – from diagnosis to follow-up

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Introduction

Adrenal incidentalomas (AIs) are defined as adrenal masses measuring 10 mm or more in diameter, incidentally discovered on imaging exams performed for a non-adrenal disorder. The aim of this study is to provide a clinical and imagiological characterization of patients diagnosed with AIs followed in our institution.

Methods

We conducted an observational and retrospective study that included patients with AIs evaluated at our institution between 2008 and 2018.

Results

Two hundred and twenty-three patients were included, 63.1% of the female gender ($n=147$), with a median age at diagnosis of 62.6 ± 11.3 years and a mean follow-up of 43.2 ± 29.6 months. The most prevalent comorbidities were hypertension (76.7%), followed by dyslipidemia (47.6%), obesity (46.6%), osteoporosis (38.2%), glucose intolerance/type 2 diabetes mellitus (32.2%). The imaging technique that first diagnosed the adrenal lesion was abdominal computed tomography (CT) in 78.5%, chest CT in 6.7%, abdominal ultrasound in 6.3%, abdominal magnetic resonance in 4.9%, kidney ultrasound in 2.2% and lumbar spine CT in 1.3% of patients. The majority of AI were unilateral (88.8%, $n=198$), with a mean maximal diameter at the time of diagnosis of 23.5 mm (10–120 mm) and localized on the left adrenal gland ($n=131$). Patients with bilateral disease had a maximal diameter at the time of diagnosis of 20.7 mm in the right adrenal gland (10–30 mm) and 16.2 mm (13–21 mm) in the left adrenal gland. At the time of diagnosis, 14 patients presented AI with a maximal diameter above 40 mm. Among the 223 cases, 28 primary adrenal dysfunction was documented (pheochromocytoma 7, primary hyperaldosteronism 9, cushing's syndrome 5 and autonomous cortisol secretion in 7). Thirty three patients underwent adrenalectomy, 24 for functional autonomy and 9 according to size criteria (>40 mm). The incidence of malignancy was 1.3% ($n=3$) and in these tumour size exceeded 40mm. Pathology results revealeds 20 cortical adenomas, 7 pheochromocytomas, 2 myelolipomas, 1 pulmonary adenocarcinoma metastasis, 1 benign oncocytoma, 1 adrenocortical carcinoma and 1 retroperitoneal ganglioneuroma.

Conclusions

In our experience the majority of Adrenal incidentalomas (AIs) are benign and non-secretory. Malignancy was exceedingly rare and suggested by adrenal lesion size and radiological phenotype. AI investigation and follow up by endocrinologists is warranted in order to optimize patient care and better understand this prevalent condition.

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P841

Malignant paraganglioma of the urinary bladder-diagnosis and management – a case report

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Introduction

Paragangliomas (PGL) are rare tumours of neuroendocrine origin. Those localized in urinary bladder account for 10% of all PGL. They arises from chromaffin tissue of the sympathetic nervous system that is embedded in the muscle layer of the bladder wall. Approximately 10% of urinary bladder paragangliomas are malignant.

Case presentation

A 76-year-old female presented with a history of haematuria, hypertension, headaches and excessive sweating. A urine cytology revealed atypical cells of unknown origin. In MRI on T1- weighted imaging 5 cm lesion of urinary bladder was found. The patient was qualified to transurethral resection of bladder tumour. Due to high risk of damaging bladder wall, only endoscopic biopsy of the tumour was performed. The biopsy was consistent with a paraganglioma (positive staining for neuroendocrine neoplasm (NEN) markers without staining for keratins, Ki67 – 15–20%.) The patient was reffered to Endocrinology Department for further investigation. A 24-hour urine collection of metoxycatecholamines showed significantly elevated level of normetanephrine and 3-metoxythyramine, with metanephrine level within normal range. Alpha-blocker treatment was inititated. Computed tomography of abdomen and pelvis identified, apart from contrast-enhancing large masses of the inferior wall of the urinary bladder, suspicious, contrast-enhancing paraaortic lymph nodes and lymph nodes along right iliac vessels. 131I-MIBG SPECT/CT revealed no tracer uptake. However, 68Ga-DOTATATE PET/CT identified pathological somatostatin receptor expression lesions in urinary bladder and thoracic, abdominal and pelvic lymph nodes. Based on those results, the diagnosis of malignant, disseminated paraganglioma, was made. The patient, who refused any kind of surgery, was reffered to Peptide Receptor Radionuclide Therapy (PRRT) with 177Lu-DOTATATE.

Conclusion

Urinary bladder paraganglioma should be suspected in patitents complaining about hematuria, with accompanying hypertension and headaches. Unrevealed hormonal activity of paragangliomas, without alpha-blockage, can retard proper surgery because of severe hypertension and jeopardize patient's safety due to possible catecholamin crisis. The diagnosis of PGL requires biochemical assessment to determine the catecholamine production. Histopathologically, the lack of keratin expression in a presumed NEN should raise the suspicion of PGL. Histopathological distinction between PGL and NEN is very important because of the ability to express somatostatin receptor 2 (SSR 2) presented by paragangliomas, which can lead to misdiagnosis - when it is based on somatostatin receptor scintigraphy. Contrarily, this ability can be very useful in diagnosis and treatment of metastatic paraganglioma by the use of 68Ga-DOTATATE PET/CT and PRRT.

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P842

Hypothalamic-pituitary-adrenal axis dysfunction in drug-naive schizophrenic patients

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Introduction

Hypothalamic-pituitary-adrenal axis dysfunction (HPA) has been reported in patients with schizophrenia and bipolar disorders but findings are inconsistent and few studies have conducted direct comparaisons of HPA biomarkers in drug native patients. We aimed to assess serum and salivary cortisol in the morning in drug-naive schizophrenic patients compared to controls.

Methods

This was a cross-sectional case-control study conducted between June 2016 and July 2018 on antipsychotic-free schizophrenia patients compared to healthy controls. Patients were hospitalized at the psychiatric C department in Hedi Chaker University Hospital (UH) in Sfax. The diagnosis of schizophrenia was established according to DSM-5 criteria. The symptoms' severity was evaluated

according to the positive and negative syndrome scale. Cognitive functions were evaluated according to the Montreal Cognitive Assessment scale. The analysis of cortisol levels was performed in the laboratory of Biochemistry in Habib Bourguiba UH in Sfax.

Results

This study included 45 patients and 100 male controls. Morning serum cortisol level was significantly higher in schizophrenic patients compared to controls. (140.12 ± 49.79 ng/ml vs 122.70 ± 40.77 ng/ml; $P = 0.029$). There was no significant difference between the two groups regarding salivary cortisol levels. There was a significant and negative correlation between salivary cortisol levels and the severity of negative symptoms. Positive and significant correlations were found between salivary cortisol levels and cognitive functions.

Conclusion

This study allowed better understanding the role of basal cortisol assay in the acute phase of schizophrenia. Further research is needed to improve our knowledge about its role in the different phases of this disorder.

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P843

Efficacy of somatostatin analogues in managing hypercalcaemia due to PTHrP in a well differentiated metastatic pancreatic neuroendocrine tumour and discussion of modern treatment options: A clinical case

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Pancreatic neuroendocrine tumours are rare with an incidence of 5 per million. Of these tumours, 75% maybe hormonally functioning. They carry a better prognosis than adenocarcinoma of the pancreas. Parathyroid Hormone related peptide hypersecretion in PNETs is uncommon and is solely associated with metastatic PNETs. 31 cases are reported of PTH-rPoma in the literature. Here we describe a novel case presenting with cough. A previously well 56-year-old female presented to the acute medical take with cough and shortness of breath. Initially having been managed as asthma she was investigated for a possible acute pulmonary embolus. She was noted to be hypercalcaemic: with an adjusted calcium level of 2.68 mmol/L (NR 2.6 mmol/l). Investigations revealed the parathyroid hormone (PTH) appropriately suppressed to 1.0 pmol/l and undetectable vitamin D levels. PTH-rP levels were raised 2.0 pmol/l (NR <0.5 pmol/l). Her CTPA was negative for pulmonary embolus but revealed lesions in the liver and spleen. Further dedicated CT imaging confirmed a mass lesion in the tail of the pancreas with metastases in the liver and spleen. Tissue diagnosis was made from an USS guided biopsy of one of the liver lesions, revealing a neuroendocrine tumour of the pancreas, Ki67-7% ENETS grade 2. Octreoscan with SPECT CT demonstrated the disease was restricted to below the diaphragm: the liver /pancreas and spleen. Low grade uptake was also noted in the peritoneum. After careful discussion in the NET MDT surgery was felt to be high risk at this stage and she was commenced on Sandostatin LAR 30mg. Due to increasing somnolence Sandostatin LAR was switched to Lanreotide autogel 120 mg every 28 days which abated some symptoms. This helped to keep her adjusted calcium levels stable for 12 months. Subsequently her calcium levels were noted to have increased slightly and surveillance CT imaging showed progressive disease and assessment for Peptide receptor radionuclide therapy (PRRT) planned from the NET MDT. Predictably efficacious for both hypercalcaemia and PNET progression. In the interim there has been a dose escalation of the Lanreotide 120 mg to every 21 days. PTHrP related uncontrolled hypercalcemia is the key clinical effect of the functioning pNET and is associated to increased morbidity and mortality. There is great evidence for the targeted therapies (mTORi(everolimus) and TKI (sunitinib)) and PRRT. This case highlights the use of somatostatin analogues in managing hypercalcemia and progression in metastatic PNET and use of PRRT.

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P844

Association of neurofibromatosis type 1 and neuroendocrine tumor

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Introduction

Pheochromocytoma occurs in 0.1–5.7% of patients with Neurofibromatosis type 1(NF1). We report two cases of adrenal pheochromocytoma in patients with NF1.

Observation

A 46 year-old male was admitted to our department for further examinations of an adrenal mass. The CT-scan showed two well-defined right adrenal masses measuring each $128 \times 87 \times 86$ mm and $60 \times 52 \times 37$ mm with central necrosis and calcifications in the biggest one. It suppresses the right kidney and fills in the vertebral foramens D12-L1 and L1-L2 without osteolysis. The magnetic resonance imaging (MRI) showed the same well-defined heterogeneous masses with intense enhancement without spread to adjacent organs. The second patient is a 27 year-old female, her CT-scan showed a left adrenal heterogeneous mass measuring $80 \times 80 \times 74$ mm with central necrosis as well. In their past medical history, both patients had palpitation, sweating and headache and hypertension in one case. They had multiple neurofibromas over the entire skin, café-au-lait spots on the trunk and extremities and skinfold freckling. A left-eye-redness was noticed in one patient and the presence of Lisch nodule in his left eye was confirmed after ophthalmological examination. Biochemical tests were initiated and showed in both cases increases in norephrine and epinephrine. Aldosterone, renin and Aldosteron-renin ratio were suggestive of a secondary hyperaldosteronsim. A 131Iodine-metaiodobenzylguanidine (131I-MIBG) scan showed an intense uptake super-imposed on the adrenal gland in the CT. Adrenalectomy was indicated but the male patient refused the surgery. As for the female patient, she had left adrenalectomy with a regular follow-up.

Conclusion

Because of the increased prevalence of pheochromocytoma in patients with NF1, and the potential associated adverse effects, we emphasize the importance of periodic clinical evaluation with biochemical testing and imaging studies.

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P845

Iatrogenic Cushing syndrome due to use of intranasal betamethasone – two case reports

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Background

Iatrogeny is the most common cause of Cushing syndrome (CS), with most reported cases due to prolonged use of oral, parenteral or, rarely, topical corticosteroid preparations. Few cases of CS (and consecutive adrenal insufficiency (AI)) due to intranasal corticoids have been reported and the vast majority were documented in pediatric patients.

Case reports

We present two cases of iatrogenic CS due to chronic intranasal administration of over-the-counter intranasal betamethasone in adults.

Patient A

20-year-old female presenting for a second opinion, having been diagnosed with idiopathic AI 6 months earlier (whilst evaluated for mild hair loss). At that point, substitution with hydrocortisone was recommended, as well as topic minoxidil for hair growth restoration. At presentation in our clinic, she had ceased hydrocortisone administration for one week; lab tests showed low plasmatic 0800 h cortisol (3.27 μg/dl) and adequately elevated ACTH (52.8 pg/ml). We discontinued all medication and reevaluated the patient one month later, when physical examination revealed red striae on the inner thighs. Lab tests once again revealed low ACTH (1.95 pg/ml), low plasmatic 0800 h cortisol (<1 μg/dl) and suboptimal response to Synacthen (1 mg). The patient eventually recalled she had been using intranasal betamethasone 0.5 mg/ml several times/day in the past 2 years for chronic rhinitis. She had fortuitously stopped the medication for one month before the first evaluation in our clinic, but resumed treatment afterwards. The diagnosis of iatrogenic CS (with secondary AI) was made, betamethasone was discontinued and substitution treatment was indicated until restoration of adrenal function.

Patient B

Alarmed by his daughter's diagnosis, father of patient A presented in our clinic for evaluation one month later. He reported chronic use of both betamethasone 0.5 mg/ml (4–8 times/day in the past 6 years) and beclomethasone 100 μg (4 times/day in the past 8 months). He discontinued betamethasone 8 days prior to presentation and was intensely symptomatic (fatigued, nauseous, with diffuse muscular and osteoarticular pain and blood pressure of 100/60 mmHg (vs. previous hypertensive state)). Blood tests revealed low 0800 h cortisol (2.76 μg/dl) and

inadequately normal ACTH (26.18 pg/ml). Substitution therapy was advised, but the patient refused. He continued beclomethasone, as indicated by his pneumologist. Hypertension medication was discontinued and gradually reintroduced as adrenal function recovered in the next 4 months.

Conclusions

Nasal over-the-counter preparations are often not perceived as relevant medication by patients. Still, betamethasone is a potent long-lasting corticosteroid and its capacity of inducing CS should not be overlooked, even in intranasal form.

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P846

Adrenal lipoma: about two cases

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Introduction

Adrenal myelolipoma is a rare, benign, non-secreting tumor, often found incidentally or in the context of abdominal pain. We report the cases of two patients with adrenal myelolipoma hospitalized at the endocrinology department of diabetology and metabolic diseases of Ibn Rochd University Hospital in Casablanca.

Case 1

This is a 30-year-old patient, hospitalized for adrenal mass, revealed by right lower back pain, radiating to the right hypochondrium, moreover the patient presented headaches with night sweats. The clinical examination revealed a sensitivity of the right lumbar fossa. Pheochromocytoma and adrenal corticosteroids were found to be abnormal, including 24 hour urinary methoxylated derivatives and urinary free cortisolemia. Moreover, the adrenal CT showed on the right a mass of sharp contours, of fat density with tissue contingent, without signs of invasion, measuring 85×71×61 mm. The patient was operated by laparotomy, with an anatomic pathological examination of the adrenal myelolipoma.

Case 2

This is a 36 year old patient, admitted for management of left adrenal mass, revealed by lumbago, without signs of endocrionnian hypersecretion. The clinical examination was without particularities. The 24-hour methoxylated urinary derivatives and urinary free cortisolemia were without abnormalities, whereas the adrenal CT showed a mass of fat density measuring 118×92×85 mm in the left adrenal gland. The patient was operated on by laparotomy, with histopathological examination showing an appearance of adrenal myelolipoma with capsular intrusion without signs of malignancy.

Conclusion

The adrenal myelolipoma is a rare, benign tumor, often of accidental discovery, in our context revealed by lumbago. The average age of discovery is around fifty whereas in our series the patients are under 40 years old. The scanner directs the diagnosis by identifying the fat quota. Usually respected, the excision of the myelolipoma is indicated when it is bulky, compressive or presenting a risk haemorrhagic. Anatomo-pathological examination confirms the diagnosis.

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P847

A Adrenocortical carcinoma (ACC) presenting with episodes of intermittent hypertension: Sarcomatoid type adrenocortical carcinoma

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Introduction

Adrenocorticalcarcinoma (ACC) is a rare malignancy with an aggressive prognosis, an incidance of 1–2 cases/million/year. It is the cause of 0.2% of all cancer deaths. It is seen in the 4th and 5th decades in adults and mostly unilateral and sporadic. Herein, we present a case of sarcomatoid type ACC which is symptomatic with mass compression and hypertansive attacks.

Case presentation

A-52-year-old male was referred to our endocrinology clinic with and abdominal pain and abdominal distension. Patient's history revealed intermittent episodes of hypertension responding to nifedipine treatment. Computed Tomography (CT) revealed left adrenal mass which was 9×14 cm. The patient was admitted to the endocrinology inpatient clinic with the diagnosis of pheochromocytoma. 24-hr-urinary normetanephrine level 1058 pg/24hr (N: 88–444), metanephrine 200 pg/hr (N: 276–341). 1-mg dexamethasone-suppression test serum cortisol was 0.56 mg/dL (N: 4.6–22.8), 24-hr-urinary cortisol 39 nmol/L (N:38–208), plasma renin 2.06 ng/ml/h, aldosterone 22 pg/dL, dehyroepiandesterone sulfat (dhea-s) 110 ug/dl (N: 34.5-568.9). Tumor markers were normal. With aggravation of abdominal pain CT was performed again and it revealed a 10X14 cm wide necrotic area, heterogeneous enhancement of the left diaphragm, spleen, left renal vein and artery. The patient died on first postoperative day due to hypotensive shock. The patient was diagnosed as sarcomatoid type ACC with the presence of calretinin (−), oscar-ck (+), synaptophysin (−), chromogranin (−), cytokeratin-7 (+), smooth muscle-4 (+). According to weiss criteria the mass was evaluated as high nuclear grade atypical mitotic fugures, venous sinusoidal and encapsuleted invasion.

Discussion

There are two types of adrenocortical carsinoms; functioning and nonfunctioning tumors. Nonfunctioning ones can present with metastasis, mass compression and invasion findings. Sarcomatoid carcinoma is a rare variant of ACC. When confronted with the surrenal mass, ACC is a pathology that should be kept in mind adult adrenocortical carsinoma has poor diagnosis underscoring the importance of identifying diagnostic and prognostic markers.

Keywords: Adrenocortical carsinoma, sarcomatoid

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P848

Synchronous tumours: Neuroendocrine Tumours and Breast cancer

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Introduction:

The association of breast cancer and neuroendocrine tumours, in particular pheochromocytoma, is rarely described in the literature. We report a case in a particular context.

Observation

This is a 53-year-old patient treated with 6 courses of chemotherapy for T2N3cM0 infiltrating breast carcinoma. She was admitted to our endocrinology department for exploration of a left adrenal incidentaloma, objectified in the extension assessment, measuring 53 * 55 mm with mass effect on the superior-internal rim of the left kidney. The adrenal tumour was therefore strongly suspected to be a pheochromocytoma. On clinical examination, the patient was normotensive and reported no symptoms of catecholamine secretion. The urinary and plasma normetanephrines were raised to 9.51 µmol / 24h (VN: 0.4–2.1) and 4884.2 pmol/L (VN <1070.2) respectively. Investigations for other adrenal hormones, including an overnight dexamethasone suppression test, plasma aldosterone level were all within the normal ranges. After preoperative conditioning, left adrenalectomy was performed. The surgery was followed by a pathological examination that confirmed the pheochromocytoma diagnosis.

Conclusion

The case of our patient with a combination of breast cancer and a neuroendocrine tumour is the second published case. Some pathophysiological links between these two pathologies are mentioned but the exact relationship remains unclear.

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P849

Cervical paraganglioma: about one case

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Introduction
Paragangliomas are rare neuroendocrine tumors usually Benign, developed at the expense of sympathetic ganglia, and whose treatment is essentially surgical. We report the case of a patient presenting a cervical paraganglioma hospitalized to the endocrinology department of diabetology and metabolic diseases of Ibn Rochd University Hospital in Casablanca.
Observation
A 57 years old women, not known hypertensive, presenting a mandibular mass evolving since one year, with signs of compression, moreover the patient reported a Triad of Ménard with a slimming quantified to 10 kgs. The examination revealed lateral cervical tumefaction right under mandibular painless fixed 2 cm without lymphadenopathy. Biology has shown an increase in the level of methoxylated derivatives and adrenaline. MRI angiography showed a tissue process of the 4×3.8 cm straight carotid bifurcation arriving in contact with the parotid without separating edge, whereas the MIBG scintigraphy found a right cervical paraganglioma. The patient then underwent a lumpectomy with retrospinal lymph node dissection and the histopathological examination confirmed the diagnosis of cervical paraganglioma without signs of malignancy with reactive adenitis. The evolution was marked by the regression of the MENARD triad and methoxylated control derivatives without anomalies.
Conclusion
Pariangliomas of the head and neck are most commonly developed at the expense of the carotid body and the vagus nerve. The initial assessment is essential to highlight a secreting, multifocal or malignant form, as well as to detect other familial cases. Currently, the standard treatment of these tumors is essentially surgical

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P850

Measurement of androstenedione levels in adrenal veins for calculation of the selectivity index in adrenal venous sampling

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Introduction
Primary hyperaldosteronism (PH) is characterized by autonomous adrenal aldosterone (A) hypersecretion. Unilateral adrenalectomy is the treatment of choice, when adrenal vein sampling (AVS) indicates lateralization of A secretion. To assure that each adrenal vein (AV) has been correctly sampled, cortisol levels in each adrenal vein must be higher than in the inferior vena cava. The adrenal gland cortisol/vena cava cortisol ratio is referred to as the selectivity index (SI). In most protocols, a SI ≥ 2 is considered an indication of correct AV catheterization. However, venous anatomic variants, modifying venous drainage, can dilute AV sample. As a result, cortisol levels in AV could be reduced in spite of correct catheterisation, without invalidating the aldosterone/cortisol ratio used to calculate the lateralization index. Androstenedione measurement has been proposed as an alternative to cortisol for calculation of the SI. The aim of the study was to evaluate the use of androstenedione values for SI calculation in AVS.
Materials and methods
Retrospective analysis. Thirty-three patients with a diagnosis of PA underwent consecutive AVS in a single general hospital over a 10-month period. A, cortisol and androstenedione serum levels were measured in the both AVs and in the inferior vena cava in all tests. AVS was performed early in the day, without ACTH infusion. Venous adrenal samples were consecutive, with a 6–10 minute delay between sampling of the right and left veins. Cortisol was measured by radioimmunoassay (DRG), androstenedione by competitive chemiluminescence immunoassay (IMMULITE 2000 XPi, Siemens).
Results
Table 1 shows the Selectivity Indices calculated using Cortisol or Androstenedione: Median [Interquartile range].
When using cortisol, 19/33 (57.57%) AVS presented SI≥ 2. An additional 7 patients had SI≥ 2 using androstenedione, for a total of 26/33 (78.78%) with SI≥ 2. Regression analysis. When comparing cortisol levels of cortisol-selective studies with androstenedione levels, right adrenal $R^2 = 0.86$ ($P < 0.001$) with left adrenal $R^2 = 0.64$ ($P < 0.001$).

Table 1

SI	Cortisol	Androstendione
Right AV/cava	3.6 [1.54-16.11]	27.30 [3.08-62.85]
Left AV/cava	3.7 [1.92-7.11]	26.98 [7.05-67.63]

Conclusions
The calculation of the AVS selectivity index using androstenedione could be useful to ascertain whether adrenal veins have been correctly catheterized, in patients with low cortisol indices. In this series of patients, an androstenedione SI cut-off value ≥ 2 increased the number of selective AVS studies by 21.2%. The response of patients to AVS-based unilateral adrenalectomy when selectivity has been established by androstenedione must be evaluated before the use of androstenedione can be recommended to establish AVS selectivity.

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P851

True silent pheochromocytoma: description of a rare entity

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Introduction
With the advent of modern imaging, up to 30% of adrenal pheochromocytomas are discovered incidentally in asymptomatic patients. Smaller tumors may be 'pre-biochemical' in their secretory capacity, but truly nonfunctioning tumors over 3 cm are exceedingly rare. We describe a case of a clinically and biochemically silent pheochromocytoma.
Case report
A 65-year-old woman was found to have a left adrenal incidentaloma on an abdominal CT carried out during hospitalization for acute pyelonephritis. The mass was 3.5 cm in diameter and displayed an imaging phenotype consistent with pheochromocytoma. The tumor was also positive on ^{123}I-MIBG scintigraphy. The patient's history was notable for arterial hypertension controlled on telmisartan 40 mg/d and mixed hyperlipidemia on simvastatin 40 mg/d. She had a parathyroid adenoma removed in the past. Biochemical evaluation showed a normal overnight dexamethasone suppression test, normal plasma aldosterone/plasma renin activity, normal 24 h urine total metanephrines and VMA. Urinary dopamine was not tested. The patient underwent a laparoscopic left adrenalectomy without preoperative preparation and no perioperative complications. Histology was complatible with a neoplasm of the adrenal medulla, consisting of cells with granular oxyphil cytoplasm and regular nuclei, positive to chromogranin A and CD56 and negative to inhibin and melan A and nearly undetectable Ki-67.
Conclusion
Pheochromocytomas are recognized by their imaging characteristics in asymptomatic patients and although varying in their secretory patterns, tumors >3 cm are rarely nonfunctioning. These tumors should still be best managed by resection following adequate α-blockade.

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P852

Multiple paragangliomas (PGs) of head and neck and middle mediastinum: report of an apparently sporadic case

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Introduction
PGs are rare neuroendocrine tumours (NETs), slowly growing, derived from the neural crest cells of the autonomous nervous system. Presenting symptoms are related to catecholamine hypersecretion or to mass effect. The optimal approach is dictated by size, symptoms and anatomical relationship of tumours with neurovascular structures.

Aim
To describe a patient with bilateral carotid body and mediastinal carotid body PGs.
Case report
A 35 years old hypertensive female, previously diagnosed with bilateral non-functioning carotid body PGs at 28 years of age. Family history was negative for NETs. She initially underwent a partial resection of the right carotid body tumour and histopathological analysis revealed PG. CT imaging also detected a left carotid tumour and a middle mediastinum tumour. Angiography demonstrated large, highly vascularized masses of the carotid artery bifurcation bilaterally (9×3.5 cm on the right, 3×5 cm on the left). The patient denied any symptoms related to catecholamine hypersecretion, mass effect at diagnosis. Biochemical and hormonal assessment was unremarkable. Three additional surgeries were performed, one on each tumour. Left transpleural partial resection of the mediastinal mass led to left vocal chord palsy. During follow-up, the right cervical and mediastinal PGs slowly enlarged. The right carotid tumour was irradiated externally (45 Gy) and remained stable in size. The mediastinal mass developed mass effects leading to cough, dyspnoea and chest pain. The patient underwent a complete tumour resection via a median sternotomy. A diagnosis of PG was confirmed histopathologically. The tumour cells stained positively for chromogranin and synaptophysin and the Ki67 index was 8%. The patient recovered uneventfully, is currently asymptomatic and being followed up. Despite an apparently sporadic presentation, genetic testing for PGL genes mutation including succinate dehydrogenase subunits is required, especially given multicentric disease at a young age.
Conclusions
Multiple cervical and mediastinal PGs are exceedingly rare. In these patients, initial diagnosis and management should be followed by close observation, in order to detect multicentric tumours. Multidisciplinary collaboration is required for improved outcomes.
Keywords: Sporadic paraganglioma, middle mediastinum, multiple paraganglioma
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P853

Your young patient has severe, resistant hypertension? Do not treat her without a workup!

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Introduction/Aim
Secondary hypertension is often undiagnosed or misdiagnosed as essential in young people. We hereby present a challenging case, in order to raise awareness about this problem.
Material and methods
Review of the patient's clinical record and of the relevant literature.
Results
A previously healthy 22 year old woman complained of frequent non-pulsatile holocraneal headaches for 6 months; they were attributed to anxiety and poor sleep, and she was offered paracetamol and NSAIDs without further exploration. One night she was admitted to the emergency room with excruciating headache; her blood pressure was 237/132 mmHg. She was prescribed multiple antihypertensive treatments which proved ineffective, and was finally referred to our Outpatient Hypertension Clinic for secondary hypertension workup. The only relevant finding was plasma normetanephrine 1950 pg/mL (x 10 UNL), with normal metanephrine. Abdominal CT showed a heterogeneous 6 cm retro-peritoneal mass in the aortocaval space and normal adrenals. Even though the MIBG scan was negative, paraganglioma was suspected, and after presurgical preparation it was laparoscopically removed. The pathological diagnosis was paraganglioma with low malignancy risk (Ki67<2%). The patient remains asymptomatic and normotensive without medication and her metanephrines are normal.
Conclusions
Severe secondary hypertension may remain undiagnosed in young people, therefore signs such as unexplained headache must be pursued. An accurate diagnosis is essential in order to achieve control and eventually a cure. The sensitivity of the MIBG scan, while high for pheochromocytoma (>90%), is lower for paraganglioma (67%), hence a negative scan does not exclude the diagnosis.
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P854

Uncontrolledhighblood pressure in pregnancy: the pheochromocytoma is not to be ignored

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Introduction
The discovery of a pheochromocytoma during pregnancy is very rare. The diagnostic and therapeutic approach determines the maternal and fetal prognosis. We present the case of a pheochromocytoma discovered during a pregnancy of 16 weeks of amenorrhea.
Case report
Mrs. A.H 29 years old, primigravida, presented at 6 weeks of amenorrhea with hypertension, she was treated by alpha methyl dopa 500mg and nicardipne 20 mg; at 16 weeks she was hospitalized for an hypertensive peak at 20 mmHg without edema or proteinuria. A detailed patient history revealed pulsatile headache; heart palpitations and profuse sweats. The diagnosis of pheochromocytoma was suggested. The normetanephrine and metanephrine blood level were respectively at 4.75 nmol / l (<1.29) and at 0.19 nmol / l (<0.92). Adrenal ultrasound showed heterogeneous mass arising from the right adrenal gland of 53*66 mm. The hormonal and imaging tests detecting multiple endocrine neoplasia were negative. We have kept nicardipine and replaced Alphamethyldopa by an alpha blocker. Obstetric ultrasonography was normal. Pheochromocytoma resection by laparoscopy was decided at the end of 28 weeks. Post-operatively the rate of blood catecholamines decreased by half in one month and the patient blood pressure was easily controlled with calcium channel blockers alone. At 35th week an emergency cesarean section was performed because of an acute fetal distress, she delivered a healthy baby boy who presents a sexual development disorder that we are exploring.
Discussion
The initial diagnosis of hypertension during pregnancy is frequently attributed to pre-eclampsia rather than pheochromocytoma. This Confusion is the main cause of overlooking the diagnosis. Our patient had presented a blood hypertention since the 6th weeks of amenorrea but the diagnosis of pheochromocytoma was confirmed at only the 16 week. The lack of knowledge of the diagnosis exposes to the risks of a secretory thrust which can be fatal for the mother and the fetus. Early diagnosis and multidisciplinary medical management that prepares for the excision of the tumor is always necessary.
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P855

Adrenal surgical series - radiologic-pathological correlation

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Introduction
Adrenal surgical series are scarce in the literature. We aim to present a single institution consecutive case series and to establish a radiologic-pathological correlation.
Material and methods
A retrospective, observational and descriptive study was conducted by searching the Pathology database for surgically removed adrenal lesions. Cases were matched with the Imagiology database. Ultrasound, CT and MRI images were then reviewed by the same experienced radiologist in order to determine any possible correlation with the pathological findings.
Results
A total of 35 patients, 18 males (51.4%) and 17 females (48.6%) were evaluated. Benign lesions: 18 (51.4%); malignant lesions: 17 (48,6%). Primary adrenal lesions: 22 (62.9%); benign: 18 (81.8%); malignant: 4 (18.2%); pheochromocytomas: 6 (27.3%). Secondary adrenal lesions: 13 (37.1%), pulmonary neoplasia

metastasis: 8 (61.5%); metastasis from other origins: 5 (38.5%). Malignant adrenal lesions: primary adrenal: 4 (23.5%); secondary adrenal: 13 (76.5%). Benign lesion average features: US - average diameter 56.2 mm; right-sided, nodular shape, regular edges, solid/ cystic structure, homogeneous, hypoechogenic, without calcifications; CT - average diameter 40,7 mm, right-sided, nodular shape, regular edges, well defined boundaries, solid structure, homogeneous, average density 15.9 HU, high contrast uptake, without calcifications; MRI - average diameter 50.8 mm; right-sided, nodular shape, regular edges, well defined boundaries, solid structure, heterogeneous, hipointense in T1-weighted images, hiperintense in T2-weighted images, heterogenous contrast uptake. Malignant lesion average features: US - average diameter 85.2 mm; right-sided, nodular shape, lobulated edges, solid structure, heterogeneous, hypoechogenic, without calcifications; CT - average diameter 53.9 mm, right-sided/ bilateral, nodular shape, irregular edges, well defined boundaries, solid structure, heterogeneous, average density 28.8 HU, high contrast uptake, without calcifications; MRI - average diameter 34 mm; right-sided, nodular shape, lobulated edges, well defined boundaries, solid structure, heterogeneous, hipointense in T1-weighted images, hiperintense in T2-weighted images, heterogeneous contrast uptake. No distinctive findings were specific for pheochromoctytoma.

Conclusions

Adrenal lesions diagnosis and management can be challenging. Radiological features assessment is valuable but is not pathognomonic. Ultrasound is also a reliable method in identifying suspicious lesions.

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P856

Von hippel-lindau disease associated with bilateral pheochromocytoma and cerebellous hemangioblastoma

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Introduction

Von Hippel-Lindau disease (VHL) is a hereditary condition that predisposes to the development of benign and malignant tumors due to mutations in the VHL gene. Several clinical manifestations can be observed including the development of hemangioblastomas of the central nervous system and the retina, renal or pancreatic cysts or cancers, or more rarely pheochromocytomas. These affect 10 to 25% of patients, are frequently bilateral and often reveal the disease.

Observation

We report the case of a 26-year-old patient treated since 2013 for a bilateral pheochromocytoma falling within the framework of VHL disease. The diagnosis was retained by observing: clinically, a typical Ménard triad with paroxysmal hypertension, biologically increased methoxylated urinary derivatives, a bilateral adrenal mass revealed by an abdominal CT. The patient underwent bilateral adrenalectomy the same year. Looking at the age of discovery and the bilaterality of the mass, a genetic study was conducted and found a mutation of the VHL gene. During the follow-up, a general assessment was carried out in search of other tumoral localizations, notably a cerebral MRI showing an appearance of cerebellar hemangioblastoma. The fundus oculi did not reveal an abnormality and the abdominal CT did not find any pancreatic nor renal abnormalities.

Conclusion

This clinical case illustrates the interest of carrying out a genetic study in front of any bilateral pheochromocytoma to diagnose possible VHL disease and thus early detect all the associated clinical manifestations and suggest a screening for relatives.

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P857

Bilateral primary adrenal lymphoma

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Introduction

Adrenal gland involvement can be seen in about 25% of lymphomas. However, primary adrenal lymphomas (PAL) are rare. The most common is diffuse large B-cell lymphoma (DLBCL). It is seen usually after the age of 60 years as bilateral, large masses.

Case report

A 64-year-old woman with a complaint of abdominal pain was referred to our clinic after bilateral surrenal masses were detected upon abdominal ultrasonography (USG) and computed tomography (CT). She did not have weight loss and fever. Physical examination showed widespread abdominal tenderness without guarding or rebound. Peripheral lymphadenopathy was absent. Laboratory tests showed cytopenia with elevated levels of lactate dehydrogenase, erythrocyte sedimentation rate, and C-reactive protein. Bilateral mass lesions, 10×6 cm sized in the right surrenal lodge, about 8.5×5.5 cm in the left surrenal lodge, 30HU in density was detected upon dynamic surrenal CT. Several pathological lymph nodes with a short axis up to 23 mm in the paraaortic region on the left adjacent to the mass lesions were seen. Cortisole levels and urinary catecholamines and methanephrine results were normal. She underwent surrenal biopsy. Histopathological and immunohistochemical staining was diagnosed as CD20 positive DLBCL. No involvement was found upon bone marrow biopsy. The patient was started on rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy by hematology. The adrenal masses had disappeared after the patient had been treated with 6 courses of chemotherapy. The patient is currently being observed in remission after 19 months after the last chemotherapy course.

Discussion

PAL's are constitute $<1\%$ of non-hodgkin lymphomas. 75% of these masses are bilateral and the mean diameter is 8 cm. PAL's are usually symptomatic due to mass effect, adrenal insufficiency due to infiltration of tumor cells. Our patient's complaint was abdominal pain. Adrenal insufficiency was not found. It is difficult to distinguish lymphoma from metastatic lesions. Lymphoma can be diagnosed by biopsies or after adrenalectomy with suspicion of adrenocortical cancer. The prognosis of PAL is generally poor. Complete remission with chemotherapy has been reported in several articles in the literature. Early diagnosis is important. Although primary adrenal lymphoma is rare, it should be kept in mind among differential diagnosis especially in patients with advanced age, bilateral and large masses. Therefore our case is worth to present as a case of primary adrenal lymphoma without adrenal insufficiency to underline the importance of this pathology.

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P858

Prevalence of autonomous cortisol secretion as defined in ESE guidelines in a Swedish cohort of patients diagnosed with adrenal incidentaloma: A prospective study in regional Sweden

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Background

Resource-saving and medically safe investigations of adrenal incidentaloma (AI) is one of the challenges in modern endocrinology. The absolutely majority of AIs are benign and hormonally inactive. Mild hypercortisolemia is the most common finding in hormonally active AI and is often referred to as subclinical Cushing syndrome (SCS). SCS is associated with increased risk of type 2 diabetes, poorly regulated hypertension, osteoporosis and cardiovascular disease. There is a lack of a generally accepted definition of SCS. An overnight 1 mg dexamethasone test (DST) is usually used to diagnose SCS but S-DHEAS measurement has recently been suggested as an alternative diagnostic method. The aim of this study was to investigate the prevalence of SCS and if S-DHEAS could be used to identify SCS.

Methods

In this prospective study of all AI diagnosed in a defined area we used the ESE definitions of mild hypercortisolemia, i.e., autonomous cortisol secretion (ACS) and possible autonomous cortisol secretion (PACS). A serum cortisol ≤50 nmol/l after DST excludes ACS. Serum cortisol 51–138 nmol/l after DST is defined as PACS and serum cortisol >138 nmol/ l as ACS if overt Cushing syndrome has been excluded. S-DHEAS was analyzed in all individuals to investigate a possible correlation with subnormal level of DHEAS and ACS/PACS.

Results

98 individuals with AI were investigated with DST and S-DHEAS. The mean age was 67.5 (38–86) years and 42 (43%) were males. PACS or ACS were found in 37 (38%, PACS $n=30$, ACS $n=7$). Subnormal S-DHEAS was found in 8 (22%) patients with PACS, 2 (29%) with ACS and 4 (7%) patients with normal DST.

Conclusion
Mild excessive cortisol secretion is common in AI. However, using the ESE definition only 7% had ACS which may be slightly lower prevalence than previous studies using other definitions for SCS. DHEAS could not replace DST.

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P859

Phaeochromocytoma in pregnancy

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Phaeochromocytoma in pregnancy is an extremely rare condition. Early recognition can largely decrease maternal and fetal mortality rates. As symptoms of phaeochromocytoma are similar to those of other more common causes of hypertension during pregnancy, timely diagnosis is a challenge. There is no consensus in literature about the specific treatment nor about the optimal delivery timing or route. Case of a 32 years old woman with a single pregnancy of 30 weeks and 3 days admitted in an obstetrics department because of a paroxistic hypertension. She had been asymptomatic until the first trimester of gestation when she started with paroxysmal episodes of migraine, palpitations and precordial pain associated with hypertensive crises (systolic blood pressure 190-200 mmHg). The patient had no relevant personal medical history except a previous pregnancy and delivery without complications. Proteinuria was absent, therefore excluding a preeclampsia. Renal ultrasound showed no renal asymmetry or vascular alterations but identified a heterogeneous 44×42×41 mm mass in the left adrenal gland. Abdominal MRI confirmed the 40 mm nodule in the left adrenal gland with hyperintense and homogeneous central area in T1 and T2 and solid peripheral area hypointense in T1 and hyperintense in T2. Normal Echocardiogram. 24h hölter: sinus rhythm and multiple periods of sinus arrhythmia. Ambulatory blood pressure monitoring: non dipper profile. Fetal ultrasound: normal fetal circulation and fetus in centile 36. Analytically: metanephrine (urine): 27 ug/24h (64–301 ug/24h) and normetanephrine (urine): 4086 ug/24h (162–527 ug/24h). Diagnosis of phaeochromocytoma was established. She was initially medicated with nifedipine 30mg 2id and, at the 33rd week the patient started alpha-blockade and at the 34th week beta-blockade. We chose fenoxibenzamin (maximum 30 mg/day) and propranolol (30 mg/d) respectively. A Caesarean-section was performed at 37 weeks of gestation. Mother and child had no complications. Specifically the child had no hypotensive period. After delivery the patient kept fenoxibenzamin 40 mg/d and propranolol 30 mg/d until the left laparoscopic adrenalectomy was performed (9 days after delivery). The surgery ran without intercurrences and she stopped antihypertensive medication with good tolerance and stable arterial blood pressure. The histology confirmed a phaeochromocytoma with a PASS score of 4. One month after surgery the patient had normal plasmatic values of metanephrine (13.9 pg/ml $<$65) and normetanephrine (82.3 pg/ml $<$196). Phaeochromocytoma during pregnancy is a rare condition and as such should be treated in specialized centers with a multidisciplinary team. Important issues that need special attention include pretreatment, timing of surgery and route and timing of delivery.

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P860

Clinical presentation and management of primary aldosteronism in late childhood and adolescence: Experience in an outpatient hypertension clinic

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Aim
Description of a series of children and adolescents with Primary Aldosteronism (PA) diagnosed and treated in our Outpatient Hypertension Clinic from 1994 to 2018.

Methods
Review of the clinical records and of the relevant literature. Values are given as mean +s.d.
Results
16 of a total of 49 patients younger than 20 years of age referred to our Hypertension Clinic from 1994 to 2018 were diagnosed of PA (33%), while 27 (55%) were diagnosed of essential hypertension and the other 6 (12%) of miscellaneous causes. Two of the patients with PA (13%) already had shown transient cerebrovascular complications. Their mean age was 15.2+3.1 yr (range 8–19). Eleven (69%) were female. Their untreated blood pressure (ABPM): 164+23/96+18 mmHg, heart rate 79+13 bpm (awaken), and 158+22/89+18 mmHg, 75+14 lpm (sleeping). 13 (81%) had confirmed hypertension by ABPM. eGFR (CKD/EPI) 98+27 ml/min/1.73 m^2, low in 3 patients (19%). Kalemia: 3.2+0.7 mEq/l, low in 9 (56%). Plasma aldosterone: 58.7+36.2 ng/dl; plasma renin activity (PRA): 0.52+0.37 ng/mL per h, avoiding pharmacological interferences. Confirmation test was not performed in patients with obvious hypokalemia. Eleven (69%) underwent a captopril test, and 3 (19%) a saline infusion test. 15 had abdominal CT scan, with unilateral adenoma found in 6 (37%) and bilateral adenomas in 1(6%). Adrenal venous sampling (AVS) was performed in this patient, but aldosterone was symmetrical, and surgery was not considered. All 6 patients with unilateral adenomas underwent surgery and PA was biochemically resolved in all of them, but two of them still needed antihypertensive treatment. One patient was diagnosed of type 1 familial aldosteronism and is treated with low-dose dexametasone. The other 9 patients are receiving treatment based on mineralocorticoid receptor antagonists, and 8 of them (89%) maintain normal blood pressure, normokalemia and unsuppressed PRA ($>$1 ng/ml per h), although most maintain high plasma aldosterone. The final diagnoses were: idiopathic PA in 6 patients (37%), Lityński-Conn adenomas in 7 patients (44%), type II familial aldosteronism in 2 patients (13%) and type 1 familial aldosteronism in one patient (6%).
Conclusions
PA was the main cause of secondary hypertension, and is complicated with organ damage in 1/3 of the patients. Half had hypokalemia. Idiopathic PA and functioning adenomas had similar prevalence. Confirmation test and CT is required in most patients, but rarely AVS. Patients with unilateral adenomas achieve biochemical cure. MCRA control blood pressure, potassium and PRA in most of the rest.

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P861

Neuroendocrine neoplasms: experiences of a single tertiary referral endocrine centre in Hungary

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Introduction
Clinicopathological characterisation ofneuroendocrine neoplasms could provide improved prognostic information even at the time of the diagnosis.
Objectives
The aim of this study was to characterise the clinicopathological features of a large cohort of patients with neuroendocrine neoplasms (NENs).
Patients and methods
The study included 210 patients (95 men and 115 women) with histologically confirmed and verified neuroendocrine neoplasms in our single tertiary referral endocrine unit. Descriptive statistics were performed providing summaries of selected clinical and pathological parameters at the time of diagnosis. Factors contributing to survival were analysed. A p value of less than 0.05 was considered statistically significant.
Results
The mean age at diagnosis was 54.7±16.3 years for men and 52.3±15.1 years for women. The most common primary tumour sites were the pancreas (n=74, 35.2%), the ileocecal region (n=34; 16.2%) and the lungs (n=29; 13.8%), respectively. In 12.6% of patients, the primary tumour site remained unidentified. The mean follow-up time of patients was 4.6 years. Original histopathological reports were available in 128 patients (60.9%) who were classified according to

the 2010 WHO criteria. The most common grade was grade 2 ($n=55$; 43%), while grade 1 and grade 3 were diagnosed in 52 (40.6%) and 21 (16.4%) patients, respectively. Sufficient clinical data for staging were available in 169 patients, who were classified according to the 2009 American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) recommendations. The majority of patients had been presented with advanced, metastatic disease in stage IV ($n=122$; 72.2%). 33 patients were diagnosed in stage I, while stages II and III constituted in 7-7 patients. 5-year survival was poorer in patients with grade 3 and in stage IV tumours. According to univariate Cox regression model male gender, tumours with grade 3 and stage IV and increased 5-HIAA urinary excretion was associated with poorer prognosis. The most frequent hormone-producing tumours were insulin-, gastrin- and ACTH-producing tumours as well as tumours causing carcinoid syndrome.

Conclusion

The overrepresentation of patients with tumours in a higher stage and grade reflects the specified tertiary feature of our centre. Our results confirm previous data that higher tumour grade and stage, the presence of metastases at diagnosis are the most important factors influencing the prognosis. Patients presented with carcinoid syndrome also have a poorer overall survival.

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P862

Asymptomatic pheochromocytomas-an unelucidated physiopathology pattern

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Introduction

Pheochromocytomas (PHEOs) are tumors arising from medulla chromaffin cells. Their diagnosis is challenging due to a large clinical spectrum – from classical crisis to completely asymptomatic. Approximately 5.0–6.5% of adrenal incidentalomas are pheochromocytomas, and 8% of pheochromocytomas are completely asymptomatic, usually in a familial form.

Aim

To compare biochemical and imagistic features of symptomatic/asymptomatic PHEOs.

Methods

A retrospective study including 47 patients diagnosed with PHEO between 2012-2018, divided in two groups. Group 1: 6 with asymptomatic PHEO (3F, 3M, aged 53.8 ± 19.2 years) had MEN 2A, without any history of signs suggestive of PHEO crisis, discovered with the occasion of routine MEN2A follow-up. Group 2: 41 patients with typical manifestations of PHEO (31F, 10M, aged 56.6 ± 16 years, 2 with MEN 2A). We compared plasma free metanephrines & normetanephrines levels and tumor size (CT scan) in patients with asymptomatic PHEO with those in patients with symptomatic PHEO. The data were shown as mean $\pm$s.d.

Results

Plasma free metanephrines (normal 10–90 pg/ml) in asymptomatic PHEOs patients were 193 ± 201.7 pg/ml, compared to 93.8 ± 87.9 pg/ml, in patients with symptomatic PHEO. Plasma free normetanephrines (normal 20-200 pg/ml) in asymptomatic patients were 1247 ± 1290 pg/ml compared to 414.35 ± 709.7 pg/ml, in symptomatic patients. Although the values seemed paradoxically higher in asymptomatic patients, there were no significant differences between the 2 groups. Predominant secretion of metanephrines was observed in 66.6% of patients from group 1, as compared with 15% in group 2. Tumors were situated predominantly in the right adrenal in both groups (in 4/6 patients in group 1 and in 24/41 patients, in group 2). Bilateral tumors were noted in one symptomatic patient. The maximal tumor diameter in group 1 was 38.3 ± 19.2 mm, while in group 2 was 52.4 ± 25 mm, ($P=0.005$). Correlating tumor size with metanephrines levels, there is a statistically valid association in both groups ($P<0.001$).

Conclusion

Patients with asymptomatic PHEO had smaller tumors, but similar plasma metanephrines levels compared with patients with symptomatic PHEO. It is tempting to speculate that the poor response of peripheral tissues to catecholamine hypersecretion in patients with asymptomatic PHEOs may be due to chronic receptor down-regulation and relatively stable catecholamine tumor secretion in time.

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P863

A rare case of primary hyperaldosteronism associated with chronic kidney disease-difficulties in diagnosis and treatment

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Introduction

Primary aldosteronism (PA) accounts for 20% of patients with resistant hypertension and is one of its leading causes. Options of treatment include adrenalectomy and mineralocorticoid receptor antagonists (MRAs). Latest studies suggest that both may paradoxically lead to a decline in estimated glomerular filtration rate (eGFR), explained by the masked glomerular hyperfiltration associated to PA before treatment.

Case report

A 56 years old male patient, presented in 2010 in Italy for resistant arterial hypertension associated with hypokalemia. Further biological tests revealed elevated aldosterone level associated with low plasma renin activity and the CT scan confirmed the diagnosis of PA: right adrenal hyperplasia and two solid lesions on the left one, both with a diameter of 10 mm. The adrenal vein sampling showed no lateralization, therefore chronic treatment with MRA (canrenone, 200 mg/d) was initiated with favorable response, but pacient failed to attend revaluation. After 8 years, while presenting in our department for the investigations of a toxic nodular goiter, the laboratory testing showed severe hyperkalemia (7.4 mmol/l), hematuria, proteinuria and reduced eGFR (9.2 ml/min per 1.73 m^2). He was directed to a nephrology clinic where an abdominal ultrasound showed slightly reduced renal dimensions and the renal biopsy revealed 80% fibrosis and extensive lesions of arteriosclerosis, confirming the hypertensive etiology. At that time the patient was using multiple drugs, including canrenone 200 mg/d and furosemide 20 mg/d, hence the first step was to interrupt the latest and to start a low potassium diet. Further evaluations showed normal potasium and stationary eGFR and treatment with a low dose of Spironolactone (25 mg) was initiated, in order to reduce the risk of myocardial and renal fibrosis. A new CT scan was performed, this time revealing normal right adrenal gland and two adenomas (4.5 mm, respectivelly 10 mm in diameter) on the left one.

Discussion

This case supports the hypothesis that high levels of aldosterone lead to glomerular hyperfiltration. Multiple studies suggest pretreatment parameters like high plasma aldosterone, low plasma renin, low plasma potassium, and high eGFR are significant predictors of eGFR decline after start of treatment, also supported by our case. An explanation for the normokalemia at the present moment could be the balanced hypokalemia of primary aldosteronism with hyperkalemia of chronic renal failure. Despite normal levels of potasium and the diagnosis of chronic kidney disease, we recommend an interdisciplinary team evaluating the necesity of treatment with MRAs.

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P864

X-linked adrenoleukodystrophy phenotype evolution - is family history important?

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X-linked adrenoleukodystrophy (X-ALD) is an inherited disorder of peroxisomal metabolism, characterized by deficient beta-oxidation of saturated very long chain fatty acids (VLCFA). The accumulation of VLCFAs is associated with demyelination of the nervous system, and impairment of steroid hormone synthesis in the adrenal cortex and the testis. The range of phenotypic expression is wide and dynamic. The three presentations most commonly seen are the childhood cerebral forms, adrenomyeloneuropathy (AMN) and the Addison disease only (ADO). We reviewed the cases of eight adult males accompanied at the endocrinology outpatient's department diagnosed with X-linked adrenoleukodystrophy. The patients belonged to 5 different families, which were identified by numbers from 1 to 5. On family 1, the two patients studied were brothers, currently with 50 and 62 years, both diagnosed at the age of six with an ADO

phenotype. Afterwards, by the age of 36 and 38 years, respectively, they both developed AMN. Three of the patients studied belonged to family 2, at the present with 33, 40 and 44 years. All of them presented with ADO at the ages of 13, 14 and 18 years. Only the latter was diagnosed with AMN by the age of 40, despite remaining clinically asymptomatic. Family 3 is represented by a 38-years-old patient, diagnosed with 13 years with ADO, who developed both AMN and cerebral involvement with 29 years. Although he remained clinically stable for several years, he has presented clinical and imaging signs of disease progression for the last 2 years. From his family history, stands out a brother with X-ALD, also with cerebral involvement who died with 33-years-old. On family 4, the patient was diagnosed with 64 years, presenting with both AMN and adrenal insufficiency. Within 11 years, with 75 years, he developed cerebral involvement and died a few months later. Two of his brothers had X-ALD, both with AMN and Addison disease. One of them died after the diagnose of cerebral involvement. Lastly, we describe a patient 28-years-old, representing family 5, diagnosed by the age of 11 years with an ADO phenotype, who hasn't shown signs of disease progression. There is a family history of X-ALD on a maternal grandfather whom presented with ADO, and developed AMN at 70 years. X-linked adrenoleukodystrophy is characterized by a dynamic phenotypic expression, usually not predicted by family history. Nevertheless, in the patients studied the phenotype evolution appeared to be similar among patients belonging to the same family.

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P865

Iatrogenic secondary adrenal insuficiency due to ritonavir therapyand inhaled budesonide

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Introduction
The widespread use of highly-active antiretroviral therapy (HAART) has drastically improved the life expectancy of patients with human immunodeficiency virus (HIV) infection. However, many of these drugs show multiple interactions with other treatments; protease inhibitors (PI) are especially troublesome as they interact with the hepatic cytochrome P450. There have been previous reports of both Cushing's syndrome and adrenal insufficiency in patients treated with PI and steroids, as PI decrease the hepatic metabolism of the latter and increase its serum levels.
Case report
A 52-year-old male patient is admitted to the hospital with an altered mental status. His past medical history includes HIV infection in treatment with abacavir/lamivudine + darunavir/ritonavir and chronic obstructive pulmonary disease (COPD) in treatment with inhaled budesonide/ipratropium bromide and a papillary renal cell carcinoma treated with radiofrequency ablation. Due to the altered mental status, the patient had abruptly stopped many of his medications, including his COPD inhalers. No other source of steroid exposure was found after reviewing his baseline treatments. On physical examination his BP was 72/48 mmHg. His blood tests shown a serum sodium level of 127 mEq/l and a morning cortisol level of 2.22 µg/dl. An abdominal computed tomography (CT) scan shown adrenal glands of normal appearance. The patient was started on stress corticoid doses with gradual tapering and was discharged on hydrocortisone replacement therapy; his COPD regime was modified as well, with only long-acting beta-agonists being prescribed. On follow up, his morning cortisol level gradually recovered towards the normal range and it was possible to interrupt the steroid replacement therapy.
Discussion
Although most case reports of PI-induced steroid excess have been described with the use of fluticasone due to its higher lipophilicity, potentially any steroid administered by any route could expose a patient to higher than normal steroid levels and its associated morbidity. Most commonly, patients present with findings consistent with cortisol excess and Cushing's syndrome. However, it is important to rule out adrenal insufficiency if the clinical findings are suggestive due to the potential mortality associated with this condition. A thorough review of all steroid-containing products is paramount to find the culprit agent.
Conclusion
It is important to take into account in the management of HIV patients the interaction between potent CYP3A4 inhibitors with other commonly used drugs that are substrates of the CYP3A4 isoenzyme, in order to avoid serious complications.

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P866

Primary adrenal lymphoma: a rare cause of adrenal insufficiency

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Background
Primary adrenal Non Hodgkin Lymphoma (NHL) accounts for less than 1% of all NHL cases. Among them, Diffuse Large B Cell Lymphomas (DLBCL) are the most commonly identified. Seventy percent of cases are bilateral and adrenal insufficiency usually occurs. Here we describe a case of a DLBCL with bilateral adrenal involvement and adrenal insufficiency.
Clinical case
A 68 years male with a personal history of malaria, asthma, hypertension and cholecystectomy. He was admitted in a primary level hospital for a consumptive condition with weight lost, fever, nausea, vomiting, muscular and abdominal pain. The initial complementary study showed hyponatremia (135mmol/L) and a positive blood culture for Streptococcus. Antibiotic therapy was implemented. A thoracic-abdominal-pelvic computed tomography (CT) revealed bilateral adrenal masses with intermediate density, measuring 76 mm in the right adrenal gland and 55 mm in the left. He requested medical care a week later due to worsening of his general condition, presenting with hypotension and skin and mucosa hyperpigmentation. Laboratorial analysis showed hyponatremia (121 mmol/L) and hyperkaliemia (5 mmolL), low serum cortisol (1.4 ug/dL), and high ACTH (327 pg/mL), high plasma renin activity (4.1 ng/mL/h), low aldosterone (0.9 ng/mL) and high ß2 microglobulin (13.9 mg/L). The leukocyte blood count was normal. At this time, the diagnosis of primary adrenal insufficiency was made. He was treated with intravenous hydrocortisone and saline fluids, followed by daily oral hydrocortisone and fludrocortisone, and his health status has progressively improved. A F18-Positron Emission Tomography (PET) was performed and showed two adrenal masses suggestive of malignancy (SUV 21.4 in right adrenal gland and 20.5 in left adrenal gland). It also demonstrated intra-abdominal and testicular lymph nodes. Considering the high suspicion of adrenal malignancy, he was transferred to our Oncology Center where an adrenal biopsy was performed. A large diffuse large B cell Lymphoma, 'non-germinal center', Ki67 = 70%, was diagnosed, showing positive staining for CD20, BCL6, BCL2, MUM1 and negative for CD3, CD5, CD10, MYC. He was then treated with chemotherapy combining rituximab, cyclophosphamide, doxorrubicin, vincristine and prednisolone. One year later the 18FDG-PET showed no evidence of disease.
Conclusion
This case describes a rare primary adrenal diffuse large B-cell lymphoma, one of the most uncommon causes of adrenocortical insufficiency. Although it is a rare entity, it should be considered in the differential diagnosis of bilateral nodular adrenal lesions, particularly in the setting of exclusive bilateral adrenal 18FDG-PET uptake and adrenal insufficiency.

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P867

Associated factors with blood pressure outcome in 75 patients after adrenalectomy for primary hyperaldosteronism

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Context
Surgery performed in primary hyperaldosteronism (PAH) can achieve biological healing in almost all cases, but blood pressure healing is only obtained in 20 to 55% of cases. The aim of our study is to identify the anthropometric, biological and pathological factors that would be statistically associated with blood pressure outcome in patients after unilateral adrenalectomy for primary aldosteronism between 1996 and 2016.
Method
This is a monocentric retrospective study performed in Lille University Hospital. Patients have benefited from a preoperative evaluation and at least from a one year postoperative evaluation. They were considered; 1) cured on the blood pressure level if systolic blood pressure (SBP) one year postoperatively was lower than 140 mmHG and if diastolic blood pressure (DBP) was lower than 90 mmHG and without treatment, 2) improved if there was a decrease of 20 mmHG of the consultation SBP and/or a decrease of 10 mmHG of the consultation DBP one year postoperatively with either the same treatment or with less treatment or if the blood pressure was the same with less treatment 3) not improved if systolic and diastolic consultation blood pressure at one year postoperatoire was stable or increased and the number of treatments unchanged or increased.

Results
Seventy-five patients were included with a sex ratio of 40 women for 35 men. The average age of 51 years (±10 years). 68 patients had Conn's adenoma and 7 patients had unconventional pathology of Conn's adenoma. In terms of blood pressure, 18 patients (24%) were cured, 47 patients (62.7%) were improved and 10 patients (13.3%) were not improved postoperatively. Patients are more likely to be cured if they are female ($P=0.009$), if they are young ($P<0.005$), if the body mass index is low ($P=0.006$), if the level of pulsed blood pressure is low ($P=0.029$), or if there is no renal failure ($P=0.034$).
Conclusion
Unilateral adrenalectomy for PAH can cure or improve hypertension in 86% of patients. Female sex, young age, low body mass index, low preoperative pulsed blood pressure level and absence of renal insufficiency are good prognostic factors concerning blood pressure outcome of patients undergoing surgery for primary aldosteronism.

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P868

Uncontrolledhighblood pressure in pregnancy: the pheochromocytoma is not to be ignored

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Introduction
The discovery of a pheochromocytoma during pregnancy is very rare. The diagnostic and therapeutic approach determines the maternal and fetal prognosis. We present the case of a pheochromocytoma discovered during a pregnancy of 16 weeks of amenorrhea.
Case report
Mrs. A.H 29 years old, primigravida, presented at 6 weeks of amenorrhea with hypertension, she was treated by alpha methyl dopa 500mg and nicardipne 20mg; at 16 weeks she was hospitalized for an hypertensive peak at 20 mmHg without edema or proteinuria. A detailed patient history revealed pulsatile headache; heart palpitations and profuse sweats. The diagnosis of pheochromocytoma was suggested. The normetanephrine and metanephrine blood level were respectively at 4.75 nmol/l (<1.29) and at 0.19 nmol/l (<0.92). Adrenal ultrasound showed heterogeneous mass arising from the right adrenal gland of 53*66 mm. The hormonal and imaging tests detecting multiple endocrine neoplasia were negative. We have kept nicardipine and replaced Alphamethyldopa by an alpha blocker. Obstetric ultrasonography was normal. Pheochromocytoma resection by laparoscopy was decided at the end of 28 weeks. Post-operatively the rate of blood catecholamines decreased by half in one month and the patient blood pressure was easily controlled with calcium channel blockers alone. At 35th week an emergency cesarean section was performed because of an acute fetal distress, she delivered a healthy baby boy who presents a sexual development disorder that we are exploring.
Discussion
The initial diagnosis of hypertension during pregnancy is frequently attributed to pre-eclampsia rather than pheochromocytoma. This Confusion is the main cause of overlooking the diagnosis. Our patient had presented a blood hypertention since the 6th weeks of amenorrea but the diagnosis of pheochromocytoma was confirmed at only the 16 week. The lack of knowledge of the diagnosis exposes to the risks of a secretory thrust which can be fatal for the mother and the fetus. Early diagnosis and multidisciplinary medical management that prepares for the excision of the tumor is always necessary.

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P869

An unusual case of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency diagnosed in the adulthood

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Introduction
Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (classic 21-OHD CAH) is the most common form of congenital adrenal hyperplasia, characterized by simple virilizing or salt wasting forms. The saline loss picture develops after birth and it can evolve in a short time to a severe picture of hypotonic dehydration and hypovolemic shock with lethal consequences if not diagnosed and treated. Herein we present an unusual case of classic 21-OHD CAH with salt wasting diagnosed in the adulthood.
Case report
A 46-year-old man with no relevant personal history was admited in Internal Medicine department referring astenia, nausea and vomiting and with important dehydratation and hypotension. Laboratory tests revealed a severe hyponatremia (104 mmol/L) and hyperkalaemia (6.2 mmol/L) with elevation of plasma ACTH (662 pg/ml) and low cortisol levels (0.43 mcg/dl). Abdomen CT-scan was normal except for hyperplastic adrenal glands with a pseudonodular imagen of 1.7 cm on the right one. After starting treatment with corticosteroids and mineralocorticoids, it improved both clinically and analytically so he was discharged with Addison disease diagnosis. Few weeks later he was reviewed in Endocrinology consults and we completed the study finding negative anti-adrenal antibodies and elevated levels of 17 OH progesterone (>8 mcg/l) that were confirmed with a second test. In this point, we asked for a genetic study which revealed the presence of 2 severe mutations: mutation 655G of intron 2 (related to salt wasted forms) and mutation Ile172Asn of exon 4 strongly related to simple virilizing forms. In addition, by questioning the patient, he revealed that he had twin brothers who died short time after birth, but he did not know the reason. According to this, the diagnosis changed to classic 21-OHD CAH with one severe mutation for salt wasting form and one severe mutacion for virilizing form, that is the reason why probably our patient could survive until adulthood without any treatment.
Conclusions
Classic 21-OHD CAH englobe a heterogeneous group of clinical pictures, which can manifest in the neonatal period, in childhood, in adolescence or in adulthood and where the synthesis of glucocorticoids, mineralocorticoids and androgens can be affected globally or partially.

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P870

Successful percutaneous radiofrequency ablation of a secreting juxtaglomerular cell tumour

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Introduction
Juxtaglomerular cell tumour (JCT) or Reninoma, is a rare cause of curable secondary hypertension, usually presented as a small renal tumour and treated by tumorectomy or partial nephrectomy (PN). Minimally invasive treatment such as percutaneous radiofrequency ablation (PRFA) has gained popularity over the last decade to treat small tumors. We report the case of a woman with secondary hypertension due to JCT, successfully treated with PRFA.
Case report
Hypertension appeared at 68 years old, initially treated with Ramipril. Six months later, patient was admitted in hospital in emergency for severe hypertension (systolic blood pressure (BP): 220 mmHg) and delirium. She presented with hypokalaemia (1.9 mmol/l), hyponatremia and alkalosis. Shortly after treatment of malignant hypertension and hypokalaemia, aldosterone and renine levels were respectively 3116 pg/ml (30–146) and 4301 mUl/l (2.8–39.9), potassium was 3.5 mmol/l. In order to control BP and potassium, 3 antihypertensive drugs (Nebivololol 5 mg/d, Lercanidipine 10 mg/day and Urapidil 60 mg twice daily) and oral potassium supplements (32 mEq/d) were progressively added. Two months later aldosterone and renin levels were respectively 400 pg/mL (17.6–232) and 106 pg/mL (1.5–22.2), confirming secondary hyperaldosteronism. The CT-scan showed a 13×10 mm mass of the lower pole of the left kidney with enhancement after contrast media injection. On MRI the nodule had discreetly T2 hyposignal, T1 hyposignal, and was moderately and progressively enhanced after injection of gadolinium. Due to lower limbs oedema, Lercanidipine has been replaced by Valsartan 80 mg/d, with a mean BP at home of 135/85 mmHg. In view of the size and location of the tumour, percutaneous RFA were performed under CT-control and local anaesthesia. Pre-procedural biopsies were negative. Patient did not experiment any complication, including increase of creatinine level. Antihypertensive drugs were tapered off and stopped after the procedure: Urapidil after 48 hours, Valsartan after 2 weeks and Nebivolol after 1 month. The potassium substitution was discontinued on day 5. After 2 months, BP was 120/76 mmHg, potassium level was 4.1 mmol/l, aldosterone level was 147 pg/ml, renin level was 4.7 pg/ml. CT-scan showed scar of PRFA, no tumor was detected.
Conclusion
This case shows efficacy of PRFA to cure secondary hypertension, due to JCT, which is almost always a benign tumour. PRFA appears to be an effective alternative to PN and a minimally invasive with few per and post-intervention complication.

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P871

A misleading presentation of auto-immune diabetes associated with somatostatinoma: a case report

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Somatostatinomas are rare neuroendocrine tumors diagnosed at a rather young age (mean age at diagnosis from 40 to 60 years). Non-auto-immune diabetes may associate with somatostatinoma as a result of abnormal somatostatin secretion, which inhibits insulin release. Steatorrhea and cholelithiasis are two other classical symptoms of these tumors. Here we report a case of somatostatinoma discovered while exploring a recently diagnosed diabetes, whose clinical and biological features were compatible with type 1 diabetes. A 43 year-old lean male, with no significant (personal or family) medical history presented with canonical symptoms of insulin deficiency and diarrhea since 2 months. HbA1c was 8.1%. Anti-GAD antibodies were positive at 5.1 UI/mL ($N < 1$). Insulin treatment alleviated all the symptoms but the persisting diarrhea. The abdominal CT scan revealed a Vater ampulla mass. Pathological examinations of endoscopic ultrasonography-guided biopsies showed a 2 cm well-differentiated G2 neuroendocrine tumor (Ki-67 was 3%). Elevated values of serum somatostatin, i.e. 88 pmol/L ($N < 50$) were consistent with somatostatinoma. The tumor was labelled by 18F-DG PET imaging but not by Somatostatin receptor scintigraphy. Pancreaticoduodenectomy was performed and pathological examination of the resected tumor disclosed a pT3 N1 M1a, grade G2 neuroendocrine carcinoma. Insulin therapy was maintained after surgery but with reduced doses. Hence we report a misleading initial presentation of type-1 diabetes with positive anti-GAD antibodies, which was, in fact, due to the underlying presence of a somatostatinoma. Diarrhea was the only atypical symptoms, which prompted us to broaden our initial investigations. The origin of antibody production in that context is discussed.

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P872

Adrenocortical cancer: our experience in a tertiary center of endocrinology

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Adrenocortical cancer is a rare, aggressive disease, requiring a fast and multidisciplinary approach. The genetics is heterogeneous so is also the clinical course. In the last 10 years, we have diagnosed and treated a number of 20 cases, aged at diagnosis between (34–74 years) (mean 55.9 ± 12.87), followed up between (2–77 months) (mean 25.75 ± 23.58). The maximal diameter of the tumor was (5.5–25) (mean 10.95 ± 5.43). The secretion profile was Cushing syndrome in 11 cases, androgen secreting tumor 1 cases, mineralocorticoid secreting tumor in 2 cases, while 6 cases were nonfunctional. Hypokaliemia was encountered in 2 cases. At diagnosis, the majority of cases (15) had local invasion, and 8 of which needed also nephrectomy and or splenectomy. All were submitted to open surgery. The Weiss score distribution of cases (3–8) was available in 13 patients. After the first surgery, 17 cases were submitted to oncologic approach using mitotane, which was gradually increased to target recommended dosage (14–20 mg/dl). Additional chemoterapeutic agents were used in 5 cases. The follow-up was done at 3 months with hormonal assays as well as oncologic imaging (CT scan). A number of 15 cases developed primary adrenocortical failure and requested oral substitution with hydrocortisone, on average with 35 mg/day in 2 or 3 administrations with doses higher than those requested for other causes of Addison disease. Relapse cases were submitted again to surgery in 7 patients. Mean progression-free survival was 3–6 months and mean mortality was at 25 months from diagnosis. Prognosis was related to Weiss score, but also to compliance to treatment. In conclusion, adrenocortical cancer is a heterogeneous disease, with high mortality and poor prognosis, requiring multidisciplinary approach.

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P873

Immunohistochemical expression of ephrines A2 and A4 receptors in neuroendocrine neoplasms: preliminary results

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Introduction
Ephrin receptors (EPHs) have a role in tumor growth, invasion, angiogenesis and metastasis of several neoplasms. Aim of the study was to investigate the expression and possible clinical significance of EPH-A4 and EPH-A2 protein expression in the pathophysiology of neuroendocrine neoplasms (NENs).
Methods
EPH-A4 and -A2 protein expression was assessed by immunohistochemical analysis along with Ki-67 proliferation index (%) on 28 paraffin embedded NENs tissue sections obtained from equal number of patients. Tumor cells' EPH-A4 and -A2 immunoreactivity was scored according to the sum of percentage of EPH-A4 and -A2 positivity (0/negative staining: 0–4% of tumor cells positive; 1: 5–24% of tumor cells positive; 2: 25–49% of tumor cells positive; 3: 50–100% of tumor cells positive), and the intensity of staining (0: negative staining, 1: mild staining; 2: intermediate staining; 3: intense staining). A case was characterized to present either low or high EPH expression if the total score was < 2 and ≥ 3, respectively.
Results
We studied 28 specimens from patients (16 males; median age 57, range: 26-83 years) with NENs: 12 pancreatic, 4 small-bowel, 4 lung, 2 gastric, 2 appendix, 1 colorectal, 1 gallbladder, 1 uterine, 1 unknown primary origin (UPO). Five specimens were taken from a metastatic focus and 23 from the primary tumor, 10 from Grade 1, and 9 each from Grade 2 and 3 NENs. Positivity for EPHA-2 was seen in 15/23 (65%) of the specimens (all with cytoplasmatic pattern) and in 21/24 (88%) for EPHA-4 (14% with cytoplasmatic, 53% with nuclear and 33% with both types of IHC pattern). In specimens taken from metastatic foci EPHA-4 was positive in all specimens and in 84% of tissues taken by primary tumors; similarly EPH-A2 was positive in 80% of specimens from metastases and in 61% of tissues taken by primary tumors. EPHA-4 was expressed in 9/11 (82%) pancreatic, in 4/4 (100%) small-bowel, in 3/3 (100%) lung, 2/2 (100%) gastric, 1/2 (50%) appendiceal, one (100%) colorectal, one (100%) gallbladder NENs assessed; EPHA-2 was expressed in 5/10 (50%) pancreatic, in 3/4 (75%) small-bowel, in 3/4 (75%) lung, one (100%) gastric, one (100%) appendiceal, one (100%) colorectal, one (100%) uterine NENs assessed, but it was not expressed in the UPO NEN.
Conclusions
Our preliminary data indicate a higher prevalence of EPHA-4 expression compared to EPH-A2 in NENs. The possible role of EPHs in NEN pathophysiology needs further investigation to shed light to their exact role in NENs.

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P874

Molecular diagnosis of multiple endocrine neoplasia type 1 (MEN 1): a single-center experience

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Background
Multiple endocrine neoplasia type 1 (MEN1) (OMIM 131100) is an autosomal dominant disorder associated with a high risk of developing parathyroid hyperplasia (90%), digestive neuroendocrine tumors (30–70%) and pituitary adenomas (30-40%). Prevalence of MEN1 is 2-10/100.000, there are no differences between men and women and usually, it is diagnosed before 40 years old. It is related to different mutations of the MEN1 tumour-suppressor gene (OMIM: 613733) which is located on chromosome 11 (11q13), has 10 exons and encodes a nuclear protein of 610 amino acids. More than 100 genetic variants have been identified and most of them are located in coding regions.
Method

We retrospectively analyzed fifteen cases in the last five years. We selected all the patients with two or more tumors associated with MEN1 consequently they were evaluated by a multidisciplinary team who decided to do MEN1 genetic diagnostic test. After a complete clinical-biochemical assessment of each patient, samples were taken. MEN1 gene was amplified by PCR and sequenced. This study does not allow to detect large deletions. Pathological variants were confirmed by Sanger sequencing.
Results
The average age of patients is 42 ± 14.52 years, 80% are women and 20% men. Also, 90% of the patients present primary hyperparathyroidism. A genetic test revealed the presence of heterozygous variants within the coding region in two women (13%). These variants are missense mutation with a changed aminoacid and they have been described as pathogenic and moreover associated with MEN. No other variants were detected in the other patients. However, large deletions in MEN1 were not analyzed.
Conclusions
In patients with suspected MEN1, the gene should be studied by sequencing it and If no mutations are detected the laboratory should look for large deletions through Multiplex ligation-dependent probe amplification (MLPA) (1–3% cases). There are other genes whose mutations give rise to syndromes similar to MEN1. For this reason, it is important to evaluate other genes like CDKN1B or AIP especially when we do not find any mutation in the MEN1 gene. An interesting option could be to use genetic testing with comprehensive gene panels because this will allow us to detect more genes alterations and different pathologies.

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P875

Clinical spectrum of MEN1: what about other non-endocrine neoplasias?

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Introduction
Multiple endocrine neoplasia type 1 syndrome (MEN1) is a hereditary autosomal dominant disorder caused by germline mutations in the MEN1 tumour-suppressor gene and is typically characterized by parathyroid adenomas, duodenopancreatic neuroendocrine tumors (NETs) and pituitary adenomas. Breast cancer has recently been identified as manifestation of MEN1 and female patients have early onset elevated breast cancer risk.
Case report
Female patient, 51 years old, with personal history of ovarian mucinous borderline tumour, breast cancer, recurrent typical carcinoid lung tumour (surgery in 2010 and 2015; pT1bN0) and myeloid chronic leukaemia, treated with 2nd line therapy (bosutinib). She was referred to the Endocrinology Department for PTH-dependent hypercalcemia: PTH 133.4 pg/mL (18–80 pg/mL) ionized calcium 1.33 mmol/L (1.19–1.26 mmol/L) and osteoporosis on dual energy x-ray absorptiometry (DEXA), with T-score at the lumbar spine -3.8. The patient had no family history of malignant neoplasms. She complained of mild dyspepsia and was taking pantoprazole 20 mg/day. Physical examination revealed several lipomas. MEN 1 syndrome was suspected, given the diagnosis of primary hyperparathyroidism (PHPT), carcinoid lung tumour and breast cancer. Genetic testing for MEN1 was positive and the workup revealed an increased prolactin 42.51 ng/mL (<25 ng/mL), normal IGF-1, with normal brain MRI; Chromogranin A was increased 280.3 ng/mL (<102 ng/mL) under treatment with pantoprazole, with normal gastrin and pancreatic polypeptide. Chest CT was normal and upper endoscopy showed no gastric NETs. Abdominal MRI showed bilateral adrenal nodules (12 and 6 mm), but no signs of pancreatic NETs. These nodules were proven to be non-functioning. It was decided not to perform surgery for PHPT, given the patient's multiple comorbidities, the stable levels of calcium and stable T-score on DEXA, as well as increased risk of post-surgery hypoparathyroidism. She started treatment with alendronic acid 70mg/week, with good tolerability
Discussion
The clinical spectrum of MEN1 has evolved in recent years and breast cancer is now a proven MEN1-related tumour. It remains to be confirmed whether other neoplasias, namely leukaemia or ovarian tumours are part of this spectrum. There is also concern with increased risk of cell injury from ionizing radiation in these patients, who need serial imaging monitoring. Other challenges include identification of index cases and selection of tumours that need appropriate therapy or active surveillance.

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P876

An interesting case of a familial insulinoma

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A 42 year old lady presented to the Endocrinology clinic with a longstanding history of exertional dizziness, increasing in frequency over the preceding two months. She reported marginal symptomatic improvement with the introduction of frequent carbohydrate rich meals. She was asymptomatic in the post-prandial period. She had no associated nausea, confusion, palpitations, diaphoresis, collapse or weight gain. She was on medication (SSRI) for anxiety. Her father and paternal grandmother both had successful pancreatic surgeries for treatment of insulinoma. Biochemical evaluation in clinic revealed random plasma glucose of 2.7 mmol/L (asymptomatic), HbA1c of 24 mmol/mol, and no evidence of pituitary, liver or thyroid dysfunction. A synacthen test was normal. The impression was that this lady had clinical evidence of an insulinoma. She was admitted for a 72-hour fast. During the 72-hour fast the patient remained haemodynamically stable and asymptomatic despite plasma glucose levels being persistently below 3 mmol/l. The fast was terminated at hour 55 due to the patient developing an episode of symptomatic neuroglycopenic hypoglycaemia with plasma glucose of 2.2 mmol/l. The patient recovered after administration of IV glucagon with plasma glucose of 3 mmol/l at 5 min post-injection, and 5 mmol/l 50 min post-injection. When the patient was symptomatically hypoglycaemic and had plasma glucose levels of 2.2 mmol/l, the insulin level was 43.8 pmol/l with a C-peptide level of 463 pmol/l. Growth hormone, IGF1 and proinsulin levels were normal. A sulphonylurea screen was negative. A beta hydroxybutyrate level was mildly elevated at 1070 umol/l. Overall the biochemistry was consistent with endogenous hyperinsulinaemia. Preliminary imaging on this patient failed to localise the site of the insulinoma. CT scan of the abdomen and pelvis and MRI of the liver and pancreas were normal. There was no evidence of abnormal radioisotope uptake on planar and SPECT CT octreotide scintigraphy of the thorax, abdomen and pelvis. Endoscopic ultrasonography is pending. If there remains difficulty localising the insulinoma, a selective arterial calcium stimulation test with hepatic venous sampling and/or PET scanning with either Gallium or GLP-1 will be considered. The patient's father previously tested negatively for the MEN-1 gene mutation. Insulinomas are rare neuroendocrine tumours with an incidence of 1-4/1,000,000. In 5% of cases, insulinomas are associated with the MEN-1 genetic mutation. The percentage association of insulinomas with MEN-4 has not yet been defined. This is an interesting case of a likely familial insulinoma with to-date no association with MEN-1 syndrome. We await the results of repeat MEN-1 testing and MEN-4 testing.

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P877

Accuracy of adrenal imaging studies in predicting histological tumor dimension following adrenalectomy

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Introduction
Although computed tomography (CT) is the best mean to identify adrenal neoplasms there is still controversy of the concordance of the estimated radiological and histological size of the lesion. Since the size of adrenal tumours is a major criterion for surgical excision, we investigated whether recent and more sophisticated imaging techniques, can more accurately predict tumor's size.
Methods
We have retrospectively analyzed a series of 109 patients who underwent adrenalectomy at a referral center during the period 2017 and 2018. Medical records from histological and imaging studies were registered. Radiological adrenal size (RS) was defined by CT and magnetic resonance imaging (MRI). The adrenal tumors were divided according their histological size (HS) in the following groups, A: ≤ 3 cm, B: >3 and ≤ 6 cm, C: >6 and ≤ 9 cm, D: >9 and ≤ 12 cm, E: >12 cm; 1: ≤ 2 cm, 2: >2 and ≤ 4 cm, 3: >4 and ≤ 6 cm, 4: >6 and ≤ 8 cm, 5: >8 and ≤ 10 cm, 6: >10 cm. The major dimension of HS (median value) was compared with the major dimension of RS (median value) by kappa statistic to define their agreement.

Results
Patients (64% females) with mean age 56.2 (range: 18-79 and one child of 10) years were submitted to adrenalectomy (71 right, 36 left, 2 bilateral). The HS had mean and median values 7.24 and 7.00 cm (range: 2–22), respectively; the RS had mean and median values 5.03 and median 4.50 cm (range: 1–22), respectively. Group A and 1 included one tumor 1.8 cm with RS 1.10 cm, group B, included 41 tumors with HS:5.5 cm versus RS:3.30 cm; group C, 57 with HS:7.5 cm versus RS:5.00 cm; group D, 7 with HS:10 cm versus RS:5.00 cm; group E, 3 with HS:19.3 cm versus RS:15.00 cm; group 2, 3 with HS:4 cm versus RS:3 cm; group 3, 38 with HS 5.50 cm versus RS 3.45 cm; group 4, 47 with HS 7.4 cm versus RS 4.8 cm; group 5, 14 with HS:9 cm versus RS:5.5 cm; group 6, 6 with HS:14.05 cm versus RS:9.8 cm. A slight agreement was seen in group B (kappa value $=0.013$ in total imaging and 0.028 in CT), and in group 4 (kappa value $=0.015$ in total imaging and 0.029 in CT),
Conclusions
The present study confirmed previous findings that adrenal imaging, either CT or MRI, cannot predict the real size of adrenal tumours implying that despite the progression of imaging technology clinicians have to consider a larger size of adrenal tumours when a decision to remove an adrenal incidentaloma has to be taken.

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P878

Metabolic profile of non-functional adrenal adenomas

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Aim
Metabolic syndrome rates have been studied especially in adrenal gland secreting cortisol and studies on nonfunctional adenomas are limited. In this study, we investigated metabolic parameters and metabolic syndrome frequency in non-functional adrenal adenomas (NFA).
Materials and methods
In our study, 55 patients (15 men (27.3%), 40 women (72.7%) who were diagnosed incidentally, unilateral or bilateral localized, hormone-inactive, and with adenoma-compatible features in imaging studies were included in the study. Anthropometric parameters (BMI, waist circumference (WC)), clinical and biochemical blood indices were evaluated. As exclusion criteria; 1) <18 years old patients, 2) Pregnancy, 3) Alcoholism /substance use disorders, 4) Liver/kidney failure (Child B and C, creatine clearance <60 ml/min) 5) Glucose and weight gaining medical treatment or steroid use, 6) Acromegaly, uncontrolled hypo/hyperthyroidism, causes of secondary obesity, 7) Severe neuropsychiatric diseases, 8) Severe disease in case of septic and organ failure, 9) Post-transplantation, 10) Malignancy.
Results
The mean age of patients 53.62 ± 8.1 years old, mean body mass index (BMI) 31.42 ± 5.9 kg/m^2, body weight 83.5 ± 6.15 kg was found. In the laboratory examination; glucose: 101.95 ± 16.9 mg/dl; insulin 9.3 ± 7.63 uU/ml; HOMA index 2.34 ± 1.8, HbA1c 5.8% 0.72, LDL-cholesterol 136.2 ± 34.5 mg/dl; triglyceride 132.5 ± 51.2 mg/dl; HDL-cholesterol 50.2 ± 10.8 mg/dl; total cholesterol 212.8 ± 39.5 mg/dl; uric acid 5.12 ± 1.01 mg/dl was observed. Hyperuricemia was observed in 14.5% ($n=8$) of the patients. The adenoma size was 17.11 ± 7.61 mm and It was observed that 29.1% ($n=16$) of the adenomas were localized in the right ($n=16$), 58.2% ($n=32$) in the left and 10.9%($n=6$) in the bilateral. 25.5% ($n=14$) of the patients had diabetes mellitus (DM), 32.7% ($n=18$) had prediabetes, 27.3% ($n=15$) had insulin resistance, 14.5% ($n=14$) had hyperlipidemia and 45.5% ($n=25$) had hypertension (HT) was detected. 12.7% ($n=7$) of the patients had normal weight, 38.2% ($n=21$) had overweight, 23.6% ($n=8$) had mild obese, 16.4% ($n=9$) was moderately obese and 9.1% ($n=5$) were morbidly obese. The rate of metabolic syndrome in our study was 41.8% (n: 23).
Conclusion
In our study, the prevalence of metabolic syndrome was found to be high in NSAID patients according to IDF 2006 diagnostic criteria. We suggest that screening for metabolic syndrome in NFAs will be useful for monitoring the function in addition to Cushing and subclinical cushing syndrome,

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The role of selected adipokines as predictors of excessive secretion of cortisol in patients with incidental adrenal tumors

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The diagnosis of subclinical hypercortisolemia in patients with incidental adrenal tumors remains a challenge, as there are no unambiguous criteria for diagnosis. The discovery of a substance whose secretion increases under the influence of cortisol would make it easier to make therapeutic decisions. Hypercortisolism causes a change in the distribution of adipose tissue, so it can be assumed that it also affects secretion of proteins secreted by adipocytes (adipokines). The aim of the study was to assess adipocyte concentration of selected adipokines, ie chemerin, A-FABP, omentine and visfatin depending on the degree of suppression of cortisol secretion in the nocturnal dexamethasone suppression test, and the occurrence of metabolic disorders likely to have relationship with excessive secretion of cortisol. The study group consisted of 100 patients with adrenal incidentalomas, 58 women and 42 men, middle-aged 62 (± 8.4) years old, who were hospitalized in the Department of Endocrinology and Diabetology at University Hospital No. 1 in Bydgoszcz. On the basis of the night-time inhibition test with dexamethasone, the patients were divided into two groups: with suppressed secretion of cortisol, i.e. ≤ 1.8 mg/dl, this group was defined as DST ≤ 1.8 (60 people) and with possible excessive secretion of cortisol, i.e. >1.8 µg/dl, this group was defined as DST >1.8 (40 people). The control group consisted of 36 people, who showed no pathology in the adrenal glands in imaging studies and excluded hypercortisolemia based on the dexamethasone suppression test (cortisol ≤ 1.8 µg /dl). There were no statistically significant differences in the concentration of A-FABP, omentine and visfatin between the groups. In contrast, the concentration of chemerin was statistically significantly higher in the DST $>$ 1.8 group compared to the DST $\leq 1,8$ group and the control group ($P=0.0027$, $P=0.0006$). No differences were found in the concentration of A-FABP, omentine and visfatin between the: DST >1.8, DST $\leq 1,8$ and control group taking into account the occurrence of carbohydrate metabolism disorders, hypertension, dyslipidemia or metabolic syndrome. On the other hand, the concentration of chemerin in patients from the DST >1.8 group with accompanying metabolic disorders (except for glucose tolerance disorders) was significantly higher compared to the remaining groups, regardless of the diagnosis of these disorders. In summary, the presented study showed that high concentration of chemerin can act as a predictor of excessive autonomic secretion of cortisol, especially in patients with known hypertension, lipid profile disorders or metabolic syndrome.

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P880

Cardiovascular and metabolic risk factors in children and adolescents with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Background
Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is associated with an increased cardiometabolic risk in adult life. Nevertheless, data regarding pediatric age is scarce. We aimed to evaluate cardiometabolic risk factors in patients with CAH due to 21-hydroxylase deficiency in pediatric age.
Methods
We reviewed the clinical records of patients with CAH evaluated in a Pediatric Endocrinology Unit in a central hospital. Patients ≥ 6 years-old performed an oral glucose tolerance test (OGTT). A Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) ≥ 3.5 or a Matsuda index <2.5 were considered as positive results regarding insulin resistance.
Results
We included 8 patients (5 females), with a mean age of 11.4 ± 4.5 years-old. Four patients presented the salt wasting form and were diagnosed during the neonatal period. Three patients had the simple virilizing form and 1 patient the non-classic form. These patients were diagnosed during workup for precocious pubarche, with a mean age of 6.7 ± 0.9 years-old. Currently, 2 patients are prepubertal, 3 pubertal and 3 postpubertal and they present a mean time of follow-up of 7.62 ± 0.2 years (2–14). Six patients are treated with hydrocortisone (mean dose $11.41 \pm$

1.8 mg/m^2) and 5 patients are treated with fludrocortisone. Two patients were submitted to genital reconstructive surgery. Half of this sample is normo-weighted, 1 has low weight, 1 weight excess and 2 obesity. All patients had systolic and diastolic blood pressure below the 90th percentile (for age, sex and stature). Mean cholesterol level, LDL-cholesterol, HDL-cholesterol, non-HDL cholesterol and triglycerides was 138 ± 31.9, 72.71 ± 24.2, 59.86 ± 12.1, 78.43 ± 26.7 e 55 ± 14.4 mg/dl, respectively. One patient had elevated non-HDL cholesterol and 2 presented borderline LDL-cholesterol and HDL-cholesterol, respectively. Fasting mean glucose and median insulin was 77.14 ± 4.3 mg/dl e 19 uUI/ml (9.6–27.3), respectively. Patients presented a median HOMA-IR of 3.81 (2.8–5.3) and 3 patients demonstrated insulin resistance. In the OGTT, none of the patients evidenced dysglicemia and the median Matsuda index was 8.96 (5.9–17.6).

Conclusion

In this study, 3 patients had weight excess/obesity and 3 evidenced insulin resistance. Globally, half of the patients presented at least one cardiometabolic risk factor. Despite the young age, these patients seem to present already different cardiovascular risk factors. Our results call attention to the necessity of take into account the cardiometabolic profile when evaluating patients with CAH. It is also fundamental to promote healthy life styles in order to reduce the prevalence of cardiovascular disease in adult life.

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P881

Epidemiology and evolution data on gastroenteropancretic and pulmonary neuroendocrine tumors

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Neuroendocrine tumors (NETs) includes a broad family of tumors, the most frequent ones are in the gastrointestinal tract, lung, thymus, and pancreas. Gastrointestinal and Pulmonary NETs may present with symptoms attributable to hormonal hypersecretion, which include intermit-tent flushing and diarrhea, or symptoms related to Cushing Syndrome. The variability of clinical manifestation may lead to late referral or misdiagnosis. In this retrospective study we analyzed 27 patients with NET of various primary tumor sites treated at our department during 2006–2018. Tumors were graded and staged according to histopathological criteria and their extent of metastases. Hormonal analyses have been done at each presentation. Immunohistochemical (IHC) staining for specific hormonal markers was executed in all tumors. 20 patients (12 women) presented with gastroentero-pancreatic tumors, 10 with pancreatic localization, 6 jejuno-ileal, 3 rectal and 1 gastric determination. 17 were referred to our department after surgery, with no hormonal work-up prior surgery, 3 had been primary endocrine investigated, all had developed symptoms a few years before diagnosis, and all presented with IHC staining for Synaptophisin and Chromogranin A, 2 of them got lost in follow-up. We investigated 7 patients with pulmonary NET, 5 of them were diagnosed primary in our department with ectopic Cushing, with a positive outcome after surgery and the other 2 were referred with atypical forms, requiring chemotherapy; 3 out of 27 patients have been lost in follow-up. The study revealed that neuroendocrine tumors often are late referred or misdiagnosed, and still a challenge, emphasizing the importance of multidisciplinary cooperation.

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Diabetes, Obesity and Metabolism 3

P882

Vitamin D receptor gene polymorphisms and lipid profile in different vitamin D status women

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Objective(s)

Vitamin D deficiency and vitamin D receptor (*VDR*) gene polymorphisms can be associated with atherogenic lipid profile. The results of recent studies in different populations are contradictory. The aim of study was to assess serum lipids in women with different vitamin D status carrying various *VDR* gene variants.

Materials and methods

We examined 697 women aged 35 to 55 y.o. (mean 43.4 ± 0.3). Anthropometric parameters (height (m), weight (kg), BMI, waist circumference (cm)) were measured. 25(OH)D serum level assessment was done by immunoassay (AbbottArchitect8000, USA), serum lipid profile – standard method. *VDR* gene variants rs1544410 (*BsmI*), rs7975232 (*ApaI*), rs731236 (*TaqI*), and rs2228570 (*FokI*) were evaluated by polymerase chain reaction-restriction fragment length polymorphism method.

Results

Result showed high prevalence of abdominal obesity (75.5%), dyslipidemia (69.6%), vitamin D insufficiency/deficiency (90.6%) in the study population. Women with vitamin D deficiency had increased risk of HDL cholesterol reduction (OR2.60[1.04-6.49]Cl95%). Serum 25(OH)D level did not differ between rs1544410 (*BsmI*), rs7975232 (*ApaI*), rs731236 (*TaqI*), and rs2228570 (*FokI*) *VDR* genotypes. BB genotype carriers of rs1544410 (*BsmI*) demonstrated higher triglyceride levels than subjects with Bb and bb genotypes (1.54 ± 0.09 *vs* 1.32 ± 0.04). A allele carriers of rs7975232 (*ApaI*) had higher total cholesterol (5.52 ± 0.07 mmol/l *vs* 5.14 ± 0.15 mmol/l) and LDL cholesterol levels (3.54 ± 0.06 mmol/l *vs* 3.25 ± 0.12 mmol/l) compared to women with aa genotype.

Conclusion(s)

The study revealed decreased HDL level in women with vitamin D deficiency and the association between rs1544410 (*BsmI*) and rs7975232 (*ApaI*) *VDR* genotypes and atherogenic dyslipidemia.

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P883

Impact of the overweight and fatty liver in chronic hepatitis B treatment

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Background

More than 1.9 billion people in the world are suffering from overweight. Damages can be caused to the liver such as fatty liver or even Cirrhosis. The aims of this study are to determine the prevalence and the impact of steatosis and overweight on therapeutic response in chronic hepatitis B.

Methods

This is a descriptive transversal study enrolled from 01/2010 to 09/2018. All patients with chronic hepatitis B investigated by liver biopsy were included. Alcoholic consumption and hepatitis C were the exclusion criteria. Data were collected and analyzed with SPSS (significant $P < 0.05$).

Results

76 patients were included in the study. The average age of patients was 36-year-old with a sex ratio (M/F) = 1.92. Four patients were diabetic. The average body mass index (BMI) was 26 kg / m^2. 58% were in overweight and 17% were obese. According to the Metavir score, hepatitis activity was graded: A0 (14.5%); A1 (60.5%); A2 (22.4%); A3 (2.6%) and fibrosis: F0 (10.5%); F1 (44.7%); F2 (40.8%); F3 (4%). Steatosis was present in liver biopsy in 26 patients (34%). 54% patients were treated, 61% by Pegylated interferon and 49% by Entecavir. A sustained virological response was obtained in (54%) of cases, a non-primary response (39%) and a relapse (7%). A second-line treatment was prescribed with a sustained virological response in 100% of cases. There was a significant difference in BMI (28.32 vs 24.83, $P < 0.005$) and hyperechoic liver (39% vs 10%, $P = 0.005$ and OR = 5.6, (1.6-18.9)). It was not the case for age, cytolysis, HBeAg status, and virological activity. The presence of steatosis was not correlated with the severity of fibrosis ($P = 0.43$). Steatosis did not influence the response to antiviral therapy (23% vs. 5%, $P = 0.08$). Even overweight (41% vs 57%, p0.09) and obesity (50% vs 50%, $P = 0.61$) did not influence the response to treatment.

Conclusion

Although the young age of patients, the absence of diabetes the prevalence of non-alcoholic fatty liver was high. The role of hepatitis B infection may be suggested. Only the overweight or hyperechoic liver were predictive of the coexistence of steatosis. Overweight, obesity and steatosis does not influence fibrosis progression or therapeutic response.

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P884

Development of diabetes after pancreatic resection

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Introduction
The development of diabetes is common after pancreatic surgery, so a close follow-up is essential in order to make an early diagnosis and start treatment as soon as possible.
Material and methods
Data from 56 patients subjected to pancreatic surgery between 2013 and 2018 are presented. Demographic and clinical-analytical characteristics are also described. We analyzed the incidence of diabetes during the follow-up (one month after surgery [PO], 3–6 months after surgery [M2] and one year after surgery [M3]) in those patients without previous diabetes and compared characteristics between those who developed diabetes and those who did not. Regarding the different surgical techniques: cephalic duodeno-pancreatectomy (CDP) with pancreatico-jejunal anastomosis (CDP-PJ), CDP with pancreatico-gastric anastomosis (CDP-PG), Distal pancreatectomy with splenectomy (DP) and total pancreatectomy (TP). Patients subjected to TP were excluded from the analyses, as it necessarily produces diabetes.
Results
We collected data from 56 patients, 64.6±8.6 years old, 59.6% males. 28.8% with previous diabetes. Type of surgery: 34.6% CPD-PJ, 25% CPD-PG, 15.4% TP, 25% DP. Pathological anatomy: 73.1% adenocarcinoma, 7.7% neuroendocrine tumor, 19.2% others. Cumulative incidence of diabetes was 50% (68.7%[PO], 18.75%[M2], 12.5%[M3]). Comparative characteristics between both groups are shown in Table 1. We see that those who developed diabetes were older than those who did not. To analyze the factors related to the development of diabetes, we grouped the patients by the surgical technique they were subjected: CPD and DP. In the logistic regression analysis (using as dependent variable the development of diabetes after surgery), although the age is close to the statistical significance, we did not find any factor which was independently associated with the development of diabetes: age (OR 1.136; CI 95% 0.995–1.303, *P* 0.059), sex (OR 0.869; CI 95% 0.151–4.994, *P* 0.875), type of surgery (OR 2.227; CI 95% 0.290–17.118, *P* 0.442).

Table 1

	Development of diabetes	Non-development of diabetes	*P*
Age (years)	64.8±7.2	58.4±6.1	0.029
BMI (kg/m^2)	26.5±3.1	25±2.8	0.229
Sex (%)			0.662
Female	50	41.7	
Male	50	58.3	
Diagnosis (%)			0.095
Adenocarcinoma	68.8	58.3	
Neuroendocrine tumor	18.8	0	
Others	12.5	41.7	
Pluripathology (%)			0.887
Yes	18.8	16.7	
No	81.3	83.3	
Type of surgery (%)			0.129
CDP	56.3	83.3	
DP	43.8	16.7	

Conclusions
A high percentage of patients with pancreatic resection developed diabetes. The development of diabetes was more common in the first month after surgery. Age seems to increase the likelihood of developing diabetes after pancreatic resection.

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P885

Threatening hypertriglyceridemia during pregnancy revealing laminopathy and genetic susceptibility in a patient with type 1 diabetes

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Background
Severe hypertriglyceridemia (HT) increases the risk of pancreatitis, whereas mild HT may be a risk factor for cardiovascular disease. The variety of hypertriglyceridemia origins often makes the etiological diagnosis complex.
Case report
A 24-year-old female G3P0Ab2 with type 1 diabetes mellitus (T1DM) was referred at 27th week of gestation to the Endocrinology Department in July 2017 for glycemic instability and severe hypertriglyceridemia. Type 1 diabetes was diagnosed at the age of 9 on initial diabetic ketoacidosis. AntiGAD antibodies remained 4 UI/l (N<1 UI/l) during follow-up, C-peptide and insulin undetectable. After puberty the patient developed progressive lipoatrophy of the trunk, abdomen and limbs together with moderate cervico-facial fat accumulation and axillary acanthosis nigricans. BMI prior to pregnancy was 21 kg/m^2. Long term glycemic control was insufficient (HbA1c 10–14%) under multiple daily injection despite high total daily insulin dose (TDI) 188 u/d (2.9 U/kg/d). Patient refused continuous subcutaneous insulin infusion (CSII). Medical history included humeral artery thrombosis under estrogen containing contraceptives in 2010 and embolic myocardial infarction in 2011. Oncological, rheumatic, thrombophilia markers were negative. Long term anticoagulant medication combined with rosuvastatine 10mg per day were introduced as LDL-cholesterol (LDLc) was 153 mg/dl, HDL-cholesterol (HDLc) 28mg/dl, triglyceride (TG) 192 mg/dl. Statin was stopped during pregnancy. At presentation, TG level was 810 mg/dl, LDLc 109 mg/l, HDLc 36 mg/dl, urinary protein-to-creatinine ratio 123 mg/mmol, haemoglobin 7.2 g/dl requiring a blood transfusion. Diabetic retinopathy evolved during pregnancy from moderate to severe. Despite a very low-fat diet (<10–15% of energy intake), TG level reached up to 1200 mg/dl at 30 week of gestation. CSII was introduced allowing tight glycemic control and the reduction of the TDI from 136 U/d (2 U/kg/d) to 90 u/d (1.3 u/kg/d). TG were stabilized at 1080mg/dl. At 38 weeks caesarean delivery was performed and a healthy girl was delivered. Face to the complex presentation, a genetic analysis was performed. LMNA sequencing revealed heterozygous prelamin-A mutation (p.T655fsX49). The search for a HT predisposing mutation showed heterozygous APOC2 variant (c.122A>C, p.K41T) and heterozygous GP1HBP1 variant (c.41G>T, p.C14F) that increase HT. A heterozygous LPL variant known to increase its activity (c.1421C>G, p S474X) was also found.
Conclusion
Severe hypertriglyceridemia can develop in poorly controlled T1DM during pregnancy; however atypical presentation should encourage further investigation including genetic analysis. In our case T1DM was associated with Dunningan's syndrome and genetic predisposition to HT, leading to specific therapeutic and care implications.

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P886

Perforating necrobiosis lipoidica: a new case report

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Introduction
Necrobiosis lipoidica (NL) is a rare, chronic granulomatous cutaneous disease that most often affects the lower extremities. The etiology of the condition is unknown but there appears to be some association with diabetes mellitus. Perforating necrobiosis lipoidica (PNL) is a very rare variant of NL characterized by trans-epidermal collagen elimination. We present a case of type II diabetes patient with disseminated perforating necrobiosis lipoidica (PNL).
Case report
A 52-year-old female patient suffering from long-term diabetes mellitus type II, controlled with insulin, was referred to our clinic. She complained of multiple asymptomatic firm plaques on the lower extremities that appeared about 3 years ago. These plaques started as painless, reddish papules that slowly enlarged formatting indurated centrally depressed plaques. The clinical examination revealed infiltrated plaques disseminated on the extensor surfaces of the lower extremities. The lesions were presented by brown-yellow plaques with irregular shape, slightly elevated border, and atrophic center focally studded with comedo-like papules. Microscopic examination of the lesions demonstrated a degenerated

collagen and fibrosis with peripheral lymphohistiocytic infiltrate and transepidermal elimination of necrotic material. The clinical and histologic diagnosis was perforating necrobiosis lipoidica. Initiated treatment with topical steroids was ineffective. Intralesional corticosteroid therapy demonstrated a significant improvement in the appearance of the cutaneous lesions. Diabetes self-management education was also reinforced.
Discussion
Necrobiosis lipoidica, first described by Oppenheim in 1929, is a chronic granulomatous disorder, strongly associated with diabetes. It has a prevalence of 0.3 percent of the diabetic adult population. NL often presents as slowly expanding violaceous patches located mostly on the lower legs. The advancing border is usually red with a yellow brown central area. The central areas are atrophic and have a waxy surface with telangiectasias.In approximately 85% of cases, the legs are exclusively involved. Perforating necrobiosis lipoidica (PNL) is a rare variant of NL that is almost always associated with diabetes. The histopathology of NL is a granulomatous dermatitis associated with degeneration of dermal collagen, histiocytes arranged in a palisade around zones of necrobiosis and interstitially between collagen fibres.The perforating variants show transepithelial elimination of necrotic material. Few cases of PNL have been reported in the literature. Treatment of both NL and PNL is often unrewarding. Some improvement with intralesional corticosteroid has been reported, as seen in the patient described here.
Conclusion
Perforating necrobiosis lipoidica is a rare variant of NL, which occurs mostly in diabetic patients. Although the disease has benign course, the treatment is still remains a challenge.

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P887

Management of hyperglycaemia risk in patients on medium or long-term glucocorticoid treatment: a retrospective pilot study

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Background
Glucocorticoids are used medium and long-term for a variety of inflammatory and autoimmune conditions, with increasing use in the UK. The management of their potential side effects, however, remains suboptimal, and guidelines are not comprehensive. Our institute has had cases of patients presenting with hyperglycaemic emergencies due to steroid induced diabetes.
Aims
1) To obtain an estimate of the frequency of the use of medium and long term glucocorticoids in our DGH outpatients. 2) To explore whether general practitioners were being requested to monitor for the occurrence of steroid induced diabetes in these patients. 3) To determine whether patients with diabetes on long term steroid treatment were being advised about worsening of their glycaemia
Methods
Retrospective casenote analysis of all outpatients in the specialities of haematology, gastroenterology, respiratory and rheumatology over a 1 week period in June 2018.
Results
Following the exclusion of sleep clinic and haem-onc patients undergoing chemotherapy (for whom a new protocol is being trialled), a total of 556 records were examined. 41 patients were treated with glucocorticoids (19M, 23F; mean age 61). 31 patients had prednisolone, 4 budesonide, 1 dexamethasone and 5 depomedrone (4IM, 1IA). The length of oral steroid use varied from 3 weeks to over 40 years. 6 patients had pre-treatment diabetes; 5 had HbA1cs (mean 58 mmol/mol, range 38–94). 1/6 had consideration of diabetes recorded, with none of patient information about the risk or need for increased vigilance. Of the remainder, only 1/35 had plans for consideration of hyperglycaemia.
Conclusions
About 7% of patients attending outpatients in selected specialities are on medium or long term glucocorticoid therapy. Extrapolating this data, it is possible over 1500 patients attending our hospital may be on this treatment. The monitoring of these patients from a hyperglycaemia perspective is poor, and there is opportunity for hospitals to develop protocols to inform patients and GPs of the risks to try to avoid symptomatic hyperglycaemia, and indeed hyperglycaemic emergencies.

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P888

Maturity onset diabetes of the young type 5 – report of one phenotype

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Introduction
MODYs are being identified more frequently but the rarity of some types still precludes in-dept knowledge of their natural course of disease. One of this rare forms is MODY 5, the result of a mutation on the hepatocyte nuclear factor 1 beta (HNF-1B) gene that associates with genitourinary and pancreatic malformations/dysfunction.
Case report
A 24-year-old female was referred to the Endocrinology clinic due to hyperglycaemia identified on pre-operative evaluation for lung lobectomy (Carcinoid tumour). She had also history of ureteropelvic junction stenosis that required surgical intervention at the age of 12 months. Laboratory records from preceding years showed wondering 8h-fasting glycaemia 106–142 mg/dl and maximal A1c of 5.8%, without hemoglobinopathies. Despite recurrent measurements of fasting glycemia 126–142 mg/dl, the OGGT tuned out normal (fasting 88 mg/dl, 2h 90 mg/dl). Family history of Diabetes was denied, apart from the gestational diabetes of her mother. Physical examination did not reveal acanthosis, cushingoid nor acromegaloid features and her BMI was 20.6 kg/m^2. Anti-islet-cell and glutamate decarboxylase autoantibodies were negative, C-peptide levels were low-normal (0.9–1.8 ng/ml), fasting insulin levels and HOMA-IR did not suggest insulin resistance. Creatinemia, proteinuria, magnesemia and uricemia were normal. Renal US showed the known unilateral hydronephrosis plus bilateral microlithiasis, one simple cyst and a mass suggestive of angiomyolipoma. Despite the absence of family history, the suspicion of a MODY form of diabetes was confirmed by genetic testing and identification of a deletion on the HNF1B gene. Systematic revision of common associated anomalies further identified a bicornuate uterus. She complied with a regimen of diet and regular exercise that was able to maintain euglycemia for 4 years. Today she is medicated with metformin with good glycaemic control and well-preserved renal and retinal function. Her father and grandfather had undiagnosed diabetes.
Messages
Despite de AD inheritance of MODY, family history is not always reported. There is double benefit from MODY diagnosis for both patients and family members, concerning early diabetes management and precocious identification of associated malformations. Diabetes and developmental genitourinary malformations should always raise suspicion of MODY 5. The magnitude of hyperglycaemia in MODY 5 reports is highly variable and though there is progressive pancreatic failure, initially, hyperglycaemia may present intermittently. Progression to renal dysfunction is also heterogeneous but strict surveillance is mandatory once renal function may be highly compromised due to the combination of diabetes, ureteric malformations, renal cysts, urate stones and recurrent urinary infections.

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P889

Radiation-induced loss of glycemic control in a patient with refractory lymphoma

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Introduction
PD-1 inhibitors are powerful disruptors of self- tolerance and autoimmune diabetes develops in up to 0.9% of patients. Lipodystrophic insulin reactions, although uncommon with human insulin analogs, are a recognized cause of impaired insulin delivery in patients on intensive insulin regimens. We describe a patient with resistant lymphoma and nivolumab-induced autoimmune diabetes, who suffered loss of glycemic control due to early radiation-induced subcutaneous fibrosis.
Case report
A 35-year old male with refractory Hodgkin's lymphoma, previously euglycemic developed profound antibody-negative hypothyroidism (TSH 71.8 mIU/ml, fT4 $<$0.3 ng/dl), nephrotic syndrome (20 gr proteinuria/d), positive tissue transglutaminase antibodies and insulin-requiring anti-GAD positive diabetes mellitus

(HbA1c 8.7%) after six cycles of treatment with nivolumab. The patient had previously failed to respond to first- and second line chemotherapy. He was started on a basal-bolus insulin regimen requiring about 130 IU daily, while on high dose methylprednisolone. Nivolumab was continued for another 5 cycles at 3 mg/kg and for 11 more on a lower dose. He did not tolerate adjunct oral hypoglycemic treatments, including metformin or GLP-1. Following diabetes education, he was able to perform self-monitoring of capillary glucose several times daily and maintain his glycemic control within acceptable limits (fasting glucose 140–180 and postprandial 200–220) with multiple daily injections in the abdomen, incorporating carbohydrate counting and correction factor. While still on low dose nivolumab (2 mg/kg) and methylprednisolone 4mg/d the disease relapsed in the abdomen. He subsequently received radiotherapy at a cumulative dose of 3600 cGy without adverse effects. Within days after the end of radiotherapy, his glucose measurements increased up to 400 mg/dl, necessitating an increase of 40% in insulin dosing without improvement. During this time, he used his abdominal wall for insulin injections. On clinical examination he was noted to have skin erythema and firmness over the abdominal wall, suggesting radiation-induced subcutaneous fibrosis. Upon changing the injections sites to the arms and thighs, the patient's glycemic control improved to the prior level.

Conclusion

Autoimmune diabetes is an uncommon adverse effect of nivolumab and patients often require multiple daily injections of large insulin doses, commonly delivered to the abdomen. Patients with refractory lymphoma are likely to receive multi-modality treatments, including radiotherapy. Awareness of radiation-induced damage to the subcutaneous tissue hindering systemic insulin delivery, may help prevent and manage glycemic dysregulation in cancer patients.

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P890

Auto immune hypoglycemia in individuals with type 1 diabetes, from a patient case report

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Introduction

Hypoglycemia is a severe complication of diabetes mellitus characterized by blood sugar levels lower than 0.7 g/L in individuals with diabetes. Several symptoms can be related to hypoglycemia and severe cases can be lethal. Individuals with type 1 diabetes and on insulin therapy may also experience hypoglycemic episodes but their frequency and late occurrence might indicate the presence of autoantibodies to insulin, if no other causes suggest otherwise. This condition is referred to as Autoimmune hypoglycemia in type 1 diabetes mellitus.

Case report

A 26-year-old woman known to have had type 1 diabetes for 13 years has been on Functional Insulin Therapy (FIT) with NPH and Actratpid based on her food (carbohydrate) intake. Laboratory investigations revealed diabetic nephropathy treated with a perindropil dose of 2.5 mg once daily, autonomic neuropathy with signs of gastroparesis, diabetic peripheral neuropathy with a DN4 score at least 6/10, but there are no signs of diabetic retinopathy at the back of the eye (retina) and her HbA1c level is 7.4%. The patient has been hospitalized with a 6-month history of recurrent hypoglycemic episodes reported to occur almost everyday between 2 and 3 in the morning and characterized by blood sugar levels as low as 0.20 g/l sometimes, requiring oral glucose administration.

Conclusion

It is important to note in this case report that the autoimmune origin of hypoglycemia in individuals with type 1 diabetes is a rare case and that other possible causes should be ruled out in the first place. However, in the context of autoimmunity the abnormal recurrence of hypoglycemic episodes, the human insulin immunogenicity are strong indicators of autoimmune hypoglycemia, and must in addition be confirmed by high levels of antibodies, after a thorough laboratory investigation on the origins of hypoglycemia in the patient.

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P891

Scleredema adultorum of buschke: a case report

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Introduction

Scleredema is a rare connective-tissue disorder characterized by diffuse, non-pitting induration of the skin. Scleredema is divided into three types. Pathogenesis is largely unknown. We present a case of a 56-year-old woman with non insulin-dependent diabetes mellitus who presented with a progressive history of thickening of the skin on her back.

Case report

A 56-year-old woman, suffered from type 2 diabetes diagnosed 15 years ago, presented with complaints of painless, progressive hardening of her upper back present for years. Recently, she was diagnosed of incipient nephropathy, high systolic blood pressure, and retinal hard exudates close to the macula treated with laser photocoagulation. Physical examination revealed a symmetrical, erythematous, indurated plaque with indistinct borders involving her posterior neck and upper back. Slightly restriction in range of motion of the shoulders and neck was noted. Her body mass index (BMI) was of 33.1 kg/m^2.The punch biopsy of the skin on her back showed an increased amount of interstitial colloidal iron with positive mucin consistent with scleredema.These features supported the diagnosis of scleredema diabeticorum. Our patient was asymptomatic and described mild restriction in movement. To our knowledge, her diabetes mellitus was controlled with subcutaneous insulin injections and diet.

Discussion

Scleredema is a rare condition of unknown pathogenesis. It is characterized by symmetrical, non-pitting hardening and induration of the skin, most commonly seen on the upper back, shoulder and neck, due to excessive increase in mucin deposition between the thickened and broadened collagen bundles. In rare occasions, the disease involves the face, arms, and the rest of the trunk, but not the hands and the feet that may decrease the mobility of the affected tissues. Scleredema is classically divided into three types, distinguished by their associations with infection, monoclonal gammopathy, and diabetes mellitus (scleredema diabeticorum).The third type occurs primarily in obese, middle-aged men with a long history of diabetes mellitus, as seen in the patient described here. It may be referred to as 'scleredema diabeticorum.'Although scleredema may be diagnosed clinically, diagnostic confirmation may be obtained with a tissue biopsy. Treatment of scleredema is challenging. In scleredema diabeticorum, it is judicious to advise control of blood glucose as a first step in treatment, although a relationship between glucose control and improvement in scleredema has not been firmly established.

Conclusion

The frequency of scleredema diabeticorum is underestimated. In most cases, scleredema diabeticorum is a self-limited, benign condition.

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P892

An investigation into the relationship between plasma concentrations of cortisol, testosterone, blood pressure and blood glucose levels in diabetic hypersensitive cardiovascular patients

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Diabetes mellitus type 2 (DM-2) occurs when pancreas fails to produce enough insulin or when the body cannot effectively make use of the insulin produced by the pancreas. Among other factors causing DM-2, stress is increasingly regarded as one of the causative agents that make the blood glucose levels rise, and cause DM-2. It has also been reported that DM-2 may be one of the commonest cause of hypogonadism, a lack of function in the testes, which adversely affects testosterone (T) production. Emerging evidence links insulin resistance, a key feature in DM-2 with decreased Leydig cell's secretion of T. Low gonadal steroids have been associated with metabolic abnormalities such as hyperglycemia, hypertension and subsequent development of cardiovascular diseases (CVDs). In contrast, low dose T replacement therapy is associated with

improvement of these conditions. In view of the foregoing observations, the present study was designed to determine the effect of stress in terms of release of cortisol on the development of diabetes, the interrelationship between diabetes and reproductive function in terms of release of T and their effect on the development of hypertension and related CVDs. Hundred male diabetic hypertensive cardiovascular patients and hundred age matched controls were selected from different hospitals of Dera Ismail Khan Division, KPK, Pakistan. Plasma concentrations of cortisol and T were analyzed using specific RIA kits. The Student's *t*-test, ANOVA and Pearson Correlation *r* were applied for the interpretation of results. Our results revealed that 68 percent diabetic hypertensive CVD patients had normal cortisol levels, whereas 29 percent had high cortisol concentrations. In addition, 76 percent patients had low T concentrations indicating reproductive dysfunction in these patients. Furthermore, we observed a negative correlation between cortisol and T concentrations in all groups. A positive correlation was observed between cortisol and BP and blood glucose levels. On the other hand, there was a negative correlation between plasma T levels and BP and blood glucose levels in all groups. The majority of diabetic hypertensive cardiovascular male patients belonged to age group of 51–60 years. They were illiterate, married, smokers, belonged to the lower middle income socio-economic status, overweight despite performing exercise regularly, had disease duration of 1–5 years, had no family history of hypertension and were treated with combination of RAASi and non-RAASi. In conclusion, our results indicated that most of diabetic hypertensive cardiovascular patients had low T concentrations no matter whether they had normal or high cortisol concentrations.

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P893

Necrosis of the nasal pyramid in a type 1 diabetic after prolonged intubation: in the light of a case

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Introduction
Necrosis of the nasal pyramid is mainly of traumatic origin, among the other possible causes, those induced by systemic diseases, in particular Wegener's granulomatosis…We report a case of necrosis of the nasal pyramid secondary to prolonged intubation in a type 1 diabetic.
Observation
Patient T.T, 28 years old, followed for a poorly balanced type 1 diabetes, admitted to a blood clot in a table of diabetic ketoacidosis. The patient was sedated and intubated endo-tracheally. The course was marked by CRP elevation at 68 mg/l, pancytopenia, persistence of acidosis state and rapidly nasal ischemia of the nasal pyramid, facial CT was realized objectifying the filling of the nasal fossae with a hematic material, without any other notable anomaly.
Discussion
Nasal necrosis is one of the maxillofacial complications of prolonged endotracheal intubation. It can also be secondary to many systemic diseases, in particular Wegener's granulomatosis, systemic lupus erythematosus and/or antiphospholipid syndrome, sarcoidosis or cryglobulinemia. Clinical manifestations are polymorphic and nonspecific, but asymptomatic forms of fortuitous discoveries are common. The various pathophysiological mechanisms evoked are ischemic, infectious and inflammatory.
Conclusion
The maxillofacial complications of prolonged intubation are fortunately rare, but especially if they occur on a precarious vascular site. The treatment of these complications is essentially preventative.

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Revelation modalities of latent autoimmune diabetes of adults

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Introduction
Latent autoimmune diabetes in adults (LADA) is autoimmune diabetes occurring in a subject over 30 years of age with positive anti-island antibodies and insulin therapy after 6 months. Inaugural ketosis is an unusual presentation at the time of diagnosis due to the slow progression of beta cell destruction. The purpose of this work is to point out the different revelation modalities of LADA patients
Patients and methods
A cross-sectional descriptive study was conducted in 27 LADA patients hospitalized in the endocrinology department of the Mohammed VI University Hospital of Marrakech.
Results
The mean age of patients was 47.6 years and the mean age of discovery was 39.7 years with extremes of 30 to 56 years. The sex ratio was 1.4 with a female predominance. The circumstances of discovery were hyperglycemia in 2/3 of the cases and an inaugural ketosis in 1/3 of the cases. 50% of our patients have normal BMI, 15.3% are thin, 15.3% are overweight and 19.2% are obese. Waist circumference was pathological in 57% of patients and 19.2% had hypertension.
Conclusion
Our study showed that Diabetic ketoacidosis, although rare, may be the first manifestation of latent autoimmune diabetes in adults, and should be insulin-treated

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P895

Neuroendocrine neoplasia and obesity

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Neuroendocrine neoplasia (NENs) are rare tumours that show features of neuroendocrine differentiation. Generally, NENs can be subdivides into high-grade neuroendocrine carcinomas (NECs) and low-to-intermediate grade neuroendocrine tumours (NETs). The most common Endodermal NETs' localisations are the lungs, ileum, appendix, and rectum. Neuroectodermal NETs include medullary thyroid cancer (MTC), pheochromocytoma (PHEO), and paraganglioma (PGL). Nets are estimated to occur with an incidence rate of 1 –– 3.5 per 100.000 in the general population. We report two cases of NET that were incidentally identified in the absence of any symptoms in obese women programmed to undergo bariatric surgery. Case 1: A 45-year-old white female with liver steatosis was scheduled to undergo bariatric surgery. An endoscopic investigation showed a sessile duodenal lesion with 1 cm of height. The patient denied any symptoms of carcinoid syndrome. Magnetic resonance revealed a tumour in the left adrenal gland of two cm. PET scan detected lesion in pancreas with somatostatin receptors. The patient underwent surgical removal of pancreas head and body and tumoral resection in duodenum. Pathology studies identified neuroendocrine tumour with immunohistochemistry positive for AEI, chromogranin A, synaptophysin and K1-67. Patient is now three months postoperative with BMI of 38 kg/m^2. Resting metabolic rate 2187 kcal/day with Harris Benedict resulted 126%. Case 2: A 39-year-old Hispanic asymptomatic female was programmed to bariatric surgery. A preoperative USG and MRI showed a wide expanding lesion in the right kidney measuring $17\times16\times14$ cm, with moderate hydronephrosis. A nephrectomy was performed with pathology studies identifying a well-differentiated neuroendocrine tumour presenting immunohistochemistry positive to AEI, chromogranin A, synaptophysin and K1-67. Six months after surgery her BMI is 36.3 kg/m^2. Resting metabolic rate 2430 kcal/day and Harris Benedict resulted 140%. Although NETs are considered rare, their incidence is higher in the obese population compared to general populations. As they are asymptomatic, their finding can occur during preoperative examinations. Indirect calorimetry showed normal basal energy expenditure in both patients. Obesity may play a role in the pathogenesis of these tumours. In the light of this association, this present case report denotes the need for meticulous preoperative evaluation in this population.

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P896

NME7 gene is associated with the shape of glucose curves during oral glucose tolerance test

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Introduction
The shape of the glucose curve during oral glucose tolerance test (OGTT) reflects the dynamic of the glucose stimulus-response, and it can be considered as predictor of the impaired glucose tolerance and Type 2 Diabetes (T2D). Nucleoside diphosphate kinase 7, non-metastatic cells 7 (NME7) is an acknowledged member of ciliome and is involved in the biogenesis or function of cilia. Due to the fact that obesity and T2D are common in several ciliopathies, we enrolled this gene into the candidate genes for impaired glucose tolerance and T2D. Previously, we have confirmed the relationship between the gene for NME7 and the parameters associated with T2D and obesity on a large set of DNAs from the Czech population.
Aim
The aim of the study was to ascertain possible association of the OGTT glucose curves with the genetic background.
Methods
The study included 1219 3-h OGTT curves (blood collection in 30 min intervals) from 997 women (age median 32 years) and 222 men (age median 31 years) with a wide range of glucose tolerance. The OGTT glucose curves were divided accordingly to their shape into four groups: monophasic, biphasic, triphasic and curves with more than three peaks. In these groups we studied the variability of the candidate genes for glucose metabolism disturbances and related diseases: *NME7*, *ATP1B1*, *BLZF1*, *GCK*, *KCNJ11*, *LRP5*, *PPARGC1A*, *PPARG, SLC30A8, TCF7L2, FTO, ZBTB16, THADA, PICALM, BIN1, CLU, CR1, MTNR1B, PNPLA3*. The polymorphisms were genotyped using TaqMan SNP genotyping assays (RealTime LC480, Roche).
Results
Most of the OGTT glucose curves were monophasic (48.4%), then triphasic (26.7%), biphasic (20%), curves with more than three peaks were rare (4.9%). The monophasic curves were connected with worse metabolic profile (the lowest insulin sensitivity and insulin secretion, worse lipid spectrum). The shape of glucose OGTT curves was associated with *NME7* polymorphisms (rs10732287, $P=0.001$; rs4264046, $P=0.01$; rs10800438, $P=0.02$) with the lowest frequencies of minor alleles in the biphasic type of curves.
Conclusion
The shape of glucose OGTT curves is variable and is connected with distinct metabolic profile. Our study found the association of the curve shape with the variability of the *NME7* gene which biological function is still not clear. We are now preparing the animal *nme7* knock-out model.
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P897

From the glucocentric model to new opportunitiesmetabolic control

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Objective
To study the parameters of carbohydrate and fat metabolism, electrolytes of urine against the background of taking SGLT-2 (i-SGLT-2) inhibitors in patients with type 2 diabetes mellitus with a GFR more than 60 ml/min
Materials and methods.
In the study, patients with newly diagnosed type 2 diabetes mellitus with excess weight and obesity (15 people) were prescribed drugs of group-i-SGLT-2 at the initial minimum dose. The level of HbA1c, the main anthropometric parameters were measured, the level of insulin, c-peptide, leptin, electrolytes of urine and of blood at the start and during the therapy 1-3-6 months after the start of treatment was assessed.
Results
In the examined group of patients, the dynamics of reduction of all the above parameters and their persistent preservation were noted, when there was no need to increase the dose of glyflozin group preparations to achieve the targets. Changes in blood electrolytes were not detected, but there was a persistent decrease in the excretion of sodium and chlorine.

Table 1

	0 start	1 month	3 months	6 months
Insulin basal, mcED/ml	10.7±0.6	5.3±0.7	4.5±0.5	4.0±0.5
Insulin stimulated, mcED/ml	21.0±0.5	9.8±0.8	7.1±0.7	6.8±0.5
C - peptide basal, ng/ml	2.6±0.5	1.9±0.2	1.8±0.2	1.7±0.3
C - peptide stimulated, ng/ml	5.5±0.6	4.5±0.4	4.3±0.3	4.1±0.2
Leptin, ng/ml	19.4±0.3	10.1±0.4	5.4±0.5	4.9±0.3
BMI, kg/m^2	31.2±2.1	30.2±2.1	29.2±3.3	27.5±3.6
HbA1c, %	8.0±1.1	-	6.9±0.5	6.7±0.3
potassium of urine - (20.0–80.0) mM/l	72.19±2.4	78.5±1.8	60.34±2.1	58.3±2.0
sodium of urine - (30.0–261.0) mM/l Chloro of urine - (30.0–210.0) mM/l	36.0±2.01 153.0±5.6	35.9±1.87 40.2±2.4	13.6±1.9 41.3±2.8	12.3±2.0 39.5±2.5

Conclusion
The appointment of i-SGLT-2 as a monotherapy in the debut of type 2 diabetes mellitus allows not only to achieve long-term glycemic control, but indirectly affecting lipid and carbohydrate metabolism, leads to the elimination of metabolic disorders through the formation of a prolonged pharmacokinetic profile in the absence of polypharmacy and disturbances of electrolyte exchange. The persistent tendency to hyponatria and hypochloruria should be discussed.

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P898

Does diabetes expose to multidrug-resistant urinary tract infections?

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Introduction
Urinary tract infection is worrying in diabetic patients especially unbalanced. Contracting a multidrug-resistant bacterium is even more alarming since it narrows the therapeutic means in a patient whose immune system is already weakened by the diabetes. The objective of this study is to describe the clinical and metabolic characteristics of a population of diabetic patients with urinary tract infection.
Methods
This is a retrospective study that included 46 diabetic patients with a urinary tract infection, hospitalised in the A Department of Diabetes and Nutrition at the National Institute of Nutrition in Tunis for ketoacidosis decompensation of their diabetes.
Results
The mean age was 46.4±10.2 years. The sex ratio was 0.02. Diabetes was type 2 in 100% of cases, evolving since 23.4±6.1 years on average. The average body mass index (BMI) was 33.2±5.6 kg/m^2. 13% were smokers. All patients were poorly balanced with a mean HbA1C of 10.6±1.7%. The mean creatinine clearance was 99.2±10.8 ml/min. 13.6% had dyslipidemia. 17.39% were hypertensive. None of these cases of urinary truct infection were complicated. The proportion of multidrug-resistant infections was quite high at 15.21%. 89.13% of these infections were in Escherichia Coli. The most prescribed antibiotics were third-generation cephalosporins in more than 90% of cases. The subpopulation infected with multidrug-resistant bacterias was characterized by a later response for resuscitation of ketoacidosis.
Conclusion
Diabetes is one of the most common factors that increases vulnerability to infections, especially urinary tract infections. The problem is now more complicated by the emergence of resistant bacterias, which can be life-threatening. The balance of diabetes and the rational use of antibiotics are the main means of combating this problem.

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P899

Impact of hypomagnesemia in type 2 diabetes mellitus

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Introduction
Magnesium is the fourth most abundant cation in the body and plays an important physiological role in many of its functions. However, an association between hypomagnesemia and insulin resistance (IR) in diabetes has recently been found.
Objective
To determine the correlation between hypomagnesemia, glycemic imbalance and the degenerative complications of type 2 diabetes.
Materials and methods
We conducted a prospective study of type 2 diabetic patients hospitalized in the Endocrinology-Diabetology department since September 2018, including 100 patients. The different variables studied were: glycemic balance, magnesemia and degenerative complications of diabetes. Patients were divided into 2 groups: Group 1 with hypomagnesemia and Group 2 with normal magnesium. Statistical analysis was univariate for all variables using SPSS software version 22.0.0.
Results
The mean age was 57 ± 8.7 years with a sex ratio (M/F) of 0.8 in Group 1 and 0.6 in the control group (G2). The mean duration of diabetes progression was 9.7 ± 2.6 years. Group 1 was more imbalanced than group 2 with an average HbA1c of 8.3 vs 2.3% respectively. With a fasting blood glucose average of 2.5 versus 1.8 g/l. This difference was statistically significant ($P=0.02$). Mean magnesium was 0.92 mmol/l with predominant hypomagnesemia in women ($P=0.01$). Diabetic retinopathy, diabetic nephropathy and neuropathy were observed in 43%, 28% and 14% of cases, respectively. These complications were more frequent in group 1, but without a statistically significant difference between the two groups ($P=0.6$). Diabetic macroangiopathy, with coronary artery disease, was more common in group 1 with a prevalence of 28%, arteriopathy of the lower limbs, while cerebrovascular disease was also found only in G1 with a frequency of 13%. This frequency was not statistically significant.
Conclusion
In agreement with the literature, hypomagnesaemia was significantly correlated with poor glycemic control, with an increased incidence of degenerative complications. It is therefore prudent to regularly monitor magnesemia in all patients with type 2 diabetes.

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P900

The results of diabetic foot syndrome screening among rural patients with diabetes in Uzbekistan

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Diabetic foot syndrome (DFS) is currently considered the most severe of all late diabetes complications, resulting in deteriorating health outcomes, increased disability and reduced life expectancy.
Aim
To study the frequency of occurrence of DFS in rural peoples with diabetes in Uzbekistan.
Methods
Upon the international project WDF08-379 'Prevention of lower limb amputations in people with diabetes in Uzbekistan', implemented by 'Umid' Charity Association jointly with Ministry of Health of Uzbekistan and RSSPCE in 2010–2012, 1262 patients were screened for DFS in 6 pilot rural regions, of them 184 peoples with Type 1 Diabetes and 1078 patients with Type 2 Diabetes, in the 25–65 age-group with duration of the disease 7–15 years. The examination of patients included determination of HbA1c and hyperglycemia level, Doppler ultrasound, ECG, the tests for vibration, pain, tactile and temperature sensitivity evaluation, as well as health examinations by multidisciplinary team (endocrinologist, surgeon, cardiologist, podiatrist).
Results
Findings from the screening showed the diabetic polyneuropathy in 83.2% of peoples with T2DM и 67.4% of those with T1DM, hyperkeratosis (64.8%), trophic ulcers (17.3%); ischemia of lower limbs vessels (24.2%), Charcot's foot (9%); gangrene (0.3%). Frequency of DFS occurrence was 55.3% (T2DM) and 31.7% (T1DM) accordingly. The greatest number of lower limb amputations (3.8%) and re-amputations (2.0%) was found in T2DM patients with disease of more than 10 years. 68% of peoples with diabetes were hypertensive. The major cause for DFS developing and further amputation was prolonged decompensation stage (HbA1c$>$ 8.6% in 94.2% of peoples with diabetes) and a poor knowledge on rules of foot care in rural regions.
Conclusions
Frequency of DFS occurrence in Uzbekistan was 55.3% (T2DM) and 31.7% (T1DM) accordingly. The greatest number of lower limb amputations (3.8%) and re-amputations (2.0%) was found in T2DM patients with 5–10 years disease duration. Decompensation stage (HbA1c $>$ 9.5%) in 94.2% of peoples with diabetes is one of principal causes of high frequency of DFS occurrence, a considerable number of amputations and development of other diabetes complications. That shows the necessity to improve the education quality on foot care in Diabetes Self-Management schools.

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P901

The role of 'Diabetic Foot' rooms in the organization of specialised help to patient with diabetic foot syndrome in Uzbekistan

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Of all the late complications of diabetes, foot lesions are the most preventable. The multidisciplinary approach to providing specialized help for people with diabetes can prevent the amputations in 49–85% diabetic foots.
Aim
The organization of specialized help to patient with diabetic foot syndrome (DFS) by the establishing the network of 'Diabetic foot' rooms and training of multidisciplinary team of specialists (endocrinologist, surgeon, GP, cardiologist and nurses-podiatrists) in order to decrease a number of lower limb amputations in peoples with diabetes in Uzbekistan.
Methods
Within the framework of an international project WDF08-379 'Prevention of lower limb amputations in people with diabetes in Uzbekistan', implemented by 'UMID' association jointly with Ministry of Health of Uzbekistan and Republican specialised scientific and practical medical Centre of endocrinology in 2010–2012, 288 'Diabetic foot' rooms were set up under 14 endocrinological dispensaries and in 274 rural district clinics. To work in these rooms, 288 special multidisciplinary teams (endocrinologist, surgeon, GP, cardiologist) and 615 podiatrists were trained to render a qualified medical help to peoples with diabetes and teach them rules of foot care.
Results
During the project, 22479 patients with diabetes have been screened and trained in the 'Diabetic foot' rooms. As a part of Diabetes Self-Management Education courses, the nurses-podiatrists educate the peoples with diabetes on DFS prevention. Annually over 23,800 peoples with diabetes undertake feet examination and training in 'Diabetic foot' rooms. The trained multidisciplinary teams (endocrinologist, surgeon, GP, cardiologist, podiatrist) from 14 regions provides specialized care to patients with DFS. The effective work of the trained team reduced a number of amputations in peoples with diabetes by 2 times in Uzbekistan.
Conclusions
Implementation of the project 'Prevention of lower limb amputations in people with diabetes mellitus in Uzbekistan' improved a specialised help to people with DFS due to launching a network of 'Diabetic foot' rooms and an effective work of podiatrists; training of multidisciplinary teams in 14 regions which resulted in the decreasing a number of amputations in peoples with diabetes by 2 times in Uzbekistan; increased awareness of rural people with diabetes on prevention of DFS.

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P902

Corticoid induced diabetes: where? when?

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Introduction
Corticosteroid-induced diabetes (CID) is a common and potentially harmful problem in clinical practice. Its pathophysiological mechanisms are multiple,

from increased hepatic neoglucogenesis to peripheral insulin resistance or direct toxic effect on the β cell. The aim of our study was to study the clinical profile of patients who developed corticosteroid-induced diabetes and its factors of occurrence.
Method
We report a retrospective study conducted from January 2017, on the patients followed in consultation of Endocrinology - Diabetology of Ibn Rochd University Hospital of Casablanca. Every diabetes discovered after long-term corticosteroid therapy (>3 months) was considered as cortico-induced diabetes. The studied parameters were: age, sex, BMI, family history of diabetes, duration and dose of corticosteroid therapy, treatment adopted. The statistical analysis was unified using SPSS software version 22.0.0.
Results
Our study focused on 36 patients who developed CID, with an average age of 58±4.7 years, a female predominance with a F/H ratio of 1.7. The average BMI was 28.5±5.8 kg/m^2. Family history of Diabetes was found in 56% of cases. Glucocorticoid was orally in the majority of cases with an average dose of 30 mg/day. The average duration of onset of CID was 2.8 years, with an HbA1c average of 6.8%. The risk factors significantly associated with the development of CID were: high age (>65 years) ($P=0.03$), duration of corticosteroid therapy ($P=0.012$), BMI ($P=0.005$), diabetic heredity ($P=0.02$) and elevated HbA1c ($P=0.01$). The dose of corticosteroid therapy was frequently associated with no significant result ($P=0.67$).
Discussion
Corticosteroids-induced diabetes is a common problem, whose risk factors are similar to those of type 2 diabetes, hence the need for rigorous monitoring of patients at risk.

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P903

Short term metabolic outcome following bariatric surgery; A single center experience from Asia

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Background
Obesity and related co-morbidities have become an emerging major health concern in South Asia. In addition to the efficacy in weight control, bariatric surgery improves metabolic disorders, thus is a recognized mode of treatment in obesity.
Objectives
To review the outcome of metabolic disorders in a group of obese patients in Sri Lanka following bariatric surgery.
Methods
Patients who underwent bariatric surgery at Professorial Surgical Unit, Colombo South Teaching Hospital, Sri Lanka from January 2014 to October 2017 were identified from a prospective database. Patients who had completed 12 months of post-operative period were included. Changes in the metabolic parameters at 1-year post-operative were statistically analyzed using paired-t-test.
Results
A total of 31 Sri Lankan patients were analyzed. Mean age was 37.7 years (range: 22–53). 28 (90.3%) were females. All patients had undergone sleeve gastrectomies. Initial mean weight 103.4 kg has reduced to 74.08 kg ($P<0.001$). Mean percentage expected weight loss was 60.28%. Mean BMI shows significant reduction from 42.7 kgm^{-2} to 30.8 kgm^{-2} ($P<0.001$). 13 (42%) had type 2 diabetes mellitus; all showing improved HbA1c 12 months post operatively ($P<0.001$) with complete resolution of diabetes in 61.5%. Among the initial pre-diabetics (7), 71.4% showed normoglycemia. Mean systolic blood pressure was 131 mmHg (range: 110–156), with a significant drop post operatively ($P=0.001$). 7 (22.5%) were initially hypertensive, of which all became normotenstive requiring no medication. Total cholesterol ($P=0.183$), LDL ($P=0.198$), HDL ($P=0.442$) and Cholesterol/HDL ($P=0.856$) showed no significant improvement 12 months post operatively. In contrast, triglycerides levels showed an improvement ($P<0.001$). Pre-operative fatty liver (9/31; 29%) showed an improvement in 88% of patients at 12-months post-bariatric surgery.
Conclusion
Metabolic parameters at 12 months post-operatively following bariatric surgery for obese Sri Lankan patients show significant improvement, comparable to similar studies in other parts of the world.

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P904

Case report: Bullous pemphigoid in a patient with type 2 Diabetes on treatment with linagliptin

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Introduction
The association of bullous pemphigoid (BP) with the use of dipeptidyl-peptidase 4 (DPP-4) inhibitors among patients with diabetes has recently emerged. The risk of developing BP during treatment with new DPP-4 inhibitor agents like linagliptin is yet to be established. The clinical features and the prognostic outcomes of patients with DPP-4 inhibitor-associated BP are yet to be established.
Objective
To report a case of BP on a patient with type 2 Diabetes, which showed a clear temporal relationship between the introduction of linagliptin for the treatment of diabetes and the onset of BP.
Case report
Woman of 78 years old, diagnosed from type 2 Diabetes in 2004, with medical history of chronic kidney disease stage 3. She was on treatment with 40 units of insulin Tresiba daily and Repaglinide 1 mg, two tablets in breakfast, lunch and dinner. Linagliptin was sarted in order to improve A1C and fast glucose levels. 6 months later she was referred to the dermatologist, complaining of a diffuse eruption of bullae and erosions with slight erythema on his head, trunk, and limbs. A skin biopsy was performed and she was diagnosed from BP. Linagliptin was discontinued and she was started on steroids (Prednisone 15 mg/day). After the withdrawal of linagliptin, the cutaneous lesions were improved in 2 weeks and prednisone was tapered down until withdrawal.
Conclusion
The number of reported cases of BP induced by linagliptin has been increasing during the past few years. A large-scale analysis of BP induced by DPP-4 inhibitors was performed using the European pharmacovigilance database. According to the data, the proportional reporting ratio for linagliptin and BP was the second highest after that for vildagliptin. In conclusion, DPP-4 inhibitors, specially vildagliptin and linagliptin, should be considered as a possible trigger of BP and we reccomend discontinuation of DPP-4 inhibitor treatment when BP is diagnosed.
References
1. Mendonca FM, Martin-Gutierres FJ, Rios-Martin JJ, Camacho-Martinez F. Three cases of bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors – one due to linagliptin. Dermatology. 2016;232:249–53.
2. Harber R, Fayad AM, Stephan F, Obeid G, Tomb R. Bullous pemphigoid associated with linagliptin treatment. JAMA Dermatol. 2016;152:224–6.

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P905

Epidemiological research on diabetic rethynopatia prevalence in newly diagnosed people with type 2 diabetes in Uzbekistan

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Diabetic retinopathy (DR) is one of the most frequent and serious complications of diabetes and the leading cause of blindness worldwide. Nevertheless, in Uzbekistan there is no precise statistical data on the prevalence of DR in patients with newly diagnosed diabetes mellitus.
Purpose
To study the incidence of DR in newly diagnosed people with type 2 diabetes in Uzbekistan.
Materials and methods
Within the framework of the grant 'Prevention of Diabetes in the Rural Population of Uzbekistan' from WDF in 6 pilot regions of Uzbekistan, the screening was conducted for early diagnosis of DR among 2998 patients with newly diagnosed diabetes. Average age was 59.39±10.22 years, 62% of women and 38% of men. They studied: the level of glycemia, HbA1c. The ophthalmologist's examination included: visual acuity determination, biomicroscopy, autorefractometry, direct ophthalmoscopy, photographing of the fundus of the non-miraculous hand-held portable funduscamera.

Results
A comprehensive ophthalmologic examination of patients with newly diagnosed T2DM revealed: DR - in 11.5% (a non-proliferative stage of 8.7%, a pre-proliferative stage of 2.5%, and a proliferative stage of 0.24%). Diabetic cataract (DC) was detected in 27.3%, glaucoma 4.7%, pterygium 39.6% and refractive error 24.8%. Our data do not confirm the data of the national registry for the frequency of occurrence of DR in the same category of patients (average amount 47%), which indicates an incorrect diagnosis of DR by regional doctors. The HbA1c was > 6.5%–23.4%; Within 8–9% −63.9% and >9%–12.7%, indicating a prolonged hyperglycemia and prescription of the disease, which are the main factor in the progression of complications of diabetes such as DR.
Conclusions
1. Frequency of occurrence of DR in patients with newly diagnosed type 2 diabetes in Uzbekistan according to the screening data was 11.5% (of which the non-proliferative stage is 8.7%, the pre-proliferative stage is 2.5%, and the proliferative 0.24%), this amount almost in 5 times less in comparison with the national registry data, which indicates an incorrect diagnosis of DR by regional doctors.
2. A comprehensive examination of the ophthalmologist of patients with newly diagnosed diabetes obligatorily should include: determining the visual acuity; Biomicroscopy; Autorefractometry; Direct ophthalmoscopy; Photographing on the funduskammer not only for the early detection of DR, but also for other eye disorders leading to decreased vision in patients with diabetes.

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P906

Gestational Diabetes in Early Pregnancy – what does fasting glucose tell us?

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Introduction
The association of fasting glucose (FG) in early pregnancy (EP) with adverse outcomes for the mother and her offspring is well known, although the best cut-offs for diagnosis of Gestational Diabetes (GD) are not consensual.
Objetive
Evaluate the impact of FG in EP in the management of pregnant women and obstetric and fetal outcomes.
Methods
Retrospective cohort of pregnant women with GD diagnosed before 24 weeks of gestation using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, attending Baixo Vouga Hospital Center, in Portugal, with follow-up between January 2015 and June 2018. FG was stratified into 3 categories: 1 – 92–94 mg/dl; 2 – 95–99 mg/dl; 3 – 100–125 mg/dl. Maternal and fetal outcomes were evaluated. Statistical analysis was performed using *Statistical Package for the Social Sciences*® v. 24.
Results
A total of 222 women were included, 15.3% of which had GD in a previous pregnancy. Mean age at diagnosis was 33.0 ± 5.5 years and mean FG was 96.7 ± 5.9 mg/dl (92–125). Of these, 47.3% ($n=105$) were treated with nutritional therapy (NT) only, 18.0% ($n=40$) with oral antidiabetic drugs, 27.9% ($n=62$) with insulin and 6.8% ($n=15$) with both. Preterm labour occurred in 18 women (8.1%) and cesarean delivery was performed in 71 (32.0%). Within the offspring, 11.3% ($n=25$) were large for gestational age and 16.7% ($n=37$) had perinatal morbidity. Maternal prepregnancy Body Mass Index (BMI) was positively correlated with FG ($r=0.192$, $P<0.05$). FG did not correlate with adverse obstetric, fetal or neonatal outcomes. Mean FG was significantly higher in women with prior GD, as well as in those who required pharmacological therapy (PT) (97.7 ± 6.6 mg/dl vs 95.2 ± 4.4 mg/dl under NT, $P<0.05$). When divided into categories, FG was still significantly related with PT (required in 44.7% women in category 1, 51.5% in category 2 and 70.0% in category 3 ($P<0.05$)). Using logistic regression, FG didn't have predictive value for the need of PT [$P=0.107$; OR 1.107 (0.978 – 1.253)].
Conclusion
Pregnant women who needed PT had higher levels of FG at diagnosis, but these weren't predictive of need for PT or associated with worst obstetric and fetal outcomes. These results were similar when FG was analyzed in categories.

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P907

Weight change of a population of diabetic patients previously educated and having fasted the month of Ramadan

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Introduction
The objective of our study was to study the evolution of the weight of a population of diabetic patients previously educated and having fasted the month of Ramadan.
Methods
This is a prospective study that involved 140 patients who wish to fast the month of Ramadan (2016) and who have presented themselves at consultations dedicated to preparing diabetic patients wishing to fast, organized at the National Institute of Nutrition of Tunis (Departement C). These patients were given an interview, a thorough clinical examination and a biological assessment and were well informed about the risks they face. They had the appropriate therapeutic adaptation (ADA recommendations of 2010), as well as adequate hygiene and dietary education. We have totally banned fasting for unbalanced patients.
Results
The average number of days fasted was 24.57 ± 10.5 days. The sex ratio was 0.94.The average age was 55.75 ± 10.83 years. Diabetes has averaged 8.17 ± 6.9 years, poorly balanced in 71% of cases. 23% were insulin-dependent. The average fasting glucose level was 9.74 ± 3.76 mmol/l. The mean HbA1C was 8.28 ± 1.61%. The mean body mass index was 29.19 ± 5.03 kg/m^2. 20% had a normal corpulence with an average BMI of 23 ± 1.68 kg/m^2. The others were either overweight or obese with an average BMI of 30.73 ± 3.51 kg/m^2. After fasting, there was a slight weight gain of 0.05 kg, with no significant difference compared to the weight before fasting. This weight gain was seen in patients with normal body size and those with overweight or obese with averages close to 0.05 kg and 0.06 kg respectively. The frequency of weight gain was the same (21.44%),for both normal and overweight/obese patients. The weight loss was more marked in overweight or obese patients with a frequency of 24.11% compared to 10.71% in patients of normal body size. Weight loss was between 2 and 3 kg in normal body weight, and 1 to 2 kg in overweight or obese subjects. The weight gain was 0.5 to 2 kg and 1 to 4 kg, respectively. The weight remained stable in more than 50% of patients regardless of their initial body size.
Conclusion
The change of the weight in diabetic patients after Ramadan fasting depends on several parameters such us BMI before the fast. It involves changes in insulin sensitivity, changes in the sleep cycle often interrupted by the 'shour' meal and changes in the composition of specific dishes of the month of Ramadan.

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P908

Association of dipeptidyl peptidase 4 inhibitor use with risk of bullous pemphighoid

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Introduction
Recent studies suggest that the use of dipeptidyl peptidase 4 inhibitors (DPP-4i) may be associated with an increased risk of developing bullous pemphigoid; which has led to publication of several pharmacovigilance alerts.
Objectives
To characterize the potential association between the use of DPP-4i and the risk of developing bullous pemphigoid.
Material & methods
Observational, retrospective study based on clinical practice. Patients diagnosed with bullous pemphigoid with histological confirmation in our center were collected, from January 1, 2017 to December 31, 2018.
Results
Seventeen patients diagnosed with bullous pemphigoid were included, 52.9% males, with a mean age of 80.1 ± 8.7 years. 52.9% had diabetes mellitus type 2, 76.5% hypertension and 47.1% dyslipidemia. In their usual treatment, 26.5% had an ACEI, 47.1% an ARB-II, 41.2% a statin and 35.3% an oral anticoagulant. Among those patients with diabetes mellitus, 66.7% were on treatment with metformin, 55.6% with a DPP-4i and 66.7% with basal insulin. Regarding the DPP-4i used, in 2 cases it was vildaglitpine, in 2 other cases linagliptin and in 1 case alogliptin. The average time of use was 929.9 days. There were no significant differences in terms of demographic variables, comorbidity or treatment groups among patients with bullous pemphigoid with and without treatment with DPP-4i.

Conclusions
1. The appearance of bullous pemphigoid is frequently associated with the use of DPP4i in our environment. 2. Due to the frequency of use of these drugs, more studies are needed to confirm this association and rule out the possible relationship with other drugs of frequent use in the elderly patient.

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P909

Circulating microRNAs expression profile in individuals with obesity compared to healthy controls

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Context
Obesity is a global epidemic and an independent risk factor for several metabolic disorders. Emerging evidence suggests a role for epigenetic factors, such as microRNAs (miRNAs), in the development of obesity. MiRNAs are small non-coding RNAs that regulate gene expression. Moreover, circulating miRNAs are potential noninvasive biomarkers because they are stable in body fluids and can be detected using validated techniques, such as quantitative PCR. However, the identification of the specific miRNA expression profile involved in obesity remains incomplete.
Objective
To investigate a miRNA expression profile in plasma of patients with obesity compared to non-obese individuals.
Design
In this case-control study, the expression of 96 miRNAs was investigated in plasma of 54 age- and gender-matched subjects: 34 patients with obesity (BMI $\geq$30 kg/m^2) and 20 non-obese individuals (BMI $<$ 25 kg/m^2) using miRCURY LNA miRNA Custom PCR Panels (Exiqon). Body mass composition was estimated by dual-energy X-ray absorptiometry (DEXA). All statistical analyses were performed using SPSS 20.0.
Results
Seven miRNAs (miR-142-5p, miR-146a-3p, miR-15a-5p, miR-22-3p, miR-29c-3p, miR-33b-5p, and miR-375) were significantly downregulated ($P<$ 0.05) in plasma of patients with obesity compared to non-obese individuals. MiR-146a-3p, miR-22-3p, and miR-33b-5p were negatively associated with body fat percentage. MiR-146a-3p and miR-22-3p were also correlated with waist circumference. Moreover, miR-146a-3p expression was also negatively associated with visceral adipose tissue mass.
Conclusions
Our study demonstrates a differentially expression of miRNAs in patients with obesity, and some miRNAs are also associated with adiposity parameters. MiRNAs could constitute potential biomarkers and therapeutic target of this metabolic disease for early diagnosis and management.

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P910

Gestational Diabetes: what to say about body mass index and outcomes? The influence of prepregnancy body mass index on obstetric and neonatal outcomes of women with gestational diabetes

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Introduction
Due to the growing prevalence of obesity, more women are overweight in early pregnancy, leading to adverse neonatal and obstetric outcomes.
Objective
To evaluate the influence of maternal prepregnancy body mass index (BMI) on blood glucose levels at diagnosis of gestational diabetes (GD), obstetric and neonatal outcomes.
Methods
Retrospective observational study including women with GD and singleton pregnancy, with follow-up at Baixo Vouga Hospital Center between January 2015 and June 2018. Statistic analysis: SPSS 24.
Results
Sample of 462 pregnant women, medium age 32.65 years (SD 5.45) and medium BMI 27.29 kg/m^2 (SD 5.57), with no differences in terms of history of macrosomia and GD between maternal BMI groups. Only in pregnant women with normal BMI the percentage of familiar history of GD was less than 50% (P 0.001). In respect to the trimester (T) of diagnosis of GD, 53.7% of women with normal BMI and 55.8% with BMI$>$30 Kg/m^2 were diagnosed in the 1stT (P 0.011). BMI positively and significantly correlated with fasting glucose level (FGL) in the 1stT ($r=0.213$, P 0.001) and 2ndT ($r=0.210$, P 0.001), despite not correlating with glucose level at 60 and 120'. In what weight gain was concerned, 44.9% women with pre-obesity and 40.2% with BMI$>$30 Kg/m^2 had excessive weight gain ($P<0.05$) and 65.1% of them required pharmacological treatment (P 0.05). There were no differences between groups in terms of pre-eclampsia, hydramnios and prematurity, but gestational hypertension was more frequent in obese women (P 0.004). Although there were no differences in neonatal morbidity, the majority of cesareans (40.3%; $P<0.05$) and large-for-gestational age (LGA) birthweight (50%; P 0.035) occurred in women with BMI$>$30 Kg/m^2. By adjusting for maternal age on logistic regression, BMI had a predictive value only for macrosomia (aOR 1.177 (1.006–1.376) P 0.041). BMI and weight gain are positively correlated with weight at birth ($r=0.132$ P 0.005 e $r=0.188$ P 0.005) but not with gestational age.
Conclusion
Maternal obesity is related with a major probability of diagnosis of GD in 1stT and fasting hyperglycemia in 2ndT, a consequence of the associated insulin resistance. Those women require, more frequently, pharmacological therapy and, similarly to previous studies, are associated with gestational hypertension, cesarean delivery and fetal macrosomia. In these women, there was no increase in the number of stillbirth, pre-eclampsia or neonatal morbidity.

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P911

Assessement of magnesemic status in patients with metabolic syndrome

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Introduction
The association between hypomagnesemia and insulin resistance in diabetes and arterial hypertension has been strongly found, but its role in the metabolic syndrome has not been established.
Objective
To determine the magnesium status of patients with metabolic syndrome.
Materials and methods
We conducted a prospective study on patients followed in the service of Endocrinology-Diabetology since September 2018 including 109 patients. The patients were divided into 2 groups: Patients with or without metabolic syndrome according to the criteria of (NCEP-ATP III), with measurement of magnesemia in all patients. Statistical analysis was univariate for all variables using SPSS software version 22.0.0.
Results
A total of 64 patients (F/M ratio: 4) with metabolic syndrome were compared to 55 control patients (F/M ratio: 3.2), with no significant difference in age (42.3$\pm$7.3 years versus 41.5$\pm$8.5 years, $P=0.34$) or sex ($P=0.17$) between the 2 groups. Mean abdominal perimeter was 101.3$\pm$9.3 versus 79.5$\pm$7.3 cm in men and 92.4$\pm$8.32 vs 72.1$\pm$5.6 cm in women. Hypomagnesemia was found in 6.4% of control subjects compared to 59.5% of patients with MS ($P<0.01$), with mean magnesium level of 0.92 mmol/l and predominant hypomagnesemia in women ($P=0.01$). In the metabolic syndrome group, hyperglycemia was identified in 28 cases (43.7%), with an average HbA1c at 7.6% versus 6.7% in the control group. Obesity, dyslipidemia and hypertension were observed in 36.3%, 51.8% and 18.7%, respectively, whereas in the control group, none of patients were hyperglycaemic, and the frequency of obesity, dyslipidemia and hypertension were 13.6%, 8.9% and 5.7%. The lowest serum magnesium levels were observed in dyslipidemic patients (2.34$\pm$0.49 mg/dl), versus 5.46$\pm$0.75 mg/dl in the control group ($P=0.05$).
Conclusion
A significantly higher frequency of magnesium deficiency was observed in the metabolic syndrome, hence the need for a systematic evaluation of magnesemic status in these patients with the correction of possible abnormalities.

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P912

1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) and lipid accumulation in liver cells: A role for epigenetic mechanisms?

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Context
Vitamin D is a fat-soluble vitamin which requires the hydroxylation into 1,25-dihydroxyvitamin D (1,25-$(OH)_2D_3$) to be fully active. Vitamin D deficiency is a worldwide health problem associated to a wide range of acute and chronic diseases. On other hand, vitamin D supplementation has been proposed to reduced the risk of metabolic dysfunctions including obesity, type 2 diabetes and cardiovascular disease. Vitamin D interacts with the epigenetic machinery on multiple levels, but little is known about those regulatory mechanisms where vitamin D is involved.
Aim
To analyze the effects of 1,25-dihydroxyvitamin D on lipid accumulation and epigenetic changes in a human liver cell line.
Design
Lipid accumulation was induced in HepG2 cells by treating with a mixture of fatty acids (oleic acid and palmitic acid; 1 mM). To study the potential prevention of lipid accumulation, cells were also exposed to 1,25-$(OH)_2D_3$ (25, 100 and 250 pM) for 24 hours. In a second approach, to analyze if 1,25-$(OH)_2D_3$ could reverse lipid accumulation, cells were pre-incubated with fatty acids for 24 hours and then, were treated with 1,25-$(OH)_2D_3$. Cell viability was determined using MTS, lipid content was measured with Nile Red Stain, and expression of genes involved in lipid metabolism (*ACOX1, PPARA, SREBP1, GPAM, FASN, TET1, TET2*) were quantified by qRT-PCR by using specific probes.
Results
Treatment with 1,25-$(OH)_2D_3$ for 24 hours did not affect cell viability. The simultaneous exposure to 1,25-$(OH)_2D_3$ and fatty acids showed a trend to a decrease in lipid accumulation without changes in classic metabolic genes, but the expression of *TET1* and *TET2*, key enzymes in DNA methylation, was down-regulated. The exposure to 1,25-$(OH)_2D_3$, after the fatty acids load, increased lipid accumulation in a dose response manner. This increase in fat deposition was associated with a reduction in mRNA levels of *ACOX1, PPARA, SREBP1,* and *FASN.*
Conclusion
The exposure to 1,25-$(OH)_2D_3$ and fatty acids induced changes in lipid accumulation associated to a differential gene expression that requires further analysis to evaluate the participation of epigenetic mechanisms. Indeed 1,25-$(OH)_2D_3$ might contribute to reduce liver fat accumulation, although it could have detrimental effects when hepatic steatosis is already present.

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P913

Blood pressure objectives in diabetic patients: about 588 cases

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Introduction
Hypertension (HTA) is a common condition in patients with type 2 diabetes and is associated with a high risk of cardiovascular disease. Optimal control is the major goal of clinicians to reduce cardiovascular risk. The objective of this study is to determine the prevalence of blood pressure goals in hypertensive diabetic patients.
Methods
Retrospective descriptive study including 588 diabetic patients hospitalized in the endocrinology department of Casablanca Ibn Rochd Hospital between January 2016 and May 2018. Hypertensive patients considered balanced according to the recommendations of the American Diabetes Association (ADA 2018): a goal blood pressure $<140/90$ mmHg in the majority of patients and $<130/80$ in patients with very high cardiovascular risk. The variables studied were the characteristics of diabetes and arterial hypertension, treatment administered and the measurement of blood pressure. Statistical analyzes were performed by SPSS 25.
Results
588 hypertensive diabetic patients with female predominance (75% of cases). Average age was 62.8 years old. HTA was 53% systolic-diastolic, 74.2% Grade 1 and 31% grade 2, with mean systolic blood pressure ranging from 140-160 mmHg and mean diastolic pressure between 70 and 110 mmHg. 42.8% of hypertensive patients were treated with monotherapy (ACEI or AIIRA), 37% with dual therapy (ACE + diuretic or ACE inhibitor + calcium channel blocker or AIIRA + diuretic/calcium channel blocker), only 8% were on triple therapy. 67% of patients treated achieved their blood pressure goal, and 39% of patients did not reach their blood pressure goal. The etiologies of the not controled blood pressure were the poor therapeutic observance observed in 38% of elderly patients with polypathologies, in 20% of cases because of the extra cost of treatment, in 54% of cases because of poor compliance.

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P914

miRNAs-target genes, miRNA-lncRNA, and miRNA-small molecules interactions involved in metabolic diseases

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Context
Metabolic diseases affect millions of people in both developed and transition countries. In addition to genetic inheritance of risk alleles, emerging evidence has shown that these diseases are also linked to lifestyle and inherited epigenetic pattern interactions. The strong link between epigenetics and metabolism may offer attractive clinical applications to counteract and manage the escalating prevalence of metabolic diseases, such as obesity, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), among others. Regarding the epigenetic factors, microRNAs (miRNAs) are a class of small non-coding RNAs that regulate gene expression. Moreover, evidences suggested a role for miRNAs in the pathogenesis of metabolic disorders, supporting that they may represent potential biomarkers or targets for prevalent chronic diseases. However, current results are often controversial.
Objective
To feature the associations between miRNAs-mRNA, miRNA-lncRNAs, and miRNAs-small molecules in human metabolic diseases, including obesity, T2DM, and NAFLD.
Design
The metabolic-related miRNAs were obtained from the Human MicroRNA Disease Database (HMDD) and miR2Disease database. Search on the databases Matrix Decomposition and Heterogeneous Graph Inference (MDHGI) and DisGeNET were also performed. MiRNAs target genes were obtained from three independent sources: Microcosm v5.0, TargetScan v7.0, and miRTarBase v4.4. The functional enrichment analysis of miRNA-target genes was performed to retrieve Gene Ontology (GO) and KEGG pathways using the plug-ins BiNGO v3.0.3 and ClueGO/Cluepedia v2.3.5. The interactions between miRNAs-lncRNA and miRNA-small molecules were performed using the miRNet web tool. The associations were corrected for multiple hypotheses using the Benjamini & Hochberg False Discovery Rate test and interactions with a q-value <0.05 were considered strongly enriched. All network analyses were performed using Cytoscape software v3.7.0.
Results
A total of 20 miRNAs were found associated with metabolic disorders in our study. Interestingly, 6 miRNAs (miR-17-5p, miR-29c-3p, miR-34a-5p, miR-103a-3p, miR-107, and miR-132-3p) were found in the four databases (HMDD, miR2Disease, MDHGI, and DisGeNET) used for these analyses, presenting a stronger association with the selected diseases. The functional enrichment analysis of miRNAs target genes reflected the complex biological behavior of metabolic diseases, being associated with multiple signaling pathways. Moreover, interactions between miRNA-lncRNA and miRNA-small molecules were also originally evidenced, suggesting that some molecules can modulate gene expression by such indirect way; although others studies are required to understand these outcomes.
Conclusion
The construction of miRNA-mRNA, miRNA-lncRNA, and miRNA-small molecules networks provides a novel approach to investigate the metabolic diseases pathogenesis and for the personalized treatment in the future.

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P915

Profile of patients using continuous subcutaneous insulin infusion in portugal

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Introduction
Continuous subcutaneous insulin infusion (CSII) represents a treatment option that helps patients with type 1 diabetes (PwT1D) to achieve better glycemic control, reduces hypoglycemia and improves quality of life. In Portugal, the National Health System (SNS) affords CSII treatment to PwT1D, according to certain criteria. Over the years, the number of patients treated with CSII devices supported by SNS has grown exponentially. We analyzed these patient's profile.
Methods
Descriptive analysis of PwT1D registered in the National CSII platform on January 1, 2019 (corresponding to Continental Portugal SNS registers). Data on gender, birth date, diagnosis date, eligible criteria for CSII, date of initiation of CSII treatment and treatment center were collected. The SPSS 23 program was used for statistical analyses.
Results
There are currently 2364 PwT1D registered as being under CSII treatment. 54% are females and 46% are males. Mean age is 22 ± 15 years-old, and 56% have 18 years-old or less. Mean age at diagnosis was 10 ± 9 years-old ($n = 1644$) and initiation of CSII treatment occurred 14 ± 11 years later ($n = 381$). 958 patients have eligible criteria for CSII treatment filled in their records. Of those, 58% had high glycaemic variability; 57% had HbA1c level over 7.0%; 40% were 14 years-old or less; 38% needed a more flexible lifestyle; 28% used small doses of insulin; 26% suffered from hypoglycaemia unawareness; 8% presented dawn phenomena; and 2% were preconception women. Continental Portugal is divided into five health care regions and CSII spreading is not uniform. Accordingly, each health region, assists the following proportion of PwT1D using CSII: North 39,8%; Center 17.7%; Lisbon and Tejo's valley 40.0%; Alentejo 1.4%; Algarve 1.1%.
Discussion and conclusion
There are currently 2364 patients on CSII treatment in Continental Portugal, supported by the SNS. Most of them are young, and the main reasons for CSII treatment choice were paediatric age, glycaemic variability and poor glycaemic control. Over the last years, CSII treatment has quickly expanded in Portugal. This year we expect that more than 850 new CSII systems will be made available by the SNS, namely covering all eligible children with 18 years old or less. In 2010 there were only around 500 patients treated with CSII systems, but by the end of 2019 this number is expected to overcome 3000. The National Diabetes Program will keep efforts to increase the availability of CSII systems and to promote the best health care practice for PwT1D.

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P916

Genetic variants of TCF7L2 gene in Lithuanian women population with previously diagnosed Gestational Diabetes Mellitus compared to General Population

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Introduction
TCF7L2 is a commonly investigated gene in women with gestational diabetes mellitus (GDM). *TCF7L2* different SNP's are associated with GDM risk in women of different races and ethnicities, however, the relationship between the genetic variants of *TCF7L2* and GDM has not been completely evaluated.
Objective
To determine the association of genetic variants rs7901695, rs7903146, rs7895340, rs11196205, rs12255372 of transcription factor 7 like 2 (*TCF7L2*) gene in Lithuanian women population with previously diagnosed GDM compared to general population.
Methods
Women with previously diagnosed GDM (GDM group) participated in the study. Carbohydrate metabolism was evaluated. *TCF7L2* single nucleotide polymorphism (SNP) common variants (rs7901695, rs7903146, rs7895340, rs11196205, rs12255372) were set. The prevalence of *TCF7L2* the same SNP alleles were also evaluated for women of the general population. This group comprised of 300 women who were selected from the random sample of the Kaunas city (Lithuania) population. Statistical analysis was made with the statistical package IBM SPSS Statistics version 21. Qualitative variables presented as absolute numbers and percentage. ANOVA test was used, for the comparison between three or more groups. Categorical variables were compared using chi-square test. Odds ratios (OR) with 95% CIs were presented. The results were considered statistically significant at $P < 0.05$.
Results
158 women with previously (15–47 years ago) diagnosed GDM participated in the study. Carbohydrate dysmetabolism in GDM group was set for 57.6%. 11 (7.0%) were diagnosed with IFG, 14 (8.9%) with IGT, type 2 DM was diagnosed for 58 (36.7%), type 1 DM for 7 (4.4%), MODY2 – 1 (0.6%) patients. Following the analysis of the prevalence of *TCF7L2* SNP alleles in GDM group separate carbohydrate metabolism groups, differences were not detected ($P > 0.05$). An analysis of the prevalence of *TCF7L2* SNP alleles in GDM group women compared to Kaunas city (Lithuania) general population women showed statistically significant difference in three *TCF7L2* SNPs: higher prevalence of rs7901695 CC/CT, rs7903146 CT/TT, rs12255372 GT/TT alleles were found in GDM group women. The OR of being in GDM group with *TCF7L2* rs7901695 CC/CT was 1.703 (95% CI 1.153–2.515); having rs7903146 CT/TT – 1.708 (95% CI 1.149–2.538) and rs12255372 GT/TT – 1.575 (95% CI 1.058–2.343).
Conclusions
TCF7L2 SNPs did not differed in separate carbohydrate metabolism groups in women with previously diagnosed GDM, though a significantly higher incidence of *TCF7L2* rs7901695 SNP CC/CT, rs7903146 SNP CT/TT, rs12255372 GT/TT alleles in GDM group compared to general population women were observed.

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P917

Angiotensin-converting enzyme (ACE) gene I/D polymorphism and angiotensin II type 1 receptor (AGTR1) gene A1166C polymorphism and diabetic kidney disease

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Background
Polymorphisms in angiotensin-converting enzyme (ACE) gene and angiotensin II type 1 receptor (AGTR1) gene have been assessed in previously multiple studies for association with diabetic nephropathy (DN), but results are still controversial.
Aim
The aim of our study was to find out the role of ACE (I/D) and AGTR1 (A1166C) in genetic susceptibility of diabetic nephropathy in Belarusian population.
Methods
The present case-control study investigated the association of the I/D polymorphism in the ACE gene and A1166C polymorphism in the AGTR1 gene with DN. The study included 101 patients with type 1 and type 2 diabetes (67 subjects with DN) and 100 normal controls. DNA was isolated from peripheral blood leucocytes, and genotyped using allele specific PCR (ACE ID) or PCR (AGTR1) methods.
Results
Genotype frequencies of the ACE (I/D) and AGTR1 (A1166C) polymorphisms were in accordance with the Hardy-Weinberg equilibrium. In subjects with DN, the frequencies of the DD, ID and II genotypes (ACE) were 0.409; 0.227 and 0.364 respectively. The frequencies of the AA, AC and CC genotypes (AGTR1) were 0.554; 0.355 and 0.091 respectively. We found no significant association of the ACE I/D polymorphism with DN in genotype, allele, dominant, and recessive models. Homozygosity for the A allele, of the AGTR1 (A1166C) polymorphism, was associated with increased risk of DN (OR = 3.06; 99%CI = 1.02–9.08), independently of the other associated variables: age, duration of diabetes, sex and HbA1c.
Conclusion
Our preliminary data did not reveal significant association of the ACE I/D polymorphism with diabetic nephropathy. The risk of having diabetic nephropathywas increased in patients homozygous for the A1166 allele AGTR1 gene. However, more investigations are required to further this association.

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P918

Risk factors for diabetic retinopathy: About 454 patients

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Introduction
Diabetic retinopathy (DR) is a common and serious complication of diabetic microangiopathy. The aim of our study was to evaluate the frequency of DR and to analyze the various factors associated with its development and progression.
Patients and methods
Analytical prospective study including 454 diabetic patients requiring an eye examination, hospitalized at the endocrinology-diabetology department of the University Hospital of Casablanca between January 2016 and January 2018.
Results
The mean age of our patients was 45 years (14–81 years), with type 2 diabetes predominating in 67% of cases, the mean HbA1c level was 10.2% and average duration of diabetes was 8.2 ± 9.53 years. We noted a prevalence of 53% (242 cases) of diabetic retinopathy and 25% (113 cases) of diabetic maculopathy. The distribution of cases by stage of DR was: minimal non-proliferative DR in 32% of cases, moderate non-proliferative DR in 22%, severe non-proliferative DR in 9% and proliferative in 8% of cases. The prevalence of DR was correlated with the age of diabetes ($P < 0.005$) and the glycemic control ($P < 0.001$). The presence of high blood pressure or diabetic nephropathy was not associated with a higher prevalence of RD ($P = 0.2$). No statistically significant association was found for age, sex, type of diabetes.
Conclusion
The prevalence of diabetic retinopathy increases statistically significantly with poor glycemic control and age of diabetes, highlighting the need for long-term glycemic control.

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P919

Diabetes Eruditus: Characteristics of type 1 diabetes of long duration

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Introduction and aim
Type 1 diabetes mellitus (T1DM) presents as a challenge for both health care providers and patients looking to avoid chronic complications and early mortality. Clinical features of patients with long duration T1DM are still poorly studied and debated. The aim of our work was to describe the clinical features of subjects with long duration T1DM.
Methods
Cross-sectional study of patients with T1DM with more than 40 years of evolution followed at our Endocrinology outpatient clinic. Clinical (age and symptoms at diagnosis, insulin dose and regimen, diabetes complications and other medical illnesses), laboratory (HbA1c of the last 6 months, lipid profile, urinary albumin/creatinine ratio [UACR]) and anthropometric data were collected. We excluded patients submitted to pancreatic transplantation with a functioning graft and those lost from regular follow-up.
Results
Forty-seven patients (53.2% male) were included. Their mean age was 60.6 ± 9.3 years with a median age-at-onset of diabetes of 12.5 (1.1–40) years. The median body mass index at last evaluation was 24.1 (19.1–39.5)kg/m^2.Classical diabetes symptoms were found at diagnosis in 85.1% ($n = 40$) of the individuals; clustering of other autoimmune diseases was identified in 31.9% ($n = 15$), exclusively thyroid dysfunction. Concerning current treatment, 53.2% ($n = 25$) were on a multiple daily injections regime, 29.8% were on a functional insulin therapy (half of them with continuous subcutaneous insulin infusion); with a median total daily insulin dose of 0.48 (0.28–1.08) units/kg. Flash-glucose monitoring was used by 63.8%($n = 30$) of the individuals. Last mean HbA1c was 8.0 ± 1.3%; median of total, LDL and HDL cholesterol, and triglycerides was 148.0 (95–381), 77.0 (38–267), 54.5 (33–101) and 78.5(39–352) mg/dl, respectively. Last mean glomerular filtration rate (MDRD formula) was 73.3 ± 26.5 ml/kg per 1.73 m^2; 46 patients had UACR available, of those, 58.7%($n = 27$) had a normal UACR(< 30 mg/g), 26.1%($n = 12$) moderately increased (30–300 mg/g) UACR and 14.9%($n = 7$) had albuminuria(UACR > 300 mg/g). None of the patients had end stage renal disease.Concerning to other diabetes complications, 93.6%($n = 44$) of the individuals had at least one; diabetic retinopathywas present in 91.5%($n = 43$), followed by neuropathy (distal sensorimotor or autonomic) in 46.8%($n = 22$); and nephropathy in 41.3%($n = 19$).
Conclusion
Our group of patients with long duration T1DM, despite out-of-target HbA1c levels, are fairly protected from diabetic nephropathy. Their clinical features, with a relatively low total daily insulin dose and singular lipid profile with relatively high HDL-cholesterol and low triglycerides levels, may represent a long survival feature. This study should prompt the analysis of early prognosis markers in T1DM.

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P920

The Soft tissue infections in diabetic patients

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Introduction
The diabetic patient in times of imbalance is susceptible to infections with a risk five times higher than non-diabetics. The aim of our work was to determine the clinical and paraclinical manifestations of soft-tissue infections in diabetic patients, to identify contributing factors and etiologies.
Patients and methods
Prospective study, conducted from October 2017 to September 2018, in the endocrinology department of Ibn Rochd University Hospital, in patients with soft-tissue infections outside the diabetic foot.
Results
Our series included 120 patients, mean age 40 ± 13.8 years with a sex ratio H/F of 0.76, an average BMI of 24.9 ± 3.9 kg/m^2, diabetes mellitus Type 2 predominant 62.5%, average seniority 7.2 ± 4.45 years, average HBA1c 10.14 ± 2.4%. The various infections found were: a simple dermohypodermitis 34.2%, complicated 8.3%, a folliculitis 4.2%, gangrene supply 9.2%, nasolabial cellulitis 10.8%, abdominal 5.8%, diaper abscess 10%, injection site 5%, back 8.3% and anthrax 4.2%. The front door was trauma (38%), intertrigo inter-toe (28.6%). Infections were related to neuropathy ($P = 0.02$). Clinical signs were fever (36%), infected site pain (60%) and asymptomatic 4%. The results achieved found a high CRP (65%), hyperleukocytosis (60%), abscesses unique to ultrasound (32.4%). Staphylococcus aureus and streptococcus were the main isolated organisms. Treatment consisted of intensified insulin therapy, antibiotic injectable monotherapy (60%), dual therapy (30%) and triple therapy (10%). Surgical drainage achieved in 40%. The evolution was favorable in 95% and 5% of patients lost to follow-up.
Conclusion
Our study highlights the high prevalence of infections in young people due to poor hygiene, the feature is sometimes the absence of germ found. The most often favorable evolution, the means of prevention by an education, the glycemic balance are necessary.

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P921

Diabetic foot education: patient satisfaction (about 151 cases)

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Introduction
Therapeutic education is the cornerstone of foot care for the diabetic patient. The purpose of this work was to evaluate the satisfaction of patients who have benefited from diabetic foot education sessions.
Methods
This is a prospective study involving 151 patients with risky feet who benefited from the diabetic foot awareness and education day in our service during the following period (January 2018 to December 2018). For this work, we used a satisfaction survey created by the doctor in charge and completed by the patients at the end of the education session. This survey was scored on a scale from 0 to 6 (the number 0 is 'not satisfied' and the number 6 is 'extremely satisfied').

Results
The average age of our patients was 54 years old (40–65 years old). The average duration of diabetes was 15 years (5–20 years). The average HbA1C of the patients was 9.6% (8.1–12.4%). 91% of our patients had Grade 2 feet according to the TEXAS classification. After the education session, the questionnaire showed that 78% of the patients were satisfied with the methodology and the course of the session, 70% of participants felt more involved in handling and monitoring their health problem. 83% of the cases found that the information they received was clear and simple and that the education sessions helped correct misunderstood foot care concepts and 82% of the patients were willing to recommend these education sessions to other patients.
Conclusion
Therapeutic education on the diabetic foot has had a beneficial impact on the involvement of patients in handling their pathology, and has improved the knowledge of our patients regarding foot care.

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P922

The cardio-metabolic profile of elderly patient with diabetes mellitus type 2 (about 300 case)

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Objective
Old age represents a real factor for many co-morbidities dominated by metabolic disorders and cardiovascular disease and, which are the major challenges of health. Diabetes in the elderly is the sixth leading cause of mortality at this age. Our study has the objective to assess the Cardio Metabolic profile among patients with type 2 diabetes in hospital environment.
Methods
It is a descriptive study conducted on 300 diabetics type 2, over 65 years of age, followed in our unit, during the period between April 2016 and October 2017.
Results
The average age was 71 $\pm$6.7 years (65–92) with a predominance of women (59.3%). Diabetes was unbalanced in 44.3% of patients with a duration exceeding 5 years in 70% of patients. All the subjects of our study have had degenerative complications like a type of microangiopathies: retinopathy (31%), neuropathy (50.3%) and nephropathy (40%), or a type of macroangiopathies (48.6%). In these patients the other cardiovascular risk factors found was: dyslipidemia (50.3%), hypertension (63.6%), smoking exclusively observed in male patients (14%), android obesity (21.3%), diabetic nephropathy (40%). A personal history of cardiovascular accident has been noted among 48.6% of our patients. The frequency of the metabolic syndrome diagnosed according to the criteria of the IDF (International Diabetes Federation) 2005 was 48%.
Discussion
The risk of cardiovascular diseases is increasing in parallel with age. The therapeutic preventive strategy requires a good medical management of diabetes and various associated risk factors. This study has shown that the association to cardiovascular risk factors is frequent among the elderly diabetics, which alters their quality of life and aggravates the functional and vital prognosis requiring a multidisciplinary coverage while knowing that the objectives and the therapeutic modalities will be adapted according to the patient the metabolic and age status.

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P923

Flash glucose monitoring system in children under 18 years old with diabetes mellitus type 1 in the southern hospital area of Granada: preliminary results

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Objective
To evaluate the baseline characteristics and their evolution three months after implantation of the Flash glucose monitoring System (Freestyle Libre), after financing by the Andalusian Health Service in patients under 18 years old with type 1 diabetes mellitus (DM1) in our hospital area.
Material and Methods
A descriptive observational and retrospective study that includes patients with DM1 under 18 years old from the southern hospital area of Granada who are implanted with the Flash System for glucose monitoring. Variables analyzed: sex, age, time of evolution of diabetes, previous HbA1c, period with glycemia ni range (70–180 mg/dl) and number of hypoglycaemias ($<$70 mg/dl) post-implantation of the system.
Results
Forty-two patients (54.8% were men), mean age 16.5 years. Median time of evolution of diabetes 5.95$\pm$4.71 years. 85.7% of patients were in treatment with bolus-basal therapy, 14.3% on ISCI therapy. Baseline HbA1c of 7.87$\pm$1.62%. All patients received a preimplantation education session of the device. After implantation, the average glucose was 177.18$\pm$41.9 mg/dl, with an estimated HbA1c of 7.61$\pm$1.3%. 59.5% of the patients presented glycemia within range (70–180 mg/dl) and 31% were above it. The number of hypoglycaemias register in that period was 11.78$\pm$12. Device usage: mean number of daily scans of 7.78$\pm$5.29 with an average of 77.04% of data captured by the reader. 9.5% of patients did not use the device, the main reasons were: disinterest on the part of the patient (7.1%) and one case due to problems with the device.
Conclusions
The preliminary results of the implantation of the flash system in a population younger than 18 years in our environment showed:
1. Tendency to improve metabolic control
2. An acceptable although improvable percentage of glycemias in rango
3. An optimal acceptance by the patients with an acceptable percentage of use.

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P924

Candidiasis infections in the diabetic About 307 cases

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Introduction
Unbalanced diabetes mellitus predisposes to bacterial and fungal infections especially candidiasis. Candidiasis can have several localizations including digestive, genitourinary or mucocutaneous. The purpose of this work was to analyze the characteristics of candidiasis in all these forms in the patient.
Materials and Methods
Descriptive cross-sectional study from January 2012 to December 2018, including 307 diabetic patients presenting with candidiasis and hospitalized in the endocrinology department of the Ibn ROCHD University Hospital of Casablanca. Collection of patient data was done from medical records. Oesogastroduodenal fibroscopy confirmed the diagnosis of gastrointestinal candidiasis. The statistical analysis was done with the software Epiinfo.7
Results
The mean age of our patients was 45.04 years (15–80), with a female predominance of 67.75%. Diabetes was type 2 in 204 patients with an average seniority of 6.40 years $\pm$ 5.29 and an average BMI of 27.94. The average glycemic level was 2.92 g/l and that of HbA1c was 10.12%. Candidiasis occurred in the wake of an inaugural ketosis in 5 patients, diabetic ketoacidosis in nine patients, major hyperglycemia in seven patients, chronic glycemic imbalance in 162 patients and in the wake of ketosis in 124 patients. It was genital in 149 patients or 48.53% (1balanite, vulvitis and vulvo-vulvitis vulvitis), oral in 115 cases or 37.45%, cutaneous in 43 cases or 14% affecting large folds, digestive in 21 cases or 6.84% and urinary in 6 cases or 1.95%. The majority of mycological samples isolated candida Albicans (80.36%) followed by candida Glabrata (19.64%). No other favorable factors have been found. Therapeutically, all our patients received antifungal treatment either by the general route (32.57%) or by the local route (67.42%). The evolution has been good in all cases.
Conclusion
Our study confirms that diabetes is an implicated factor in the occurrence of candidiasis so obtaining a glycemic balance would be necessary to prevent the occurrence of candidiasis

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P925

The diabetes mellitus type 2 in elderly patients: comorbidities and polymedication (about 300 cases)

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Objective
Polymedication is particularly common among elderly diabetes patients because of the frequency of co-morbidities, of certain chronic diseases and disabilities, of the growing demand for care, therapeutic progress, but also of some of the excess of requirements. The objective of our study is to assess the frequency of comorbidities in a population of elderly diabetic type 2, analyze the drug consumption.
Methods
It is a descriptive study conducted in 300 diabetics type 2, over 65 years of age, followed in our unit, during the period between April 2016 and October 2017.
Results
The average age of our patients was 71 ± 6.5 years with extremes of 65 to 92 years. Women represent 59% of our sample. Diabetes was unbalanced in 44.3% of patients with a duration of diabetes mellitus exceeding 5 years in 70% of patients. All of the subjects of our study have had degenerative complications like types of microangiopathies: retinopathy (31%), neuropathy (50.3%) and nephropathy (40%) or types of macroangiopathies (48.6%). Our results showed that 81% of patients suffer from between 2 and 5 chronic pathologies including dyslipidemia (50.3%) and hypertension (63.6%). Other co-morbidities were found in our population: 13.4% had mobility deficits and were totally dependent, depression in 2.6%, dental disorders among 58.3% as well as swallowing disorders among 7.6% and nutrition problems (assessed by MNA test) at 14.3%. The number of drugs prescribed (all galenic forms combined) exceeded three a day among 56.4% of our patients.
Discussion
Poly-medication is common among the elderly diabetic subject due to the association to other chronic diseases or the presence of complications. The high risk of adverse effects in this fragile population, as well as the frequency of mnestic disorders related to the age and the vascular troubles requires a good coordination between the different prescribers in order to avoid the abuse of prescription and to ensure the good therapeutic education of patients and their entourage.

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P926

Factors influencing the practice of physical activity in youth with type 1 diabetes mellitus

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Introduction
Physical activity (PA) improves physical performance and glycemic control in type 1 diabetes mellitus (T1D). Many factors determine access to a normal sporting life and therefore its benefits. The aim of this study was to evaluate the practice of PA in T1D and the factors influencing it.
Patients and methods
Descriptive and analytical cross-sectional study including any patient with T1D admitted to the Endocrinology-Diabetology department at Ibn Rochd University Hospital, over the age of 14 and diabetic over 6 months. Statistical analysis was done by SPSS.
Results
A total of 110 patients were included. The average age was 23 years old (14–48 years old). Mean A1c level was 9.2%. Among our patients, 29% practiced a regular sporting activity, 66% of the activities being limited to domestic work and daily life activities. Intensive activities were practiced by 25% of our patients. Only 23% of our patients had received therapeutic education on PA. Glycemic self-monitoring was only assured by 18% of patients. Hypoglycaemia was found in 45% of cases. The occurrence of hyperglycemia was less common. The lack of sports was more frequently related to lack of time (35%), fear of hypoglycaemia (30%), difficulty of access (23%) and limitation of physical capacity (20%).
Conclusion
Our study showed the need for therapeutic education and support for patients to control glycemic variations, wich remains the principal obstacle.

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P927

Reasons for consultation in diabetological emergencies

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Goal
Diabetes is a common condition, affecting the young and the elderly, which can lead to acute accidents such as ketoacidosis, diabetic ketosis, hypoglycemia and hyperglycemia with various decompensation factors, which may be of cardiac origin, neurological or infectious. The objective of the study was to clarify the epidemiological and clinical profile of diabetic patients, to establish the reasons for urgent consultations in diabetic patients.
Methods
Cross-sectional descriptive study for one year (August 2017–July 2018) carried out on the patient registers seen during this period, including all diabetic patients who consulted in the urgency of Ibn rochd Casablanca Hospital.
Results
502 diabetic patients were seen in the emergency department of Ibn Rochd Hospital Casablanca with an average age of 52.4 years. We noted a female predominance of 56.3%. Diabetes was type 2 in 390 patients (77.68%), type 1 in 110 patients (21.9%) and 2 patients (0.3%) had gestational diabetes. The reasons for consultation were dominated by diabetic ketosis with a prevalence of 22.3% followed by major hyperglycemia (21.3%), diabetic ketoacidosis (5.3%) and hypoglycaemia (5.3%). Revealing ketosis was found in 1.42% of cases. The decompensating factors found were foot infections with a frequency of 19.9% and other infections (urinary, bartholinitis, pneumopathies...) with a frequency of 6.17% each. Neurological disorders found in this population were mainly ischemic attacks with a prevalence of 2.14%, myocardial ischemia accounted for 0.36%. Only patients whose vital and functional prognosis were not involved were admitted to the service, the others were referred in intensive care, in neurology in cardiology, pneumology according to the clinical picture.
Conclusion
The involvement of the emergency department in the care of the diabetic patient and in prioritizing their urgency is necessary to optimize the resources available to the emergency physician.

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P928

Assessment of therapeutic education in diabetes patients on insulin at the pharmacy

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Introduction
Increasing the prevalence of chronic diseases, including diabetes, is an important public health issue. Beyond the actions already carried out in pharmacies, the place of the pharmacist is essential in the therapeutic education (ETP) and the actions of accompaniment of the patients. The objective of our work was to evaluate the level of education of patients in insulin therapy at the pharmacy level and to deduce the reasons for poor compliance.
Patients and Methods
Prospective study conducted over 3 months in patients presenting themselves voluntarily in several pharmacies of Casablanca. The variables studied were the characteristics of diabetes and the level of education in insulin therapy. The data was analyzed by SPSS version 25.
Results
Our series included 50 diabetic patients, mean age 51.3 ± 17.2 years, sex ratio 0.72 H/F, married (56%), mean BMI 25.3 kg/m^2 and predominant type 2 diabetes (70%). An average HbA1c of 8.5 ± 1.72%. Degenerative complications were retinopathy (6%), neuropathy (2%), hypertension (9%), dyslipidemia (11%). The type of insulin used was analogs (94%), human insulin (6%). An education on insulin therapy received by the attending physician (78%) and the nurse (22%). The glycemic imbalance was strongly correlated with the frequency of hypoglycemia (78.5%, RR 0.09, 95% confidence interval [CI]: −0.53 to −0.02, $P = 0.04$, $r = -0.3$). Therapeutic compliance related to confidence in the efficacy of treatment (good 48%, $P = 0.04$) and knowledge about the rules of insulin therapy (76%, $P < 0.0004$). The factor of poor compliance was mainly bleeding from the injection mark (64.7%, $P = 0.012$).

Conclusion
Our study found that the pharmacist-led drug dependence monitoring program can improve optimal diabetes management by involving patients in the health care team. The ability of the clinical pharmacist to build trusting relationships with patients and providers is critical to the success of such a program.

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P929

Idiopathic versus autoimmune type 1 diabetes – long-term differences

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Introduction
The American Diabetes Association proposed two subcategories for type 1 diabetes: autoimmune type 1 diabetes (ADM) and idiopathic type 1 diabetes (IDM). The absence of β-cell autoimmune markers and lack of association with HLA haplotypes define the second category, whose pathogenesis remains unclear. Only a minority of patients with type 1 diabetes fall into this subcategory which is considered by several authors similar to type 2 diabetes.
Objective
The aim of this study is to compare long term (ten years) differences between these two categories.
Methods
Retrospective cohort study, based on clinical records of patients with undetectable c-peptide, in which β-cell autoimmune markers were performed (islet cell antibodies, insulin antibodies, glutamic acid decarboxylase antibodies, islet antigen-2 antibodies). Only patients with assays at the time of the diagnosis of diabetes were considered and were excluded patients with suspicion of another specific type of diabetes. We obtained two groups of patients: ADM - with positive autoimmune markers ($\geq$ 1 positive antibody), and IDM - with negative autoimmune markers. We analysed the following differences: body mass index (BMI), A1C, lipid profile, hypertension, total diary dose of insulin (TDDI), microvascular and macrovascular complications. Statistical significance - P value 0,05.
Results
We obtained 37 patients, 29 with ADM - median age 23,0(9) years; and 8 patients with IDM - mean age 38.1 $\pm$ 12.8 years. Evaluation of BMI showed no statistical difference between groups (ADM:25.14 kg/m^2; IDM: 22.58 kg/m^2; P=0,079). Relative to A1C we found statistical difference, (ADM:8.7%; IDM: 7.4%; P= 0.008) as well as the TDDI (ADM:52.35 units; IDM:33.5 units; P=0.017). Although there was no difference in the proportion of patients with dyslipidaemia, it was higher on the ID group (44.8%-ADM; 62.5%-IDM). Relative to the lipid profile (total cholesterol, LDL and HDL cholesterol and triglycerides), there was no significant difference, however the LDL cholesterol and triglycerides were higher on the IDM group. The proportion of patients with hypertension was higher on IDM group (17.2%- ADM; 25%- IDM group), although there was no significant difference. Relative to microvascular complications, there was no difference in the proportion of retinopathy, neuropathy and nephropathy, but that was higher on the ADM group. There was no difference on the macrovascular disease.
Conclusion
This study showed that at long-term follow-up, patients with ADM have a poor metabolic control, with higher A1C and higher TDDI. Although no significant, patients with IDM have a tendency to more comorbidities (hypertension, dyslipidaemia) and lower microvascular complications.

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P930

Whole body cryotherapy effect on weight gain and metabolic parameters of metabolic and type 2 diabetic patients

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Introduction/Aim
The incidence of type 2 diabetes in Belarus continues to grow. Alongside with the standard treatment search for the new methods of intervention still continued. Whole body cryotherapy appears to be a promising method of metabolic correction. Study aim was the estimation of various low-temperature regimen influence on biochemical parameters and BMI characteristics of patients with metabolic syndrome and type 2 diabetes and selection the optimal low-temperature intervention routine.
Methods
A target group — adult patients with diagnostically proven type 2 diabetes, or metabolic syndrome were selected for the study. The protocol of low temperature influence supposed two regimens — intensive (10 procedures 2 times a week) and mild (10 procedures, once a week) whole body cryotherapy. Alongside, a standard treatment intervention was performed without additional modification: life-style correction, diet correction, medication agents — metformin + glycemia lowering drugs if required, in standard dosages. Anthropometry for BMI, waist circumference, blood pressure and blood samples for biochemical and cytokine parameters were measured before the beginning of the intervention and 3 months after the entrance to the research. The protocol was approved by the institutional ethics committee and informed consent was received in all participating patients.
Results
A group of 51 patients volunteered to take part in the study. Average age was 34 $\pm$ 7.4 years (M $\pm$ SD), BMI in all patients was in the range between 26.5 – 30.2 kg/m^2, glicated hemoglobin varied from 5.8 to 6.1% and in type 2 patients exceeded 6.2%. In 2 months after the cryotherapy course, both intensive and mild, patients with type 2 diabetes showed significant imrovement of glycaemic levels (6.2 $\pm$ 0.75 mmol/l for mild and 5.6 $\pm$ 1.32 mmol/l for intensive cryo-treatment) and non-significant reduction of HbA1c. Leptin levels were reduced more effectively, compared to initial findings, in a prolonged cryo-treatment (24.97 $\pm$ 12.8 ng/ml) vs. intensive – 28.3 $\pm$ 22.04 ng/ml. Metabolic syndrome patients have had a similar protective shift of leptin levels in case of more intensive, but not prolonged treatment.
Conclusion
Whole body cryotherapy showed to be an effective additional method for compliance improvement in all groups of patients, being especially effective in metabolic syndrome group, helping patients to improve biochemical parameters and reduce the weight gain with the short, but high intensity of influence, while mild cryo helped type 2 patients to reduce average glycemic and leptin levels. A long-term effect of the single short term intervention still requires further observation.

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P931

Sexual dimorphism in the mechanisms for insulin resistance

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Insulin resistance (IR) is a condition where beta cells are producing insulin, sometimes in large amounts, but the peripheral targets develop an inadequate response to the hormone. Classically insulin resistance has been associated with pathologic conditions. However, there is also physiological IR, associated with the last period of pregnancy and in different moments of the development. We have previously characterised a period of physiological IR, around the ablactation period, in male Wistar rats. We have also described insulin resistance in the metabolic syndrome due to 20% sucrose in drinking water in the same animal. The objective of this work was to identify changes in insulin signalling in adipose tissue and skeletal muscle in Wistar, comparing males and females. We observed that at 20 postnatal day (20 pnd) both sexes present glucose intolerance, compared to adult animals. The peripheric response to insulin and the insulin-stimulated glucose-uptake was lower at 20 pnd, compared to adults. At 20 pnd phosphorylation of the threonine 389 site in the kinase P70S6K was higher in adipose tissue than in muscle. Moreover, the phosphorylation of serine 473 site in Akt was more elevated in adipose tissue and lower in the muscle of 20 pnd rats, compared to adults. Interestingly, the phosphorylation of serine 101 site on IRS1 was higher in adipose tissue of males than in females. These observations suggest that over-activation of the kinase P70S6K during development down-regulates the insulin signalling way. In both sexes, but more in males than female rats GH levels are higher than in adults. This fact could also contribute to the insulin resistance at this stage. It is clear from this date that IR shows sexual dimorphism. The adult model of metabolic syndrome also shows an evident sexual dimorphism, being faster

more affected males vs females. Sexual hormones could be contributing to this phenomenon, but there are other variations in this type of dimorphism. Supported by: Conacyt CB-253222, PAPIIT UNAM IN210817 y 213114, Mexico.

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P932

Glucosuric drugs + immune checkpoint inhibitors: A recipe for diabetic ketoacidosis?

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Introduction/Aim
Diabetic ketoacidosis is a rare complication in type 2 diabetic patients treated with SGLT2 inhibitors; usually there is a triggering factor (major trauma or surgery, sepsis) or misdiagnosis (type 1 diabetes or LADA). Nivolumab is an anti-CD279 monoclonal antibody used as a second-line immunotherapy in non-small cell lung carcinoma; its use has been associated with fulminant type 1 diabetes and other autoimmune endocrine diseases. We hereby present a case of diabetic ketoacidosis in a type 2 diabetic patient, in order to raise awareness of the possible interaction between nivolumab and SGLT2 inhibitors.
Material and Methods
Review of the patient's clinical record and of the relevant literature.
Results
A 59 year old, ex-smoker patient had been diagnosed with type 2 diabetes at 49, and treated with basal insulin plus metformin and empagliflozin in the last 2 years.He had no metadiabetic complications, and required no prandial insulin but his metabolic control was suboptimal (HbA1C 7.7%). After a chest x-ray showed a 4 cm lung mass he was diagnosed with epidermoid carcinoma of the lung, stage IIIB (cT2N3M0), and received treatment with radiotherapy (total 111 Gy, with good tolerance) and chemotherapy Paclitaxel + carboplatinum), followed by immunotherapy with nivolumab. After the third nivolumab session, the patient reported hyperglycemia with capillary blood glucose > 400 mg/dL and his basal insulin dose was increased; however a week later he was admitted in the Emergency Room with diffuse abdominal pain, nausea and vomiting, without fever or diarrhoea. Diabetic ketoacidosis was diagnosed (venous pH 7.17) and standard therapy with iv fluids, insulin and HCO3 was prescribed. The evolution was favorable but after the discharge the patient's glycemia could only be controlled with basal + prandial insulin, and his anti-GAD antibodies had turned intensely positive. A few weeks later, the patient also developed primary hyperthyroidism, in relationship with autoimmune thyroiditis, which is the most common endocrine adverse effect of nivolumab.
Conclusions
The interaction between empagliflozin and nivolumab has not been established so far, but the well-known ketogenic effect of SGLT2 inhibitors may have facilitated the triggering of diabetic ketoacidosis by nivolumab in our patient. We conclude that ketogenic drugs such as empagliflozin should be avoided in patients treated with nivolumab.

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P933

The Oral status of elderly patient with diabetes mellitus type 2: a real factor of risk of malnutrition (about 300 cases)

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Introduction
Oral disorders are quite frequent in patients with diabetes mellitus type 2 in particular elderly patients. Their presence at this type of persons may influence the glycemic balance and entail a reduction of the masticatory potential with a risk of malnutrition. The purpose of the work is to establish the relationship between the oral disorders and the nutritional status of the elderly subjects with diabetes mellitus type 2.
Patients and Methods
This is a descriptive study conducted in 300 diabetics type 2, over 65 years of age, followed in the service of Endocrinology, Diabetology and nutrition of the CHU in Casablanca during the period between April 2016 and October 2017. We assessed the nutritional status by MNA (mini nutritional assessment)
Results
The average age of our patients was 71 ± 6.5 years with extremes of 65 to 92 years. Women represent 59% of our sample. Diabetes was unbalanced in 44.3% of patients with an illness duration exceeding 5 years in 70% of patients. The oral dental disorders -were present in 58.3% of patients with swallowing disorders in 7.67% of cases. A bad oral health state with the presence of dental caries was found in 28.3% of patients, 17.6% had a dental prosthesis poorly adapted, 7.6% complained of a dry mouth, 2.6% of patients were toothless and 3 patients reported dysgeusia. The evaluation of the nutritional status of these patients has shown that 54.2% had a risk of malnutrition and 19.4% were malnourished. The comparison of this group with the other patients of the sample having a good oral state showed a statistically significant association between the presence of oral disorders and risk of malnutrition ($P = 0.00002$) as well as the presence of malnutrition ($P = 0.00001$).
Conclusion
Our study reveals that the frequency of oral disorders in elderly diabetic patients. These disorders can foster malnutrition and may influence the vital prognosis, hence the importance of the systematic evaluation of oral state of our elderly diabetic patients.

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P934

Glycemic equilibrium of cancer patients with diabetes

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Introduction
Diabetes and cancer are common, chronic and life-threatening diseases that coexist frequently. In addition, many cancer patients are already diabetic or are developing hyperglycemia as a result of a tumor or anti-cancer therapies. The aim of our work was to evaluate the glycemic balance of diabetic patients with cancer and its impact on the prognosis of the disease. Patients and methods: This are a prospective study carried out within the endocrinology department of IBN ROCHD CHU Casablanca, in one year from 2017–2018. The statistical analysis done by SPSS version 25.0.
Results
We included in our study 69 patients, mean age of 56.3 ± 12.45 years with a male predominance of 55%. An average BMI of 23.6 ± 5.3 kg/m^2, an average HBA1c (9.7%) with a self-monitoring glycemic (30.4%) and an irregular follow-up (76%). Degenerative complications include retinopathy (43.5%), nephropathy (20.3%), neuropathy (27.5%), hypertension (20%). Ketosis decompensation (40.6%). The treatment for diabetes consisted of insulin therapy (72.5%) and oral antidiabetic drugs (24.7%) with insulin therapy in 15.7%. A frequency of glycemic surveillance (52.3%). The cancers found were cerebral (2), Stomatological (2), Thyroid (2), Bone (2), Urinary (3), Digestive (5), Pancreas (6), Otorhinolaryngology (7), Pulmonary (8), Gynecology -mammary (10), Hematologic (22). After adjuvant treatment, observed remission (14.5%), healing (4.35%). Glycated hemoglobin was strongly correlated with cancer prognosis (Poor 37.7%, [RR] 0.59, 95% confidence interval [CI] 0.42-0.73, $P < 0.0001$), but not related to risk of infection ([RR]: 0.0026, 95% confidence interval [CI]: -0.28 to 0.18, $P = 0.67$).
Discussion/Conclusion
Diabetes and cancer comorbidity requires rigorous management in order to optimize self-management and to obtain an appropriate glycemic balance in this context of particular clinical fragility and to improve the vital prognosis of these patients which can be engaged in acute complications of diabetes or opportunistic infections.

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P935

Management of diabetic patients with cancer

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Introduction
Managing people with diabetes and cancer during palliation is a major challenge. The aim of our work was to study the specific characteristics of diabetic people with cancer, to identify management modalities of management during cancer treatment.
Patients and methods
Prospective study including 100 diabetic patients with cancer followed in the different services of Ibn Rochd University Hospital of Casablanca between 2017 and 2018. Variables studied were the characteristics of diabetes and tumors. Statistical analyzes were performed by SPSS version 25.0.
Results
The mean age of our patients was 59 years with a sex ratio of 1.23, an average BMI of 24 ± 5.3 kg/m^2, a type 2 diabetes predominating 74%, average seniority of 7.2 years and an average HBA1c of 9.7 ± 2.3%. Parenteral nutrition (12%). During adjunctive therapy diabetes was decompensated in ketosis mode (29%) and hyperglycemic (34%), 39% of patients were initially treated with oral antidiabetic agents requiring the use of intensified insulin therapy. The various cancers found were cerebral (2%), Otorhinolaryngology (7%), Stomatological (2%), Thyroid (2%), Pulmonary (8%), Pancreas (33%), Digestive (5%), Urinary (3%) %), Gynecologic (14%), Bone (2%), Hematologic (22%). 56% had a relapse, disabling pain reported (10%) with opioids, cognitive instability (10%), sleep disorder (15%) and opportunistic infections (43.5%) undergoing antibiotic therapy. The cancer treatment consisted of an iratherapy (2%), hormone therapy (4%), surgery (18%), chemotherapy (26%), combined (40%) and 20% under steroids. Despite patient empowerment and structured interventions, an education on diabetes management and psychological support for the family in 90% and 10% had a poor prognosis.
Conclusion
The therapeutic management of a person with diabetes associated with cancer requires a multidisciplinary involvement, in order to find a balance between therapy and the patient's well-being in a disabling chronic disease.

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P936

Let use results of foot examination for guiding diabetes mellitus therapy

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Background and aims
After two decades of silence in classification system od type 2 diabetes there are some indices that the dibebtic retinopathy might be the sign for introduction of insulin therapy. The aim of this study was to examine associations between measures of diabetic foot in people with diabetes complicated by nonproliferative retinopathy (NPDR), maculopathy and proliferative retinopathy (PDR).
Materials and methods
People were included had following clinical examinations: fundoscopy, VPT(vibration perpection threshold), ankle reflexes (AR), sudomotor function using Neuropad, Continous wave Doppler and biochemical investigations. Presence of hypertension, cardiovascular disease, neuropathy symptom score (NSS) were documented. All tests were undertaken as part of routine clinical care.
Results
Of 469 people, 46.1% were male and 68.4% had T2DM. 252 had no evidence of retinopathy, 89 had NPDR 98 had maculopathy, 30 had PDR. Compared with people without retinopathy, those with retinopathy were older (58 ± 12.5 vs 52.3 ± 15.1 years), with lower VPT (5.1 ± 2.8 vs 6.6 ± 2), more often with missing AR (2.9 ± 1.3 vs 2.0 ± 1.6), higher prevalence of LEAD (18.4% vs 7.9%) and arterial hypertension (52.9% vs 36.5%), higher waist circumference (96.3 ± 12.6 vs 91 ± 13.6 cm) and longer diabetes duration (18.2 ± 8.7 vs 12.2 ± 8.6years); all $P < 0.01$. After multivariable logistic regression analysis (MVLR), the differences in VPT, AR and diabetes duration all persisted ($P < 0.01$). People with PDR compared with controls had worse VPT (3.8 ± 3.3 vs 6.6 ± 2; $P < 0.001$). In a univariate model PDR was related to creatinine (OR 1.014 (95% CI: 1.005–1.023)), triglycerides (1.022 (1.02–1.46)), duration of insulin therapy (1.057 (1.015–1.101)); all $P < 0.01$. After MVLR the differences remained significant ($P < 0.01$) for creatinine and duration on insulin therapy. People with maculopathy had worse sudomotor neuropathy (10 ± 7.3 vs 7 ± 5.7min; $P < 0.001$). In a univariate model maculopathy was related to NSS (OR 2.19 (1.35–3.04)), Neuropad time (1.07 (1.033–1.109)); T2DM (77.6 vs 62.3%), HbA1c 1.083 (1.058–1.108)); all $P < 0.01$, and to fasting cholesterol (1.035 (1.05–1.71); $P = 0.02$). After MVLG the significance remained: for NSS, Neuropad time, HbA1c (all $P < 0.05$). Both PDR and maculopathy in univariate analyses was related to proteinuria (OR 1.000 (1.0–1.001)) and after MVLR with creatinine clearance (0.976 (0.98–0.99)) and highest life BMI (1.067 (1.029–1.106)); all $P = 0.000$.
Conclusion
Our data showed associations between the presence of different clinical measures and peripheral neuropathy with both retinopathy and kidney disease. Diabetic neuropathy reinforce the need to strive to optimise metabolic control, including introduction of insulin therapy, on time.

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P937

MicroRNA-26a, microRNA-33a, and microRNA-33b in patients with obesity: association with coronary artery disease

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Introduction
Obesity and type 2 diabetes mellitus (T2DM) are commonly associated with coronary artery disease (CAD). Recent studies demonstrated that microRNAs (miRNAs) are involved in the pathogenesis of CAD.
Aim
To study miRNA-26a, microRNA-33a and microRNA-33b expression in patients with obesity.
Methods
MiRNAs were detected in peripheral blood samples of 66 patients, aged 48–65 years. Patients with BMI 30.0–39.9 kg/m^2 were divided into 3 groups. The 1st group included 21 patients with CAD (confirmed by coronary angiography) and T2DM, the 2nd group – 22 patients with T2DM and excluded CAD (according to the treadmill test), the 3rd group – 23 patients with obesity and excluded CAD and T2DM ('healthy obesity'). RT-qPCR assays were used for miRNA detection.
Results
Expression of miRNA-33a was significantly different in the studied groups ($P = 0.009$). MiRNA-33a was positively correlated with brachiocephalic arteries stenosis ($r = 0.453$; $P = 0.039$). MiRNA-33b was positively correlated with BMI ($r = 0.293$; $P = 0.008$) and HbA1c ($r = 0.269$; $P = 0.016$). MiRNA-33b was positively correlated with the thickness of interventricular septum ($r = 0.281$; $P = 0.012$); negatively with ejection fraction ($r = –0.397$; $P = 0.0003$) and triglycerides ($r = –0.551$; $P = 0.009$). In the third group, miRNA-33a and b were positively correlated with waist circumference ($r = 0.444$; $P = 0.034$ and $r = 0.438$; $P = 0.036$, respectively); negatively with cholesterol ($r = –0.419$; $P = 0.046$ and $r = –0.489$; $P = 0.018$, respectively). MiRNA-33b also negatively correlated with brachiocephalic arteries stenosis ($r = –0.474$; $P = 0.022$). MiRNA-26a expression was lower in patients of the 1st group (with T2DM and CAD ($P = 0.003$). In the first group of patients, miRNA-26a was positively correlated with LDL-cholesterol ($r = 0.541$; $P = 0.011$) and waist circumference ($r = 0.481$; $P = 0.027$). MiRNA-33a and -b were positively correlated with miRNA-26a ($r = 0.375$; $P = 0.001$ and $r = 0.353$; $P = 0.001$, respectively).
Conclusions
Expression of miRNA-33a differ in patients with CAD, T2DM, and 'healthy' obesity. MiRNA-33a and miRNA-33b were positively correlated with heart remodeling processes and therefore may determine the severity of cardiovascular disease in patients with obesity.

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P938

Transition of young adults with type 1 diabetes

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Introduction
The transition period to young adult counseling is a crucial period for the diabetic patient. A poor transition exposes them to a risk of disengagement from the health system and mismanagement of diabetes. The objective of this work is to describe the progress of the transition and to deduce the facilitating and restraining elements.
Patients and methods
This were a retrospective study of 120 referred diabetic type 1 patients from the pediatric diabetology department or other centers and managed by the Department of Endocrinology and Diabetology of the IBN ROCHD CHU between 2017 and 2018. The statistical analysis done by the Spss software version 25.0.
Results
The mean age at the time of transition was 15.7 ± 2 years, with a sex ratio of 0.82 H / F, mean glycemic balance (HBA1c) of $9 \pm 2.4\%$. Degenerative complications, Retinopathies (22.5%), Nephropathies (15.8%), Neuropathies (13.3%), HTA (10.8%), Dyslipidemia (5%). The associated pathologies were anemia (12.5%), hypothyroidism (19.2%), Addison's disease (12.5%). The transition was initiated by the pediatrician (58.3%), the patient himself (24.2%) and the general practitioner (17.5%). The time between receipt of the information and the last pediatric visit was 2.4 months. The ad judged at the right time 75.8% and regarding the feeling 12.5% were worried and 5% curious. Hypoglycemia was present (60%). Hospitalizations after transition 65.8% vs 50%. The treatment regimens were 79.2% basal-bolus and 20.8% premix vs 60% and 40% before transition. We noted a discontinuation of insulin therapy in 35.8% and 18% of patients reported self-monitoring of less than 3 times/week only and an irregular follow-up in 21.7%. The observed failure rate (12%). The facilitators were age at transition, parent support 58.3%, family member 31.7%, and good relationship with the health care team (55%) ($P=0.006$), $r=0.41$). And obstacles, poor adhesion to autonomy by fear and worry (16.3%), hypoglycemia, the number of hospitalizations to more than 3 (20%). The transition was beneficial 90%.
Conclusion
Continuity of care is needed to improve the quality of management of diabetic patients and cannot be achieved without a close relationship between pediatric specialists and adult physicians. Hence the need to structure this transition period.

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P939

Prevalence and predictive factors of advanced fibrosis in type 2 diabetic patient in a majoritally abstinent population of alcohol

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Introduction
Metabolic steatopathy is frequently associated with type 2 diabetes, which may progress to advanced fibrosis. The objectives of this study were to evaluate the prevalence and predictors of the severity of hepatic impairment in this population.
Methods
A cross-sectional study involving 281 type 2 diabetic patients followed in the endocrinology department in collaboration with the Hepato-Gastroenterology department of Ibn Rochd University Hospital in Casablanca between January 2018 and September 2018. Severity of liver injury was evaluated by the Fib4 score calculated according to the following formula: age x AST (U/L)/Platelets (109/L) $\times$ ALT (U/L)$^{1/2}$. A Fib4 score >3.25 is predicted advanced fibrosis. Statistical analysis was performed by SPSS 25.
Results
281 diabetic patients were included, 215 women and 66 men. The mean age was 54.15 ± 13.45 years old. 7% were smokers and only 1.4% of cases were ethyl (<20 g/d). The mean duration of diabetes progression was 10.5 ± 8.5 years. A BMI $\geq$ 30 kg/m^2 was found in 122 patients (43.4%). The ALT average was 22.01 ± 18.59 IU/L and ASAT was 21.33 ± 16.80 IU/L. Hypertriglyceridemia was found in 105 of patients (37.4%) and hypoHDLemia was found in 63 of patients(22.4%). The average Fib4 of the patients was 1.05 ± 0.72. 227 (80.8%) patients had a Fib4 <1.45. 46 patients had Fib4 between 1.45 and 3.25, and 8 patients (2.8%) had an advanced fibrosis with Fib4$>$ 3.25. In multivariate analysis, independent factors related to advanced liver fibrosis were the duration of diabetes (OR $=1.60$, $P<0.01$), elevated AST (OR $=0.99$, $P<0.03$), hypoHDLemia (OR $=1.53$, $P<0.001$) and hypercholesterolemia (OR $=1.32$, $P<0.05$).
Conclusion
Advanced fibrosis was only found in 2.8% of non-alcoholic diabetics. The low rate of alcohol users could explain our results. Duration of diabetes progression, dyslipidemia and elevated AST levels were predictive factors for advanced fibrosis.

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P940

The metabolic profile of diabetic patients during the month of Ramadan

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Introduction
Diabetes is considered by some to be a burden, it is common to meet diabetic Muslims who wish to observe the fast of the month of Ramadan. The objective of our work was to observe the effect of Ramadan fasting on clinical and metabolic parameters in type 2 diabetics.
Patients and methods
Prospective study including 160 diabetic patients, within the Endocrinology department from May to August 2018. The participants benefited from a pre (T0), per and post-Ramadan (T1) education. Anthropometric measurements and biological parameters were performed during these periods. Statistical analysis done by Spss version 25.0.
Results
We found 68.75% of fasting and 31.25% of non-fasting, a sex ratio of 0.7 H/F, a mean age of 53.3 ± 11.2 years, low school level in 70.6% and a family life of 81.2%. The duration was 10 ± 8 years, an irregular follow-up in 10.6%. An average HBA1c of T0: $8 \pm 2\%$, T1: $7.5 \pm 1.3\%$, $P=0.07$. Complications identified were: 38% hypoglycemia, 39% hyperglycemia, 35% retinopathy, 20.6% nephropathy, 27% neuropathy, 14.4% coronary artery disease, 34.4% hypertension, and dyslipidemia of 35.6%. The clinical examination noted an average BMI of 32.4 ± 8 kg/m^2 and a controlled blood pressure of 13 ± 1.6 cmhg. As dietary intakes were reduced, we noted a 2.3 ± 1 kg weight loss after Ramadan, a significantly improved fasting blood glucose level: 1.36 ± 0.4 vs 1.46 ± 0.4 g/l ($P=0.0001$). At the paraclinical, a decrease in LDL and total cholesterol of 0.25 ± 0.2 g/l ($P<0.0001$), an increase in HDL of 0.06 g/l. We did not notice any difference for triglycerides, calcemias and protidemias. In contrast, a decrease in serum uric acid of 4.74 ± 1 mg/l.
Conclusion
These data suggest that fasting could be particularly beneficial for the diabetic as a nutritional intervention. However, these effects may be transient, given the short duration of the Ramadan period, which exposes to risks of complications or deterioration of metabolic control due either to the observance of fasting or the disruption of food intake.

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P941

Increased serum resistin levels in metabolically unhealthy compared to metabolically healthy obese individuals; correlation with circulating white blood cell subpopulations

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Background
Obesity is associated with chronic low-grade inflammation that contributes to the development of metabolic syndrome (MS). Resistin, produced by neutrophils and

monocytes, displays potent proinflammatory properties and has been associated with cardiometabolic disease. The aim of this study was to (a) determine serum resistin levels among obese patients with or without MS and (b) explore the role of the subsets of circulating white blood cells as potential determinants of serum resistin levels in these subjects.
Methods
58 obese (33 metabolically unhealthy obese (MUO) and 25 metabolically healthy obese (MHO)) and 25 metabolically healthy lean (MHL) individuals participated in the study. Absolute and relative counts of circulating white blood cell subpopulations were determined and serum levels of high sensitivity C-reactive protein (hsCRP) were measured. Absolute blood counts of classical (Mon1A), intermediate (Mon2A) and nonclassical (Mon3A) monocyte subsets were measured by flow cytometry and serum resistin by enzyme-linked immunosorbent assay (ELISA). Comparisons were adjusted for gender and age.
Results
Log serum resistin levels in MHL controls were similar to those in the obese ($P=0.131$) and MHO ($P=0.612$) groups but lower compared to the MUO group ($P=0.037$). Moreover, in the MUO obese group, both log circulating resistin ($P=0.032$), Mon2A ($P=0.036$) and NeuA were higher compared to MHO ($P=0.033$). The difference in resistin levels disappeared after adjustment for NeuA. Obese patients were characterized by increased absolute neutrophil count (NeuA) ($P=0.026$), Mon2A ($P=0.001$) and Mon3A ($P=0.017$) compared to MHL individuals. Log resistin correlated positively with absolute count of total monocytes ($r=0.560$, $P=0.037$) in MHL, and with BMI ($r=0.309$, $P=0.023$), hs CRP ($r=0.311$, $P=0.022$) and NeuA ($r=0.278$, $P=0.044$) in obese patients. The resistin association with BMI disappeared after adjustment for hsCRP, while the association with hsCRP disappeared after adjustment for NeuA.
Conclusions
Serum resistin levels, absolute counts of circulating neutrophils and proinflammatory monocytes were higher in metabolically unhealthy obese compared to metabolically healthy obese individuals. In obese subjects, serum resistin levels correlated with the number of circulating neutrophils.

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P942

Discharge in the diabetic foot: means, indications and observance: about 102 cases (preliminary results)

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Introduction
The diabetic foot is a major public health problem with a significant socio-economic impact. In the presence of a trophic disorder land filling is a key element of care. The objective of our study is to identify the means and indications, to evaluate the contribution of the discharge in the prevention and the cicatrization of lesions of the diabetic foot.
Methods
This was a prospective study conducted from September 2017 to July 2018. Included were 102 diabetic patients followed for diabetic foot in the service of Endocrinology and Metabolic Diseases having a diabetic medical foot. The data was collected based on an exploitation sheet. The statistical analysis was performed using SPSS software version 25.0.
Results
A 63% male predominance, a mean age of 51 years, T2D was 85%, with an average seniority of 16 years, 72% were insulinotrates. Neuropathy was found in half of the cases. Lesions were 40% of cases of mixed ulceration, MPP accounted for 30%, 23% of patients had osteitis, 5% of acute phase Charcot foot. The Barouk shoe was the most used means of discharge in 66% of cases with an average duration of 1 month mainly in the MPP. Bed rest was indicated in 28% of cases in bilateral lesions and acute Charcot on average 2 weeks with orthopedic shoe prescription thereafter. Healing was complete in 83% of the patients who complied with the discharge. In addition, other measures such as glycemic control and diabetic foot education have been combined.
Conclusion
The land fill of the diabetic foot is the first treatment essential for the healing of foot lesions, requiring awareness of patients, caregivers and consultation with podiatry status for better optimization.

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P943

Drug interactions in diabetic patients

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Introduction
The frequent polypharmacy in diabetic patients, because of the complications of the disease, drug interactions can occur when two or more drugs are taken in combination. The objective of our work was to determine the relative frequency of these drug interactions, to identify the types and to evaluate the impact or the repercussion of these in the diabetic, in order to deduce the practical behaviors.
Patients and methods
Prospective study, conducted over 3 months from December 2017 to February 2018 in the endocrinology department of Ibn Rochd University Hospital, in 50 diabetic patients. The prescriptions were analyzed using the Vidal database.
Results
The mean age of the patients was 53 years (22–84). The sex ratio of 0.23 H/F, an average BMI of 29.58 kg/m^2. Predominant type 2 diabetes (84%), mean age of 11.48 years, mean HbA1c of 10.81 (6.2%–14.3%). Degenerative complications: Retinopathies (18%), nephropathies (4%), neuropathies (56%) and comorbidities: hypertension and dyslipidemia (58%), IDM and AOMI (4%). The number of prescriptions per prescription was 7.18, self-medication (12%) and drug interactions (52%), 2 per prescription. We noted precautions for use (71%), associations to take into account (26%) and disadvised (3%). No contra-indications were noted. The main categories of drugs at the origin of interactions: antihypertensives (98%) (calcium blockers (ICA), beta-blockers, converting enzyme inhibitors (IEC), diuretics…), insulins (96%), Oral antidiabetic agents (74%) (Biguanide, hypoglycemic sulfonamides, GLP-1 analogue), antibiotics (72%) (fluoroquinolones, cephalosporins 3G), and statins (52%). The most common adverse events observed were hydroelectric disorders with hyperkalemia (17%), hypokalemia (1%), hyponatremia (9%). The most common potential risks were hypoglycemia (19%) and low blood pressure (14%). The majority of the patients affirmed the respect of the medical prescription.
Conclusion
Particular vigilance should be given to this population in order to minimize the clinical occurrence of major drug interactions in diabetic patients.

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P944

The impact of cigarette smoking on metabolic syndrome in diabetic patients type 2: about 322 cases

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Introduction
Cigarette smoking is a modifiable cardiovascular risk factor, inducing and aggravating insulin resistance and metabolic disorders, especially in patients with type 2 diabetes (DT2). Our objective was to study the prevalence of the different components of the metabolic syndrome in patients with comparing with a group of non-smoking diabetics.
Patients and methods
This was a cross-sectional study conducted in the Diabetology, Endocrinology and Metabolic Diseases department of the Ibn Rochd Hospital of Casablanca between 2016 and 2018, involving 322 patients with type 2 diabetes (T2D) divided into two groups., the first one is group of smokers (G1, $n=98$) and the second one is group of DT2 (G2, $n=224$) who have never smoked. The different metabolic syndrome parameters defined according to the criteria of the International Diabetes Federation (IDF) were studied in both groups.
Results
Of the 322 patients with type 2 diabetes, 30.4% were smokers (G1) with a mean age of 41 ± 2.4 years and a male predominance in 89% of cases. The results of the comparative study between the 2 groups showed that the smoker group had a lower BMI, a higher average HbA1C, a higher waist circumference and more frequent lipid abnormalities ($P<0.01$) than the G2. Moreover, there was no significant difference between the 2 groups compared to HTA (89% vs 80%). For degenerative complications, coronary artery disease, arterial disease, and diabetic nephropathy were significantly higher in the smoker group (G1) ($P<0.01$)

Conclusion
The results of our study confirm that smoking associated with diabetes increases the risk of degenerative complications by worsening metabolic syndrome. Smoking cessation is typically recommended to reduce cardiovascular risk, it also allows an objective improvement of insulin resistance and lipid disorders.

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P945

The association between glycemic control and hip fracture risk – a retrospective Cohort study

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Introduction
Fragility fractures are increasingly recognized as a complication of diabetes mellitus (DM). Disease duration, poor glycemiccontrol, diabetes complication, and glycemic variability may be associated with increased risk.
Aim
To investigate the association between glycemic control and hip fracture (HF) risk in a cohort of diabetic patients.
Methods
This retrospective cohort study included all patients 50 years and older with ICD-9 diagnosis of DM or HbA1c measurement $\geq$6.5% between 2001–2016 from Southern Israel, insured by Clalit Health Services. Data included demographic and clinical information, as well as use of anti-diabetic and anti-osteoporotic medication. Association between mean HbA1c in the last year of follow-up (prior to HF or end of follow-up for patients without HF) and hip fracture risk was analyzed using logistic regression.
Results
Our cohort comprised 51381 patients. During median follow up of 8.5 years (IQR 4.75–13.16), 1377 patients (2.67%), experienced HF, 69% of which were females. Patients with HF had longer diabetes duration than patients without HF; 8 years (IQR 5–13 years) vs. 7 years (IQR 5–12) $P<0.0001$. Mean age at last year of follow-up (before fracture for HF patients) was 71.71 ± 10.329 in non-fracture patients, and 80.34 ± 9.59 in patients who experienced HF ($P<0.0001$). Mean HbA1c in the last year of follow up was higher in those who experienced HF, 7.9 (IQR 6.8–9.65) vs. 6.82% (IQR 6.26–7.77) respectively, $P<0.0001$. Patients with HF had higher rates of use of insulin, sulfonylureas, glinides and combination anti diabetic medications, lower rates of use of DPP4 inhibitors but no difference in the use of thiazolidinediones or metformin. Use of bisphosphonates (BP), vitamin D and calcium supplements were higher in the year prior to fracture among patients who suffered a HF, however, the absolute treatment rate with BP was low (12% in HF patients). Multivariate analysis adjusted for gender, age, Charlson index, duration of diabetes and glycemic variability (coefficient of variation of A1c values over the follow-up years) showed that the adjusted odds ratio (OR) for HF (reference group $6.5\%\leq$HbA1c$<7.5\%$) was 0.390 (0.309–0.491) for HbA1c$<6.5\%$, 1.685 (1.389–2.044) for $7.5\%\leq$HbA1c$<8.5\%$, 2.765 (2.208–3.462) for $8.5\%\leq$HbA1c$<9.5\%$, and 9.19 (7.507–11.25) for HbA1c$\geq9.5\%$ ($P<0.0001$ for all comparisons).
Conclusion
Worse glycemic control was exponentially associated with an increased HF risk.

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P946

Screening of abnormal glucose metabolism in cystic fibrosis could there be a place for DPP-4 inhibitors in early stages?

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Introduction
Abnormal glucose metabolism (AGM) is the most common extra-pulmonary comorbidity in people with cystic fibrosis (CF) and has a high negative impact on the underlying disease. Elevated postprandial glucose level is usually the first manifestation, which is traditionally detected by 75-gram oral glucose tolerance test (OGTT). The aim of this study was to evaluate glycemic pattern during continuous glucose monitoring (CGM) in patients with impaired glucose metabolism previously detected by OGTT. Compare both methods and examine the short-term response to DPP-4 inhibitor (DPP-4i).
Methods
We included CF adult patients with consecutively abnormal glucose metabolism by OGTT in our clinic in stable clinical situation and with informed consent. We used CGM (DexcomG4Platinum) during 2 weeks, with DPP-4i administration during the second week. We compared both screening methods and CGM glucose response to treatment.
Results
We evaluated 13 patients (seven males, aged 25 [22–38] years). Mean CF progression time was 23.2 ± 9.5 years. Eight cases met criteria for cystic fibrosis related diabetes (CFRD) by OGTT, four for impaired glucose tolerance (IGT) and 1 for indeterminate glycemia (INDET). Mean fasting plasma glucose was 94.4 ± 10.6 mg/dl. We observed glucose >200 mg/dl by CGM in four patients without CFRD initial diagnosis (corresponding in most cases to breakfast and dinner time intervals). In two patients diagnosed with CFRD by OGTT, CGM glucose >200 mg/dl was not identified. No significant correlation between CF progression time and dysglycemia was found. We observed a strong positive correlation ($r=0.8$) between mean CGM glucose and glucose >200 mg/dl by CGM ($P=0.001$). After use of DPP-4i a decrease in mean CGM glucose and in variability was noted (113.9–106.5 mg/dl and 14.2–10.5 mg/dl, respectively), $P<0.02$. % of glycemias within 131–240 mg/dl CGM range improved from $24\pm14\%$ without use of DPP-4i, to $16\pm9\%$ with use of DPP-4i ($P=0.001$). A non-significant decrease in CGM glucose >200 mg/dl without and with use of DPP-4i was found. We observed a strong negative correlation ($r=0.7$) both for CF progression time and HOMA ß ($P<0.05$) and for HOMA ß and dysglycemia, this last one non-significant.
Conclusion
Use of CGM provides additional information to traditional methods of detecting AGM in adult patients with CF. DPP-4i may be a useful therapeutic alternative in early stages of dysglycemia. The role of this treatment in the overall improvement of AGM in adult patients with CF should be confirmed with clinical studies.

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P947

Autoimmune diabetes mellitus versus idiopathic: differences at diagnosis

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Introduction
The *American Diabetes Association* proposed two categories for the classification of type 1 diabetes *mellitus* (DM): autoimmune (AI) and idiopathic (ID). The absence of autoimmune markers or association with HLA haplotypes defines the second category. Only a small minority of patients with type 1 diabetes fall into this category.
Objective
To evaluate the clinical characteristics of both categories and to analyze the differences between them.
Methods
Retrospective cohort study, based on clinical records of patients with not detected C-peptide, in which autoantibodies related to DM were assayed. Only those patients whose measurements were taken at the time of diagnosis of diabetes *mellitus* were included, to include only type 1 DM patients, without clinical suspicion of another type of diabetes. We obtained two groups: one with positive autoimmunity – type AI (≥1 positive antibody) and another with negative autoimmunity – type ID. Age, family history, anthropometry, duration of symptoms, form of presentation, blood glucose at admission, HbA1c, lipid profile and arterial hypertension were evaluated. Results were considered statistically significant with $P<0.05$.
Results and conclusions
A total of 37 patients were selected, of whom 29 had positive autoimmunity and 8 had negative autoimmunity. The age of diagnosis of the type AI differed significantly from the type ID (23 years vs 38.1 years, respectively) ($P=0.004$). The body mass index at diagnosis did not differ significantly ($P=0.435$) between the two groups. There was no statistically significant association between the groups and the family history of type 1 DM or type 2 DM. The duration of

symptoms differed significantly ($P=0.003$), with a duration of 21.8 days (AI) vs 45.0 days (ID), but there was no difference between groups and disease presentation ($P=0.744$). The blood glucose at admission did not differ significantly ($P=0.482$), as the HbA1c at diagnosis ($P=0.794$). The lipid profile did not differ significantly, although total and LDL cholesterol levels were higher in ID group. The percentage of patients with dyslipidemia and arterial hypertension did not differ significantly. The total daily insulin dose at discharge did not differ significantly ($P=0.301$). In conclusion, there was a statistic difference in the age and the duration of symptoms, that is, patients with negative autoimmunity were older and had a longer duration of symptoms, and presented a tendency for an atherogenic lipid profile, resembling a clinical phenotype of type 2 DM.

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P948

The relationship of vitamin D status, adherence to the Mediterranean diet and physical activity in obese children and adolescents

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Background
Vitamin D deficiency has been associated with a wide range of chronic diseases, including childhood obesity. Prevalence of vitamin D deficiency in obese children and adolescents ranges from 6.5% to 57% depending on the population and criteria.
Subjects and methods
This cross-sectional clinical study included 92 obese patients with BMI z score <2 and 39 healthy normal-weight subjects in the control group who were matched with the study group in terms of age, gender and pubertal status. Anthropometric assessment and fasting 25-hydroxyvitamin D (25(OH)D were measured. Obese subjects were dived in two groups depending on the presence of metabolic syndrome (MS), which was defined by IDF criteria. Adherence to the Mediterranean diet was assessed by Mediterranean Diet Quality Index for children and adolescents (KIDMED index), while physical activity was evaluated by Physical Activity Questionnaire (PAQ).
Results
Serum levels of 25(OH)D were significantly lower in obese subjects compared to the control group (52.0 ± 17.93 vs. 64.09 ± 25.82 nmol/l, $P=0.003$). After an additional stratification regarding the presence of MS and subsequent comparison to the control group, analysis showed that subgroup of obese patients with MS had significantly lower levels of serum vitamin D (46.99 ± 17.11 vs. 54.58 ± 17.93 vs. 64.09 ± 25.82 nmol/l, $P=0.003$). Obese patients with MS had lower PAQ score when compared to obese without MS and the control group (2.32 ± 0.55 vs. 2.49 ± 0.67 vs. 2.85 ± 0.63 nmol/l, $P=0.002$), while no significant differences were observed in KIDMED index (4.23 ± 1.81 vs. 4.21 ± 2.13 vs. 4.87 ± 2.29, $P=0.251$), respectively. Serum levels of 25(OH)D showed significant and negative correlation with BMI z score ($r=-0.208$, $P=0.017$) and positive correlation with PAQ score ($r=0.305$, $P<0.001$) in both control and obese subjects.
Conclusions
In conclusion, this study demonstrated that obese children and adolescents had significantly lower values of serum 25(OH)D and lower adherence to physical activity compared to healthy controls. The positive correlation between vitamin D and the degree of physical activity points to the importance of physical activity in the prevention of further cardiovascular complications. However, additional studies with long term follow-up are needed to further clarify the impact of physical activity on the status of vitamin D in obese children and adolescents.

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P949

Detection of metabolic hepatic steatosis in type 2 diabetic patient: about 281 cases

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Introduction
Metabolic liver steatosis is frequently associated with type 2 diabetes with an increased risk of progression to advanced fibrosis. Objective of this study was to estimate the prevalence of hepatic steatosis in patients with type 2 diabetes.
Methods
A cross-sectional study including 281 type 2 diabetic patients followed at the Department of Endocrinology in collaboration with the Hepato-Gastroenterology Department of Ibn Rochd University Hospital in Casablanca between January 2018 and September 2018. The HSI (Hepatic steatosis index) score was calculated for all patients according to the following formula: $(8\times\text{ALT/AST}) + \text{BMI} + 2$ (if type 2 diabetes) $+2$ (if female). An HSI$>$ 36 score predicted the presence of hepatic steatosis. The variables studied were anthropometric, biological, HSI and hepatic ultrasound. Analyzes were performed by SPSS 25.
Results
Mean age of our patients was 54.15 ± 13.45 years (27–80) with a female predominance (76% of cases), a sex ratio of 3.25. Mean duration of diabetes was 10.5 ± 8.5 years with an average glycated hemoglobin level of 10.2%. BMI was 29.9 kg / m SD^2 and the average waist circumference was 110 cm. 38.8% of the patients were hypertensive, 58% were dyslipidemic, 7% were smokers and only 1.4% were ethyl (<20 g/d). Metabolic liver steatosis prevalence was 48% based on the HSI$>$ 36 score. This prevalence is consistent with the results of hepatic ultrasound (42% of cases). Transaminase abnormalities were only seen in 6% of patients. Hepatic steatosis was significantly correlated with metabolic syndrome (<0.05). In multivariate analysis, the most predominant factor associated with hepatic steatosis was hypertriglyceridemia.
Conclusion
Non-invasive score (HSI) and hepatic ultrasound are easy tools for screening for fatty liver. A normal transaminase level in the diabetic does not eliminate the presence of fatty liver.

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P950

Relative fat mass correlates better than BMI with total body fat – experience of an obesity clinic

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Introduction
A simple linear anthropometric linear equation for total body fat quantification in adults was recently selected as the best of 365 anthropometric indexes in the American population. The authors intend to evaluate the correlation between the relative fat mass (RFM) equation and body fat determination by electric bioimpedance (EB) and compare it with BMI.
Material/methods
Retrospective, cross-sectional, observational study that selected all ambulatory patients with body composition determined by EB in our obesity department. Clinical data and prescriptions were collected from the electronic records. A total of 897 cases were evaluated from 2006 to 2018. The calculated RFM $[64-(20\times\text{height/waist})+(12\times\text{sex})]$ was compared with BMI. We used descriptive statistics presented as mean and standard deviation, student's *t*-test and Pearson Correlation for the nominal variables. For the categorical χ^2 was used. The level of significance accepted was $P<0.05$.
Results
Of the 897 patients, 82.6% were female, with a mean age of 46.2 ± 11.3 years at the first visit. The majority (84%) was submitted to bariatric surgery; the prevalence of type 2 diabetes, hypertension and dyslipidemia were high in this population. The mean fat mass was 32.1 ± 10.2%, RFM 43.2 ± 6.1 and BMI 35.7 ± 7.3 kg/m^2. The correlation between RFM and percentage of fat mass was stronger than the correlation between the latter with BMI ($P<0.001$) $r=0.70$ vs 0.66, respectively.
Conclusions
Our analysis suggests that RFM, compared with BMI, had a stronger correlation with body fat mass determined by EB. Although being EB described as a less

accurate body fat evaluation technique, our results are consistent with the available literature, which often uses dual-energy X-ray absorptiometry (DXA) as the gold standard.

Keywords: obesity, RFM, BMI, Body fat mass, bioimpedance

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P951

Characterisation of Turner syndrome glucose homeostasis; autoimmunity, adiposity and insulin sensitivity

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Introduction

Women with Turner syndrome (TS) have an increased risk of diabetes mellitus (DM) the pathogenesis of which is not well understood. International guidelines for TS recommend oral glucose tolerance tests (OGTT) but the utility of this test has not been determined. We sought to establish the rate of IGT and DM and characterise the DM-phenotype in adult women with TS.

Methods

We performed OGTTs in 37 adults with TS and obtained an additional fasting sample from 18 women with established diabetes. Anthropometric data such as body fat (%) by impedance, waist circumference and BMI was calculated. HOMA-IR was calculated and subjects were tested for DM-autoantibodies; GAD, IA-2 and ZnT8. Mean age was 36 (18–68 years).

Results

OGTTs revealed 16.2% with IGT and 8.1% with the new diagnosis of DM. 28 Women with normal glucose tolerance (NGT) were compared with 27 subjects with IGT and DM. The NGT group and had a lower BMI (25.3 ± 6.2 versus 30.6 ± 6.2 respectively, $P = \leq 0.001$), body fat (%) (29.2 ± 9.9 versus 35.5 ± 9 respectively, $P = 0.03$) and lower waist circumference (cm) (85.1 ± 13.1 versus 97.8 ± 12.4 respectively, $P \leq 0.001$) compared to women with abnormal glucose tolerance. However no significant difference was found in HOMA-IR between NGT and IGT/DM subjects (1.6 ± 1.6 versus 2.3 ± 1.6 respectively, $P = 0.23$). Positive DM- related antibodies in NGT were; GAD = 1/28 (3.6%), IA-2 = 1/28 (3.6%) and ZnT8 = 2/28 (7.1%) compared to those with IGT/DM GAD = 4/24 (14.8%), IA-2 = 1/24 (3.7%) ZnT8 = 1/24 (3.7%) ($P = .24$; $P = .91$; $P = .46$ respectively). Of the 18 DM subjects, 4 used insulin, 13 used oral anti-diabetic drugs and 1 was diet controlled. GAD positive autoantibodies were found in 3/4 insulin dependent DM subjects compared to 1/14 non- insulin dependent subjects ($P = .03$).

Conclusions

We highlight the importance of OGTT as part of management although the rate of progression to DM in TS is unknown. The rate of DM was higher than previously reported. TS-DM was characterised by a increased waist circumference and BMI and percent body fat which is consistent with T2DM. Insulin requiring DM was associated with positive GAD autoantibodies. Screening for diabetes with secondary autoantibody testing may be indicated for optimal health surveillance for women with TS.

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P952

Autotaxin level in patients with type 2 diabetes mellitus or cardiovascular disease

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Introduction

Autotaxin (ATX)[Ectonucleotide Pyrophosphatase /Phosphodiesterase family member 2 (ENPP2)] is a lysophospholipase D stimulating cell migration, metastasis and angiogenesis. ATX hydrolizes lysophosphatidylcholine (LPC) and produces bioactive lysophosphatidic acid(LPA). There are some clues about ATX–LPA pathway modulation may unlock the gate of metabolic derangement including diabetes formation or may impact formation of cardiovascular diseases via LPA's role on platelet aggregation. We aimed to investigate ATX levels of individuals having type 2 diabetes mellitus (T2DM) or those having Cardiovascular Disease (CVD). Nondiabetic patients with normal fasting plasma glucose(FPG) level were randomly selected. The diabetic patients were diagnosed as diabetic in our clinic. Among those, patients who had CVD or not,were also discriminated in the study. Blood was collected from all the participants in serum separation tubes.Serum ATX was measured by ELISA.

Results

The study enrolled 82 individuals, 42 of them were T2DM patients, 40 was nondiabetic. Of those, 57 patients were categorized as CVD(−) while 25 patients were CVD(+). Mean HbA1c level was $8.2 \pm 2.1\%$ for T2DM patients. ATX level of the patients having T2DM was greater than nondiabetic patients(4.6 ± 0.5 mg/l vs 4.4 ± 0.6 mg/l, P:0.046). CVD(+) patients had ATX levels indifferent from CVD(−) patients(4.4 ± 0.5 mg/l vs 4.5 ± 0.6 mg/l, P:0.46). In subgroup analysis, T2DM(+) CVD(−) had greater ATX levels than nondiabetic CVD(−) subjects. ATX was similar for T2DM(+) CVD(+) patients and T2DM(+) CVD(−) patients when T2DM(+) CVD(+) patients also had indifferent ATX compared to nondiabetic CVD(+) group. By regression analysis FPG(OR:0.22, P:0.05) and Hba1c (OR:0.39, P:0.01) were found correlated with ATX in the whole group. In CVD(-) patients ATX was related with FPG(OR:0.30, P:0.02) and Hba1-c(OR:0.42, P:0.02) while in CVD(+) patients there was no correlation.

Discussion

In adult human body ATX's upregulated levels have been described in chronic inflammatory diseases and cancer.The studies examining the probable relationship between serum ATX and glucose metabolism are so few, including no study on diabetic individuals. By our study, we found ATX was increased in T2DM patients compared to nondiabetics and an indifferent ATX level between CVD(+) and CVD(−) patients. In absence of CVD manifestation T2DM patients had higher ATX levels than nondiabetics, while CVD manifestation seems to destroy the difference between ATX level of T2DM and nondiabetic patients. It may emphasize that CVD manifestation impairs ATX production in diabetic patients. ATX inhibitors may be a challenge for treatment of T2DM or prevention of CVD manifestation in diabetics.

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P953

Hepatic steatosis and cardiovascular risk in diabetic patient type 2

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Introduction

Metabolic hepatic steatosis is a common condition in patients with type 2 diabetes, increasing the risk of cardiovascular morbidity and mortality in the absence of early and adequate management. The objective of this study was to evaluate cardiovascular risk in this population by comparing it with diabetic patients without fatty liver disease.

Methods

We conclucted a cross-sectional study including 281 type 2 diabetics followed in Endocrinology Department in collaboration with the Hepato-Gastroenterology Department of Ibn Rochd University Hospital of Casablanca between January 2018 and September 2018. Hepatic steatosis was evaluated by using the non-invasive score (HSI). Patients were divided into three groups with or without hepatic steatosis and group with hepatic steatosis at the advanced stage of fibrosis. The Framingham score was used to assess the risk of a cardiovascular event occurring in the next 10 years, in unknown patients with cardiopathy. A score between 5 and 10% predicts a high risk and a score > 15% at very high cardiovascular risk.

Results

Our study included 281 type 2 diabetics of whom 120 patients (42%) had fatty liver. BMI, age, sex were higher in the group of patients with steatosis compared to the group of patients without hepatic steatosis. Hepatic steatosis was correlated with metabolic syndrome ($P < 0.05$). Hepatic steatosis was found to have a very high cardiovascular risk in 44% of patients, with an average Framingham score of 18% (14–35%). This score was higher in patients with steatosis compared with patients without fatty liver (38%). In multivariate analysis after adjustment of all cardiometabolic risk factors, hepatic steatosis was an independent factor associated with a high risk of cardiovascular events (OR = 1.67).

Conclusion

Hepatic steatosis is an independent predictor of the occurrence of cardiovascular events in diabetics, hence the need for systematic screening for this condition in all type 2 diabetics and adequate management.

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P954

Doege-potter syndrome in patients with malignant extrapleural solitary fibrous tumor: a single center experience

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Introduction
Doege-Potter syndrome (DPS) is a rare paraneoplastic syndrome consistent in non-islet-cell tumor hypoglycemia associated with solitary fibrous tumor (SFT). Pathogenesis of hypoglycemia has been attributed to the production of insulin-like growth-factor-2 (IGF-2) by tumor cells. We report two DPS patients with metastatic extrapleural SFT.
Case 1
A 42-year-old man with SFT of the mesocolon that had been operated in 2010, presented with metastatic disease (lung, liver, kidney and peritoneum) 4 years later. He was not diabetic and took no medications. From 2015 to 2018 he received 2 lines of systemic therapy (pazopanib and doxorubicin). In May 2018 he had progressive disease (PD) and entered in a phase-1 clinical trial with anti-PD-L1 immunotherapy. Computed tomography (CT) in August 2018 showed stable disease (SD) after 3 cycles of treatment. In September 2018 he complained of severe fasting hypoglycemia (blood glucose: 28 mg/dl) requiring emergency treatment at home. Previous fasting glucose level was always in the normal range. Electrolytes, kidney, liver, pituitary function tests and hemoglobin A1c were normal. Low serum IGF-1 [4.8 nmol/l; normal range (NR): 9.8–28.3 nmol/l), C-peptide [0.1 nmol/l (NR: 0.26–1.44)], and insulin [4.3 pmol/l (NR: 17–120)] concentrations with high serum IGF-2 [734 ng/ml (NR: <700)] concentrations and high IFG-2/IGF-1 ratio [20 (NR <10)] were detected. A new CT in October 2018 showed progression in neck lymph nodes. Prednisone (0.8 mg/kg per day) was started, leading to hypoglycemia resolution.
Case 2
A 65-year-old-man, without any personal history of interest and no medication, was diagnosed with SFT of the prostate and operated in 2009. He presented with metastatic lung disease in January 2017 and he underwent surgery. After PD, he was treated with 3 different systemic therapy (doxorubicin, pazopanib and dacarbazine + gemcitabine). A CT in November 2018 showed PD with metastases in the pancreas. In January 2019 he went to emergency because of dizziness and behaviour alterations secondary to hypoglycemia (blood glucose: 34 mg/dl). Hemoglobin A1c: 5.7%, serum cortisol and thyroid function were normal. Low serum concentrations of GH (<0.05 mcg/l, NR <3.5), insulin (<6 pmol/l), C-peptide (0.05 nmol/l) and IGF-1 (5.3 nmol/l) were detected. Serum IGF-2 is ongoing. He received treatment with prednisone (0.7 mg/kg per day) with resolution of the hypoglycemia.
Conclusion
In the evaluation of patients with hypoglycemia and SFT a paraneoplastic syndrome induced by IGF-2 should be considered. High dose glucocorticoid therapy seems appropriate to relieve hypoglycemia.

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P955

Transgenic production of endogenous n-3 PUFA levels compared to fish oil intake differentially improve obesity-related metabolic disorders: role of the gut microbiota

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Previous studies demonstrated that n-3 polyunsaturated fatty acids (PUFA) reduce insulin resistance and non-alcoholic fatty liver disease (NAFLD). However, we previously reported that transgenic expression of the *fat-1* n-3 desaturase, inducing the endogenous production of n-3 PUFA, improved insulin resistance but not hepatic steatosis in a mouse model of obesity. Thus, we compared the effects of increasing n-3 PUFA levels through oral or endogenous approaches in diet-induced obese mice, and analyzed whether changes in the gut microbiota could account for the impact of oral n-3 PUFA on NAFLD. In the model of supplementation, C57Bl/6J mice were fed a high-fat (HF) diet and gavaged daily with either n-6- or n-3-rich oil. In parallel, hemizygous *fat-1* (+/−) mice were also fed with the same HF diet and gavaged with the n-6-rich oil. The protocol was conducted over 12 weeks and included physiological tests. Our data show that diet-induced hepatic steatosis and inflammation are abrogated whereas neither insulin resistance nor glucose tolerance are prevented in mice gavaged with fish oil. Conversely, endogenous production of n-3 PUFA in *fat-1* mice significantly improved glucose homeostasis but failed to protect against hepatic steatosis. Both routes of increased n-3 PUFA availability reduced plasma cholesterol and improve diet-induced intestinal disturbances, highlighted by the increased abundance of the *Allobaculum* genus. However, oral n-3 PUFA supplementation was found to more profoundly reshape the gut microbiome, as revealed by major shifts in microbial populations, PiCRUST data, bile acids and short-chain fatty acid production. These results reveal that oral and endogenous n-3 PUFA administration can lead to distinct but also overlapping immunometabolic benefits. However, oral supplementation appears to be required to elicit major shifts in the gut microbiome and prevent hepatic steatosis and inflammation. This project demonstrates a key role of the gut-liver axis in the preventive effect of n-3 PUFA on NAFLD.

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P956

Clinical particularities of acute pancreatitis in diabetic patients: about 60 cases

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Introduction
Acute pancreatitis is a common disease of simple evolution in 80% of cases, but burdened with increased morbidity and mortality especially in the diabetic patient because of his atypical symptomatology delaying his diagnosis. The objective of this study is to evaluate the clinical features of acute pancreatitis in diabetic patients.
Methods
Retrospective descriptive study including 60 patients followed in the endocrinology department of Casablanca Ibn Rochd Hospital for acute pancreatic between 2016 and 2018. Acute pancreatitis is characterized by a pain syndrome associated with elevation of lipase at 3 times normal. The variables studied were clinical-biological characteristics (toxic habits, clinical signs, anthropometric measurements, biological assessment, pancreatic CT).we based on the Balthazar CT classification. Statistical analyzes were performed by SPSS 25.
Results
The average age of our patients was 42 years with a female predominance (57%), of which 12 patients had a history of chronic alcoholism. 38 patients were type 2 diabetic and 10 type 1 diabetic patients. Acute pancreatitis revealed diabetes in 44% of cases. It was stage A in 22 cases, stage B in 8 cases, stage C in 24 cases, and stage E in 6 cases. Etiologies of acute pancreatitis were hypertriglyceridemia in 17 cases, lithiasis in 39 cases, hypercalcemia in one case, autoimmune origin in one case and idiopathic in 2 cases. Clinical signs of acute pancreatitis were dominated by mild abdominal pain of gravitational epigastric site in 45% of patients with food-induced vomiting in 35% of cases, 28% by ketotic decompensation. Evolution was marked by the regression of the symptomatology in 80% of the cases and a death by the infectious complications in 4 cases.

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P957

Impact of bariatric techniques in the long-term weight loss

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Introduction
Bariatric surgery (BS) has emerged as the most effective treatment for severe obesity, but weight regain after surgery is an important issue. The aim of this study was to evaluate the impact of different surgical techniques on long-term dynamic weight loss pattern.
Materials and methods
We retrospectively included 444 patients with BMI $>$ 35 kg/m^2 who underwent different BS techniques: Sleeve gastrectomy (SG; *n*: 80), Roux-en-Y gastric bypass (RYGBP; *n*: 242) or biliopancreatic diversion (BPD; *n*: 122). Patients were followed-up for 5 years. We evaluated percentage of the total weight loss (%TWL), excess weight loss (%EWL, considering ideal weight as BMI$=$ 25 kg/m^2) and weight regain (WR) $>$ 15% from nadir. Patients were classified in 3 pattern groups: a) Successful: maintained EWL $>$50% for 5-years; b) Late failure: reached %EWL$>$50% but presented %EWL$<$50% at the end of follow-up and c) Early failure: persistent %EWL$<$50% throughout the follow-up. Statistic analysis: descriptive data expressed as mean (SD), median or percentage. T-Test for unpaired data and χ^2 test for qualitative data was performed.
Results
Patients with SG were younger [40.3 (13.8)] than RYGBP [45.1 (10.6)] or BPD [46.9 (12.2)] ($P<0.01$) and less obese [BMI 43.6 (8.7)] vs 44.7 (6.3) and 46.9 (12.2), respectively ($P<0.05$). The EWL at weight nadir (1–2 years) was excellent for all BS (median 88% for SG and RYGBP and 98% for BPD). EWL% declined at 5 year-follow-up but, was similar between SG and RYGBP (median 66 vs 71%) and lower than BPD (85%; $P<0.01$). When loss weight is expressed as TWL $>$30% at 5-year follow-up, a clear inferiority is observed in patients undergoing SG (30%) vs RYGBP (51%) vs BPD (78%); $P<0.001$. Although WR$>$15% was similar in all types of BS (SG 37.5%, RYGBP 33.9%, BPD 34%), the impact on final follow-up weight loss pattern was outstanding for BPD ($P<$ 0.001) (see table below)

	SG	RYGBP	BPD
Succesful	70%	76.5%	90.2%
Late failure	21.2%	19.4%	9%
Early failure	8.8%	4.1%	0.8%

Conclusions
In this cohort, all BS lead to major weight loss in the short term. BPD presented higher percentage of success than the other techniques. No differences were found in baseline characteristics between successful, late and early failure weight loss patterns. More studies are needed to determine useful predictors of success and WR after BS.

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P958

Ramadan fasting effects on the clinical and metabolic parameters of a previously educated population of diabetic, hypertensive and dyslipidemic patients

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Introduction
Several studies have been conducted to study the effect of fasting on the clinical and metabolic parameters of patients with multiple cardiovascular risk factors, particularly diabetes, hypertension, and dyslipidemia. Our aim was to study the effect of Ramadan fasting on the clinical and metabolic parameters of a previously educated population of diabetic, hypertensive and dyslipidemic patients.
Methods
This is a prospective study that involved 140 patients who wish to fast the month of Ramadan (2016) and who have presented themselves at the consultations dedicated to preparing diabetic patients wishing to fast, organized at The National Institute of Nutrition of Tunis (departement C). Patients were given an interview, a thorough clinical examination and a biological assessment and were well informed about the risks they face.They had the appropriate therapeutic adaptation (ADA recommndations of 2010), as well as an adequate hygiene and dietary education. We have totally banned fasting for unbalanced patients.
Results
38 were diabetics (all type 2), hypertensive and dyslipidemic. The average number of days fasted was 21$\pm$4.54 days. The sex ratio was 0.31. The average age was 58.7$\pm$8.48 years. Diabetes has evolved since 9.5$\pm$6.38 years on average, poorly balanced in 71% of cases. 23.68% of cases were insulin-dependent. The body mass index was 30.64$\pm$5.67 kg/m^2. The average weight was 80.63$\pm$14.45 kg. Hypertension has evolved since 6.46$\pm$4.7 years on average and dyslipidemia since 3.77$\pm$3.37 years. The mean fasting glucose level was 9.11$\pm$3.45 mmol/L. The mean HbA1C was 8.19$\pm$1.54%. The mean systolic and diastolic arterial pressures were 13.05$\pm$1.52 and 7.46$\pm$0.93 mm Hg, respectively. Mean cholesterol, triglyceride, HDL and LDL were 4.45$\pm$0.98, 1.49$\pm$0.74$\pm$0.1$\pm$ 0.25 and 1.05$\pm$0.37 mmol/L, respectively. 3 cases of moderate hypoglycemia and 3 cases of hyperglycemia greater than 3 g/L were reported during the fast. After fasting, the average weight was 80.55$\pm$15.46 kg. The average fasting glucose level was 8.65$\pm$2.96 mmol/L. Mean HbA1C remained stable at 8.18%. Systolic and diastolic arterial blood pressures were 12.9$\pm$1.23 and 7.39$\pm$0.71 mm Hg, respectively. Mean total cholesterol, triglyceride, HDL and LDL were 4.41$\pm$0.96, 1.48$\pm$67, 1.49$\pm$0.29 and 1.04$\pm$0.34 mmol/L, respectively. The mean clearance of creatinine was 94.74$\pm$24.58 ml/min.
Conclusion
In our population with high cardiovascular risk,Ramadan fasting was well tolerated with few metabolic complications and a tendency to improve some clinical and metabolic parameters, in particular systolic blood pressure, fasting blood glucose and HDL level.

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P959

Different pattern of clinical presentation between newly onset ketone prone diabetes and type 1 diabetes in a tertiary hospital

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Introduction
A new subtype of diabetes, ketosis-prone diabetes (KPD) has been described in the last years among African, Asian and Hispanic population with characteristics similar to type 1 diabetes (DM1) such as cardinal symptoms, tendency to ketosis and decreased pancreatic reserve at onset, but with negative autoimmunity. The aim of this study was to compare this type of patients with those with type 1 diabetes at onset and their evolution.
Material and methods
Retrospective study with the last 14 admissions by KPD of new onset in our hospital, in comparison with the last 14 DM1. We collected personal and family history, demographic, anthropometric, analytical and treatment variables. The statistical program SPSS was used.
Results
The mean age of the KDP group was 43.21 years vs 28.54 in DM1 patients with significant differences between both groups (*P* 0.0001). In the first group, 92.9% were men vs 69.2% of the second, without significant differences. Most patients with KPD came from African countries (Gambia, Senegal, Morocco) and all of them had anti-GAD antibodies negative at diagnosis. No differences were found regarding family history of diabetes or presence of concomitant diseases. A higher prevalence of autoimmune diseases was observed in DM1 (vitiligo, celiac disease, autoimmune hypothyroidism (2)). The mean weight of the first group was 77.21 kg vs 63.96 kg ($P<0.05$), without significant differences in BMI (24.34 kg/m^2 vs 21.55 kg/m^2, *P* 0.09). Duration of cardinal clinic was shorter in the KPD group (2.85 weeks vs 6.38, *P* 0.01). Regarding analytical values at admission, differences were found in C peptide (0.84 vs 0.47, *P* 0.04) and bicarbonate (25.7 vs 19.3, *P* 0.02), without differences in the rest parameters studied (pH, ketone bodies, glycemia, creatinine, HbA1C (13.03% and 12.86%), triglycerides, cholesterol and liver profile). The insulin dose at discharge was higher in the group with KPD (45.57 UI/d vs. 30.77 UI/d, *P* 0.019), but 6 months after diagnosis, only 28.6% of patients with KPD continued to require insulin treatment vs 100% of DM1, without differences in HbA1C between both groups (6.49% vs. 6.58%, *P* 0.87). Of the KPD without insulin treatment, 80% required oral medication for diabetes and 20% did not need treatment.
Conclusions
In our study, KPD presents a more abrupt onset and at a later age than DM1. All patients required basal-bolus treatment at the beginning, but in most of them it could be removed after 6 months, with good glycemic control.

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P960

Prevalence of postprandial hyperinsulinemic hypoglycaemia in a random population after primary Roux-en-Y gastric bypass during a mixed meal tolerance test

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Context: Roux-en-Y Gastric bypass (RYGB) is an effective way to induce sustainable weight loss. This operation can be complicated by late dumping, also known as postgastric bypass hyperinsulinemic hypoglycemia. Much is still unknown on its prevalence and its pathophysiology.
Objective: To study the prevalence and the main driving mechanisms behind the occurrence of hypoglycemia after a mixed meal tolerance test (MMTT) in patients with primary RYGB. Design, setting and patients: This is a cross-sectional study of patients at mid-term after primary RYGB and performed in a large peripheral hospital. From a total population of 550 patients, a random sample of 44 patients completed the total test procedures. A standardized mixed meal (Ensure Plus) was used as hypoglycemia inducing stimulus. Blood samples were collected at baseline, every 10 minutes during the first half hour and every 30 minutes until 210 minutes after the start. Symptoms were assessed by questionnaires. Main outcome measures: Hypoglycemia defined as a blood glucose below 3.3 mmol/L (60 mg/dL).
Results
The prevalence of postprandial hypoglycemia in this population was 48%. Hypoglycemia developed mainly between 60 and 120 minutes after the meal and was asymptomatic in all patients. Development of hypoglycemia was more frequent in patients with lower weight at surgery ($P=0.045$), with higher weight loss after surgery ($P=0.011$), and with higher insulin sensitivity calculated by Homeostasis Model Assessment indexes (HOMA2-IR $P=0.014$) and enhanced beta cell function (insulinogenic index at 20 minutes $P=0.001$).
Conclusion
In a random population mid-term after primary gastric bypass surgery an asymptomatic hypoglycemia event was inducible by a test meal in nearly half of the patients.

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P961

The prevalence of impaired cognitive function and depression in patients with type 2 diabetes mellitus and severe insulin resistance

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Aims were
1. To evaluate the prevalence of impaired cognitive functions and depression in patients with type 2 diabetes mellitus (T2DM) and compare between groups.
2. To evaluate the association of cognitive functions and depression with age, gender, BMI, insulin dose, marital status and education in patients with T2DM.

Methods
Case-control study of T2DM where patients with high insulin doses (>1U/kg/24 hrs) and uncontrolled diabetes (HbA1c $>9\%$) referred as severe insulin resistance (IR) group (case group). T2DM patients with insulin doses less than 1 U/kg/24hrs and HbA1c $<8\%$, matched by gender, age and diabetes duration – referred as control group. Participants filled questionnaires about T2DM, duration, education, marital status. All participants with T2DM were evaluated for cognitive function with Montreal Cognitive Assessment (MOCA) questionnaire. Mental health (depression, dystymhia) was evaluated by Mini-International Neuropsychiatric Interview (MINI).
Results
45 participants with T2DM and severe IR (case group) and 17 participants in control group were included to the study. The prevalence of impaired cognitive function in diabetic patients was 82.2% (in both groups the same prevalence), depression in 30% of patients (in severe IR group −33% and control group −23%). There was no significant differences of impaired cognitive functions and depression between groups. In the study higher frequency of single ($P=0.02$), more obese ($P=0.02$) and worse HbA1c ($P=0.013$) women were found, especially this tendency was noticed in patients with severe IR. Depression and dysthymia frequency was significantly higher in married patients than single, especially this association was noticed ir patients with T2DM and severe IR. Age was related with impaired cognitive function, BMI and insulin dose. There were a negative correlations: older patients with diabetes had lower MOCA results, lower BMI and used lower insulin dose.
Conclusions
1. Impaired cognitive functions were observed for the majority of patients with type 2 diabetes, one – third of patients had depression, but it did not differ between patients with severe IR and control group.
2. Women with severe IR were more obese and had worse diabetes control than men with severe IR.
3. Married diabetic patients, especially with severe IR, more often had depression than single T2D patients with usual IR.
4. Age had a negative impact on cognitive functions in patients with T2DM. But older patients with T2DM were leaner and less IR (used lower insulin dose).

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P962

Gender differences in patients with coronary heart disease and diabetes: A multicentric retrospective study

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Introduction
There are known biological differences between men and women in coronary heart disease. It is important to know these differences in order to avoid inequalities in prevention, diagnosis and treatment of this pathology.
Methods
We designed a retrospective, descriptive study in which we included all diabetic patients admitted to 3 different hospitals in Cádiz province with acute coronary syndrome and diabetes in 2016. Demographic data and degree of control of risk factors were registered.
Results
211 patients were evaluated. 139 men and 72 women (34.1%). Average age 69.4 ± 10.8 years. The women in our sample were older at the time of the coronary event (72.3 ± 11.1 vs 67.9 ± 10.5 years, $P=0.006$), had lower percentage of a prior acute coronary event (36.1% vs 48.2%, NS), higher percentage of atypical clinic (22.2% vs 18.7%; NS), longer evolution time of diabetes (14.7 ± 9.15 vs 11.4 ± 8.3 years, $P=0.01$). We found a higher prevalence of HBP (90.3% vs 75.5, $P=0.01$) and lower smoking habit (18.1% vs 38.1%, $P=0.003$). The HbA1c levels were slightly lower in the group of women, although not satisfactory (7.28% vs 7.42%; NS) while the mean LDL levels were higher than 100 mg/dl in women and lower in the group of men (102.2 ± 1.18 vs 95.7 ± 1.45 mg/dl; NS). We found a significant difference in lethality between both groups (13.9% vs 5%, $P=0.025$).
Conclusions
As it is described in literature we observed a later development of coronary heart disease in women of our sample and more lethality. The degree of control in our group was unsatisfactory and it was slightly poorer in women. A greater awareness of the differences in presentation of acute coronary syndrome between men and women, with gender-based interpretation of diagnostic tests, is mandatory for health care professionals to improve therapeutic strategies and outcomes in women.

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P963

Delayed menarche, oligomenorrhea and hyperandrogenism in type 1 diabetes mellitus

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Aim
To investigate reproductive function disorders in young women with type 1 diabetes mellitus (T1DM).
Patients and methods
We studied 53 women with T1DM (duration 8.0±5.6 y) and 51 healthy controls with normal menstrual cycles and no clinical hyperandrogenism, matched for age (19.4±4.3 vs 20.8±3.1 years, $P=0.063$) and body mass index (BMI) (22.2±2.7 vs 21.4±1.9 kg/m^2, $P=0.088$). T1DM (insulin regimen, glycemic control, hypoglycemic episodes, diabetic complications) and reproductive (age at menarche, duration of menstrual cycle and menses, pregnancies and signs of hyperandrogenism) parameters were recorded. Morning blood samples were obtained for biochemical and hormonal assessments at the first phase of menstrual cycle.
Results
T1DM diagnosis was made at the age of 11.5±4.7 years; in 17% of patients (9/53) ketoacidosis was the presenting symptom. Patients were treated with multiple daily injections (83%, 44/53) or insulin pump therapy (17%, 9/53), with total insulin requirements of 0.7±0.22 iu/kg. Current glycosylated haemoglobin (HbA1c) was 8.4±1.8%, with 7.3±7.9 hypoglycemic episodes per month. Complications consisted of diabetic retinopathy (1.9%, 1/53) and albuminuria (5.7%, 3/53). There was no difference in birth weight (3214±629 g vs 3145±496 g, $P=0.601$). Two patients (3.8%) had not experienced menarche at the age of 15.5 and 16.6 y; for the rest, the age at menarche was delayed compared with controls (12.7±1.3 vs 12.0±1.0 years, $P=0.03$). Patients who had experienced menarche were studied 7.3±4.7 years after, with 23.5% (12/51) having oligomenorrhea. There was no difference in family history for menstrual disturbances (13.2%, 7/53 vs 15.7%, 8/51). The prevalence of hirsutism and acne was high in patients with T1DM (32.1%, 17/53 and 45.3%, 24/53, respectively). There were no differences in total testosterone (0.43±0.14 vs 0.39±0.14 ng/ml), DHEA-S (268.5±112 vs 237.5±106 μg/dl) or Δ_4-Androstenedionone (2.4±1.3 vs 1.9±0.5 ng/ml) concentrations between patients and controls ($P>0.05$). However, patients with T1DM had lower SHBG concentrations (61±17 vs 103±41 nmol/l, $P=0.001$) reminiscent of higher insulin concentrations in patients through the exogenous administration.
Conclusions
T1DM in young women is associated with delayed menarche, and increased prevalence of oligomenorrhea and clinical hyperandrogenism probably attributed to the higher free testosterone concentrations due to decreased SHBG levels. Physicians should be aware of these reproductive disorders when dealing with such women.

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P964

'Development of new dietetic approach for obese and overweight adults without metabolic factors for cardiovascular disease: preliminary results'

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Context
Developing reliable diet methods for facilitating long term weight loss outcomes my help to decrease obesity rates. It is then of paramount importance to investigate the potential benefits of the use of new dietetic approaches aiming at weight loss.
Objective
To determine the clinical efficacy of two different dieting methods.
Materials and methods
This was a randomized clinical study of dietary intervention. In total 40 healthy individuals, aged 32.5±8.58 y with mean BMI of 33.5±7.74 Kg/m^2, had been categorized in two intervention groups: intervention group which received a diet based on caloric substitiution of equivalent food choises (CSE) (20 participants) and intervention group which received a point-calorie equivalent system (PCS) (20 participants) for a 3-month period. The CSE diet included pre-planned caloric equivalent meals that the subject had to follow where as the PCS diet was a free food choice system with specific points attributed to every food and the subject had to receive an exact amount of points. The recommended energy consumption was 500 Kcal less than the predicted total energy expenditure (TEE) by the Mifflin – St. Jeor equitation (1990) for every participant in both dietetic approaches. The clinical efficacy of each method was assessed via weight loss (=weight day 0 – weight day 90) and % weight loss (=weight day 0 – weight day 90/weight day 0×100). Participant compliance was self evaluated as good, moderate or poor adherence.
Results
Both groups achieved weight loss compared to the baseline (mean initial weight for the CSE group and PCS group was 92.17±7.22 and 95.10±6.42 Kgr respectively). The CSE group had a mean % weight loss 6,60±4,60 while the the PCS group had a mean % weight loss 8.95±2.94 ($P=0.02$ and $P=0.04$ respectively). The actual weight loss in SCR group was 7,22±4.08 kgr where as in the PCS group was 8.38±3.36 kgr but these findings were not found to be statistical significant due to the variability of the initial weight of our sample.
Conclusion
These preliminary findings suggest that targeted nutritional interventions via use of a point-calorie equivalent system may have increased clinical efficacy in order to achieve better weight loss outcomes. Further studies need to be done on the level of compliance and the sustainability of the weight loss achieved between the two different dieting methods.

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P965

Prediabetes: expectations and attitudes

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Introduction
Prediabetes is a very prevalent disease. About 27.4% of Portuguese adults suffer from this condition. Prediabetes is defined as intermediate hyperglycemia state associated with the simultaneous presence of insulin resistance and β-cell dysfunction as diabetes, with increased risk of developing macro and microvascular complications. Approximately 7% of individuals with prediabetes will progress to diabetes per year. This study aims to characterize a population with prediabetes and to evaluate the risk of developing micro and macrovascular complications and progression to diabetes.
Methods
We did a retrospective observational study including 188 individuals with prediabetes diagnosis.The following variables were analysed: age, family history, disease duration, metabolic control (HbA1c), body mass index (BMI), treatment and prevalence of macro and microvascular complications. Statistical analysis performed in SPSS with significance index $P<0.05$.
Results
Of 188 prediabetic patients 60.6% were males with a mean age of 67.7 years. The mean age of diagnosis was 58 years and 37.2% had family history of diabetes. The mean follow-up was 6.6 years in which 16% evolved to diabetes. The 84% ($n=158$) of patients that remain with prediabetes presented at diagnosis, a mean HbA1c of 5.8% and a mean BMI of 30.7 kg/m^2. The most prevalent macro and microvascular complications were acute myocardial infarction (5.06%) and nephropathy (4.43%). Lifestyle therapy was recommended to all patients at diagnosis, however in 48% of patients were recommended pharmacological therapy. Metformin was the therapeutic of choice in 89.5%. Comparing prediabetic patients with pharmacological approach ($n=76$) and those who remained untreated ($n=82$), the treated group had a higher initial BMI (31.5 vs 30.1 kg/m^2, $P=0.038$), greater weight loss (−2.76 vs −2.4%, $P=0.046$) and a higher incidence of diabetic nephropathy (3.8% vs 0.63%, $P=0.041$). There was no difference in the remaining macro and microvaculares complications. Regarding the risk of progression to diabetes there was a lower progression in the treated group than in the untreated patients (9.5% vs 21.2%, $P=0.03$).
Conclusion
We found that the early pharmacological approach in patients with prediabetes was favourable in relation to the weight profile and progression to diabetes although there was a higher incidence of diabetic nephropathy.

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P966

The level of the vitamin D, osteoprotegerin and metabolic status in children with obesity

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Objective
Determination of changes in metabolic status and vitamin D, osteoprotegerin concentrations in obese children.
Methods
We examined 212 children in the University Hospital from 2016 to 2018 yrs. Their anthropometric parameters (body mass index (BMI)) were determined. Blood levels of vitamin D, OPG, insulin were determined. In the biochemical blood test, the parameters of uric acid, glucose were evaluated. All children were divided into 2 groups: group 1 children with morbid obesity - 140 patients (90 boys(B)/50 girls(G)) (BMI more than 99th percentile for sex and age) (BMI 33.04 ± 4.67 kg/m^2, age 14.17 ± 2.42years); group 2 - 72 patients (B/G = 34/38) with alimentary obesity (BMI-95-99th percentile for sex and age) (BMI 27.60 ± 2.06 kg/m^2, age 14.43 ± 2.27years). The control group consisted of 83 patients (B/G = 43/40) with normal body weight (BMI 19.86 ± 2.24 kg/m^2, age 14.32 ± 2.30years).
Results
In the subgroups of boys with obesity, there were significant differences in the concentration of uric acid in comparison with the control (alimentary obesity 424.10 ± 65.25 mmol/l vs 242.58 ± 49.90 mmol/l (P = 0.01)), morbid obesity 324.10 ± 59.33 mmol/l vs 242.58 ± 49.90 mmol/l (P = 0.01)). In boys with obesity higher concentrations of OPG were detected relative to the control group (alimentary obesity 21.89 ± 2.17 ng/ml vs 18.1 ± 1.21 ng/ml (P = 0.05), morbid 22.22 ± 2.14 ng/ml vs 18.1 ± 1.21 ng/ml (P = 0.03)). In the obese boys, the level of vitamin D is significantly lower than in the control group (alimentary obesity 29.56 ± 6.01 ng/ml vs 33.02 ± 4.10 ng/ml (P = 0.05), morbid obesity 27.56 ± 5.75 ng/ml vs 33.02 ± 4.10 ng/ml (P = 0.05)). Obese girls showed a significant decrease in vitamin D relative to the control group (alimentary obesity 24.21 ± 10.75 ng/ml vs 31.34 ± 7.35 ng/ml (P = 0.05), morbid obesity 23.52 ± 4,18 ng/ml vs 31.34 ± 7.35 ng/ml (P = 0.04)). In boys with obesity higher concentrations of insulin were detected relative to the control group (alimentary obesity 18.9 ± 12.7 μU/ml vs 9.1 ± 4.2 μU/ml (P = 0.0001), morbid 28.71 ± 7.36 μU/ml vs 9.1 ± 4.2 μU/ml (P = 0.001)). In girls with obesity, the concentration of insulin relative to the control group was (alimentary obesity 20.28 ± 6.25 μU/ml vs 14.10 ± 6.80 μU/ml (P = 0.001)) morbid obesity 23.32 ± 9.65 μE/ml vs 14.10 ± 6.80 μU/ml (P = 0.001)).
Conclusion
Children with obesity have a significant decrease in the concentration of vitamin D. There is an increase in insulin and OPG rates.

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P967

Assessment of the educational level of diabetics regarding their foot

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Introduction
Diabetic foot is known to represent a serious complication of diabetes mellitus, responsible for significant morbidity, disability and considerable financial implications. The prevention of this complication requires, first and foremost, a good patient education.
Objective
To evaluate the current state of knowledge and practices of foot care in diabetic patients and to identify factors associated with a good educational level.
Patients and methods
A transversal descriptive study was conducted in two centers, over a period of two months in 2018, including 70 diabetic patients without a prior history of foot ulcer or amputation. A questionnaire survey was designed including general knowledge questions about the importance of foot examination, mechanisms and clinical manifestations of the diabetic foot, in addition to 18 questions about foot care.
Results
The average age of the participants was 51.9 ± 16.6 years. The sex ratio was 0.66 (40% men and 60% women). Most patients had type 2 diabetes mellitus (78.6%). The mean duration of diabetes was 11.5 ± 7.7 years. Therapeutic education for diabetic foot was done in only 15.7% of cases. Half of patients didn't know any mechanism of diabetic foot while 37.1% of them didn't know any clinical manifestations. Only 11% of patients had a theoretical knowledge level higher than average. Practice level was average in the majority of cases (60%) with less than 10% of patients cutting their nails with a non-metallic object or using appropriate shoes or footwear. Having a medium or good overall educational level was significantly associated with higher education level (P = 0.002), urban area of residence (P = 0.05), type 1 diabetes (P = 0.027) and prior hospitalization for diabetes (P = 0.038).
Conclusion
The overall level of knowledge and practice was relatively insufficient, especially regarding the knowledge level. Therapeutic education, despite its importance, is not as optimal as it should be whether in Tunisia or around the world for multiple reasons.

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P968

Diabetic foot: Assessment of the diabetic patient's knowledge before and after a day of education

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Introduction
Diabetic foot problems are generally poorly understood by patients, yet they represent a major health problem. The aim of this study was to assess diabetes patients' knowledge of preventive foot care before and after a diabetic foot day.
Patients and methods
It was a prospective and descriptive study conducted in the service from January to December 2018, including 108 type 2 or type 1 diabetic patients, at risk of podiatry grade 1, 2 or 3 and who participated in the diabetic foot education day. The statistical analysis was performed by the epi. Info 6.0. software
Results
We collected 108 patients whose average age was 48 years and the sex ratio was 0,75. 70% of patients were of low socio-economic status, 64% were of low intellectual level. Type 2 diabetes was predominant in 60% of cases, with an average duration, 39% of cases had a very high risk of podiatric (grade 3), 42% of patients have already benefited from a diabetic foot education. A lot of hygiene errors were noted in our patients: absence of daily examination of the feet, (46%), no-washing of the feet and the no adequate drying (58%), no verification of the temperature water before a feet bath (52%), walking barefoot (34%), non-daily application of moisturizing creams (66%), purchase of shoes at the end of the day (62%), wearing socks with aggressive seams (56%), wearing tight shoes (28%), inspecting shoes before putting on shoes (54%), using cutting metal objects for nails (62%), application of tinted product (Henna, eosin) (68%), use of radiator or hot water to heat the feet (26%) and putting dressing directly on the skin (34%). The evaluation at the end of the day showed that only 8% of the answers were incorrect compared to 18% at the first consultation (after 1 to 2 months).
Conclusion
The therapeutic education of people with diabetes about the need for foot care appears to improve their knowledge.

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P969

Knowledge and practices of diabetic patients during Ramadan

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Introduction
The month of Ramadan is characterized by abstaining from drinking and eating from sunrise to sunset. This exposes to an increased metabolic risk in diabetics. However, even if religiously diabetics could be exempt from fasting, a large number of them practice it.
Materials and methods
We conducted a cross-sectional study and interviewed diabetic patients about their practices during Ramadan and about the presence or absence of complications, over a period of one month, in the occurrence the month before Ramadan 2018 at the department of endocrinology and diabetology of Mohammed VI University Hospital of Marrakech. The purpose of this study is to assess the level of education of patients and their awareness of all the possible complications that may occur during fasting and how these complications are managed.
Outcomes
The average age was 58.42 years with female predominance. Most patients were type 2 diabetics with an average duration of 10 years. The rate of the fasting patients was 62%. Before Ramadan, 72% of our patients said they had discussed the intention of fasting, with a doctor, or with a religious leader or with the entourage. Treatment's modification during Ramadan was noted in 54% of patients on their own initiative or on medical opinion; physical activity was practiced in 58% of diabetics. Glycemic monitoring was performed in 53% of patients. Hypoglycemia was reported in 38% of patients, and hyperglycemia in 20%, of whom 14% and 10%, respectively, broke their fast.
Discussion
Our study found that there are deficits in knowledge and inappropriate practices in Muslim patients with diabetes, and the outcomes could have major implications in the incidence of the complications related to diabetes. The development and implementation of educational programs before the sacred month, is the only guarantor to push patients to change their lifestyle during Ramadan, to avoid any potential risk associated with fasting.

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P970

Late diarrhea in diabetic patients under metformin: An undesirable effect of the molecule appearing late?

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Introduction
Diarrhea is an undesirable effect that affects almost one third of patients on metformin.When it appears late, it becomes difficult to attach it to metformin, especially in polymedicated patients or with complicated diabetes. The purpose of this study was to describe the clinical and biological characteristics of a population with chronic metformin-induced diarrhea and to characterize this diarrhea.
Methods
This is a prospective study including 40 diabetic patients on metformin who reported chronic diarrhea (defined by the WHO for more than 1 month). Clinical and biological data were collected by the interview and from medical records. All patients reported good metformin compliance.
Results
The mean age was 51.2 ± 6.5 years, the sex ratio 0.42 and the average BMI 32.9 ± 2.8 kg/m^2, 32.5% were hypertensive. 25% were dyslipidemic. Diabetes was type 2 in 100% of cases, insulin requiring in 70% of cases and evolving for 8.5 ± 4.1 years on average. All patients were on metformin with doses between 850 and 2000 mg. The mean HbA1C was 8.8 ± 1.7%. The degenerative complications found were myocardial infarction (7.5%), stroke (2.5%), chronic arteritis of the lower limbs (2.5%), diabetic nephropathy (20%) and diabetic retinopathy (30%). Diarrhea appeared on average 4.2 ± 3.6 years after the start of treatment with metformin. It was fluid in 77.5% of cases. It had been trivialized by patients and had never been reported to the treating physician.Self-medication xere seen in 87% of cases, ineffective in 77.7% of cases.
Conclusion
Adverse effects of metformin are common at the beginning of treatment. The late onset of any of these effects, especially diarrhea, is still plausible even in the presence of several other possible causes. Stopping diarrhea following stoppage of metformin poses the etiological diagnosis and spares the patient costly explorations.

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P971

Are fast insulin analogues fast enough? Switching to faster aspart may reduce glycemic variability and the risk of hypoglycemia in type 1 diabetic patients on sensor-augmented insulin pump therapy

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Aim
Comparing the effect of Faster Aspart insulin (Fiasp®) with previous insulin analogues (aspart, lispro) in type I diabetic patients with sensor-augmented pump therapy.
Methods
Patients with Minimed Paradigm® insulin pumps, Enlite® sensors and Guardian® software (able to automatically stop the pump infusion to prevent hypoglycemia) were switched from previous insulin to Faster Aspart. Data from the previous 3 months and 3 months afterwards were obtained from the Guardian® software and compared by Student's paired t-test. Satisfaction data were obtained by analogic scales. Data are given as mean $\pm$ S.D.
Results
Sixteen patients (age 23 ± 6.8 years, 69% female) were switched to Faster Aspart from lispro (25%) and aspart (75%). Their glycemic variability coefficient (100 x mean glucose/S.D.) was significantly reduced from 41.3 ± 9.2% to $34.2 + 8.9$% ($P = 0.0342$). Time on glucose <70 mg/dl was significantly reduced from 3.8 ± 1.3% to $2.9 + 0.9$% ($P = 0.0301$), Time on glucose >180 mg/dL was reduced from 6.7 ± 1.9% to $5.5 + 1.8$% ($P = 0.0766$), HbA_{1C} decreased from 7.3 ± 0.9% to $6.9 + 0.8$% ($P = 0.1940$). On a 0–10 visual analogical scale, patient satisfaction was significantly increased from 6.3 ± 1.8 to $7.8 + 1.4$% ($P = 0.0133$). No unexpected adverse effects were reported.
Conclusions
In this open, uncontrolled study, switching from previous insulin analogues to Faster Aspart was well-tolerated and significantly reduced glycemic variability and time on hypoglycemia; patient satisfaction was significantly increased, and trends for lower time on hyperglycemia and lower HbA1C were found. We conclude that Faster Aspart is an advantageous alternative to the classic fast-acting insulin analogues for patients on sensor-augmented insulin pump therapy.

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P972

The effects of metformin monotherapy on lipid profile in patients with type 2 diabetes mellitus

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Background
Due to its efficacy and safety, metformin is the most commonly used drug in a single-agent therapy of type 2 diabetes mellitus (T2DM), after lifestyle modifications failed to obtain a desirable effects. Despite his main effects in improving glycemic control, it is also stated that it has a beneficial effects on lipid profile, which may be attributable to improved insulin sensitivity, weight loss and reduction of irreversibly glycated low density lipoprotein cholesterol (LDL-C). Clinical implication of these pleiotropic actions is on potential attenuation of cardiovascular events in T2DM.

Objective
To investigate possible correlation between daily dose of metformin used as a monotherapy and a lipid profile in patients with T2DM.
Methodology
A multi-center observational epidemiological survey included patients with T2DM who were treated with metformin as a monotherapy for at least 6 months. Demographic information, anthropometric measurements, fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), cholesterol, tryglicerides, high density lipoprotein cholesterol (HDL-C) and LDL-C are recorded and data statistically analizied.
Results
The study enrolled a total of 184 patients, aged between 30 and 85 years (mean 60.55 ± 10.05 years), of whom 75 (40.8%) male and 109 (59.2%) female, with mean body mass index 29.15 ± 4.46 kg/m^2 and average HbA1c of 6.78% (range between 4.8-14.1%). Among them, the mean level of LDL-C was 3.47 mmol/l while the median daily dose of metformin was 1429.6 mg. No significant correlations are observed between metformin dose and levels of cholesterol, triglycerides, HDL-C and LDL-C. Significant positive, weak to moderate, correlation is observed between HbA1c and LDL-C (rho = 0.237; $P = 0.002$) but dispersion of extreme values makes difficult to evaluate this correlation better.
Conclusion
Patients with T2DM on metformin, administered as a monotherapy, may benefit not just from its effect on glycemic control but also from its influence on altered lipid profile which may further reduce cardiovascular risk. Based on this survey, this effect seems to be dosage-independent but larger studies are required to examine this association.

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P973

Effects of diabetes mellitus on female sexual function

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Objective
The purpose of the present investigation was to evaluate sexual function among diabetic women
Methods
In this study, diabetic women with stable partner were requested to fill out the Brief Index of Sexual Functioning for Women(BISF-W) and a general demographic questionnaire containing personal and partner data.
Results
A total of 60 women with mean 42.8 ± 10.4 years were surveyed. The prevalence of sexual dysfunction was 48.3%. The identified problems were lack of vaginal lubrication (38.4%) inability to orgasm, lack of sexual arousal (70%), decreased desire, dyspareumia. The was a correlation between the duration of diabetes mellitus and sexual dysfunction. The was no correlation between sexual dysfunction and type of diabetes mellitus. The others factors altering sexuality were age and menopause.
Conclusion
Sexual dysfunction is frequent in diabetic women. Its onset and severity are largely influenced by the duration of diabetes mellitus and age.

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P974

Canagliflozin: Ankle-Brachial index (ABPI) and risk of amputations

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Objectives
Assess the canagliflozin effect on the ABPI in patients without previous treatment with iSGLT-2 as a possible etiology of tissue hypoperfusion and a risk factor for amputations.
Material and methods
Prospective observational study where we analyzed patients diagnosed of type 2 diabetes mellitus (DM2) with poor metabolic control and without prior treatment with iSGLT-2, which is initiated treatment with canagliflozin. Clinical, biochemical parameters and baseline and after two months-advers events were analyzed. Statistical analysis (SPSS v. 20.0): Student's t test for paired samples.
Results
We analyzed 12 patients (58.3% males). 16.7% of active smokers and 41.7% of ex-smokers. 66.7% hypertensive and dyslipidemic. Microvascular complications: 25% nephropathy, 8.3% retinopathy and 16.7% diabetic neuropathy. Macrovascular complications: 25% ischemic heart disease, 8.3% cerebrovascular accident and none present chronic ischaemia. 58.3% were in the treatment with antidiabetic agents and the rest of them with insulin (basal, basal-plus and basal-bolus) and antidiabetic agents + aGLP1. Table 1 shows the basal anthropometric and clinical characteristics and 2 months after starting new treatment.Results: significant weight reduction: 3.35 kg ($P = 0.002$), basal glycaemia: 50.5 mg/dl ($P = 0.007$) and HbA1c:1.15% ($P = 0.016$).There are no significant changes in ketonemia. The reduction of ABPI or GFR was not statistically significant. Treatment was withdrawn in two patients due to genitourinary complications, there were no macrovascular events, hospitalizations or deaths.

Table 1

Variable	Mean	Standard deviation
Age (years)	48	8,64
Size (cm)	1,56	0,065
Pre-Weight (kg)	57,50	18,66
Pre-BMI (kg/m^2)	22,50	7,41
Doses of insulin (UI)	15	15,45
Pre-glucose (mg/dl)	102	55,66
Pre-HbA1c (%)	7,1	1,47
Pre-uric (mg/dl)	3,30	1,09
Pre-total cholesterol (mg/dl)	110	39,65
Pre-LDL (mg/dl)	29	35,81
Pre-HDL (mg/dl)	27	12,95
Pre-triglycerides (mg/dl)	71	108,17
Pre-creatinine (mg/dl)	12	0,77
Pre-glomerular filtration (GFR) (ml/min)	47	17,20
Pre-left ABPI	0,80	0,13
Pre-right ABPI	0,60	0,21
Pre-Ketone bodies (mmol/l)	0,10	0,04
Post-weight (kg)	56,00	18,48

Conclusions
This study shows the safety of canagliflozin in patients with reduced ABPI, with no amputations during this time period. It's advisable to expand the number of patients and the follow-up time to obtain more consistent results.

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P975

Impact of diabetes on professional activity

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Introduction
Diabetes is a chronic metabolic disease that can have a significant impact on fitness for work. The aim of our study was to study the impact of diabetes on work activity in diabetics.
Methods
It was a descriptive and analytical study. It was conducted in 200 diabetic patients at the National Institute of Nutrition in Tunis. Patients received a clinical examination and standard biological assessment.
Results
We included 200 patients with type 2 diabetes. The mean age was 52.78 ± 14.2 years. The mean duration of diabetes progression was 12 ± 8.41 years. Mean HbA1c was 9.9 ± 2.09%. In our study, 1.5% were under dietary rules only and 51% under insulin therapy. The rest (47.5%) was on oral antidiabetic drugs. Most of them were workers (38.7%), civil servants (24.7%), drivers (10.9%), farmers (9.1%) and teachers (8.9%). The rest of the population was assigned to other professions. Episodes of hypoglycemia were reported by 28.6% of patients. Absenteeism due to diabetes was observed in 55.4% of cases. The main causes of absenteeism were semi-annual controls at the consultation (38%), hospitalization (18%) and episodes of hypoglycaemia (11%). Absenteeism was significantly correlated with the imbalance of diabetes ($P < 0.005$) and complications ($P < 0.05$).

Conclusion
Diabetes is a debilitating disease that impacts the working life of the patient by reducing the chances of work but also limiting physical abilities during work. In order to limit work accidents and absenteeism among diabetic workers, regular monitoring and strict supervision is necessary.

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P976

Clinical characteristics of human POMC, PCSK1, and LEPR deficiencies

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Background
Rare genetic disorders of obesity result from an impaired central melanocortin pathway, comprised of multiple genes, including *POMC, PCSK1*, and *LEPR*. Because of their rarity and the difficulty in identifying individuals with pathogenic mutations in these genes, a complete understanding of these disorders remains unclear. We reviewed previous case reports of individuals with *POMC, PCSK1,* or *LEPR* deficiencies to understand their clinical characteristics and to identify potential features of individuals with obesity who should be genetically screened for these rare genetic disorders of obesity.
Methods
Published manuscripts and conference abstracts available in PubMed and Embase through January 1, 2019, describing the medical history of individuals with *POMC*, *PCSK1*, and *LEPR* deficiencies were included. Individuals were excluded if only limited information, such as age, sex, variant, and weight/BMI, were provided. The prevalence of each characteristic was calculated for each genotype by dividing the number of cases with the characteristic by the total number of cases.
Results
Fifty-eight articles and 18 abstracts were identified, describing clinical characteristics of 150 individuals. Hyperphagia was described in 68, 16, and 91%, and early-onset obesity (defined as occurring at $\leq$6 years of age or as described by the author) in 90, 47, and 97% of individuals with a deficiency in *POMC, PCSK1*, and *LEPR*, respectively. In individuals with a *POMC* deficiency ($n=31$), common characteristics included adrenocorticotropic hormone deficiency and hypocortisolism (68%), hypoglycemic episodes (52%), and developmental delays in childhood (39%). Only 29% had red hair, although 65% had light or pale skin for their ethnicity. In individuals with a *PCSK1* deficiency ($n=43$), common characteristics included gastrointestinal complications in the first weeks of life (usually postnatal diarrhea; 86%), hyperproinsulinemia (65%), metabolic acidosis (53%), hypoglycemia (49%), diabetes insipidus (47%), polydipsia/polyuria (47%), hypothyroidism (44%), failure to thrive in infancy (42%), and hypocortisolism (37%). In individuals with a *LEPR* deficiency ($n=76$), common characteristics included hyperinsulinemia (49%) and delayed puberty (39%); hypogonadotropic hypogonadism and a history of frequent infection were each reported in 34%.
Conclusions
This comprehensive literature search and analysis of *POMC, PCSK1,* and *LEPR* case histories suggests potential features for identifying individuals with obesity who should be genetically screened for these rare genetic disorders. Early-onset obesity and hyperphagia are common characteristics that cause substantial disease burden in individuals with rare genetic disorders of obesity and additional burdens to families and caregivers. Standardized definitions for severe obesity and hyperphagia may also help healthcare providers identify these individuals.

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P977

Association between physical inactivity and socioeconomic factors and lifestyle among Tunisian adolescents

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Background
Physical activity is associated with several health benefits, including lower obesity and diabetes risk. Many different factors influenced physical activity patterns of adolescents in a complex interactive way. The aim of this study was to assess association between physical inactivity and socioeconomic factors and lifestyle among Tunisian adolescents.
Methods
A cross-sectional study was carried out in Sousse, Tunisia during the school year 2017–2018. Study participants were enrolled by a two-stage and proportional sampling with cluster selection strategy to get a representative sample. Physical inactivity was defined as $<$300 min/week of moderate and vigorous physical activity. Anthropometric measurements, body image, socio-economic and lifestyle determinants were assessed. A self-administered questionnaire was used for obtaining information from students. We used SPSS software version.20 for data analysis. Odds ratios for physical inactivity were calculated using binary logistic regression analysis. *P*-value$<$5% was adopted for all analyses as the threshold for statistical significance.
Results
We included 1399 adolescents in our study, more than half were girls (60.5%) and the mean age was 17 ± 1.5 years. The prevalence of physical inactivity was 58%. It was significantly higher among girls (63.7%) than boys (46.5%) and increased slightly with age. Obese adolescents and those perceiving an overweight were significantly more physical inactive (73.2% and 65.9% respectively) than normal weight adolescents and those perceiving a normal weight (54.9% and 48% respectively). Physical inactivity among boys was directly related to heavier weight status, and inversely related to healthy diet, and the higher educational level of father. Physical inactivity among girls was inversely related to healthy diet.
Conclusions
The prevalence of physical inactivity among Tunisian adolescents is high, mainly among girls. Gender, parental educational levels, and unhealthy diet are important factors of physical activity practice among adolescents.

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P978

Doctor, is it cancer? A rock-hard breast lump in an anxious type 1 diabetic male-to-female transgender patient

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Introduction/Aim
Transgender people often worry about side effects of their hormonal therapy, including breast cancer, which is an exceedingly rare occurrence. Hereby we present the case of a patient with an uncommon metadiabetic complication that can be easily confused with breast cancer, with the aim of raising awareness on this condition.
Material and Methods
Review of the Clinical Record of the patient and of the relevant literature.
Results
A 26 year old male-to-female transgender patient had been treated with antiandrogenic (oral cyproterone acetate) and estrogenic therapy (oral and transdermic 17-β-estradiol) since her 14th birthday, and had often self-medicated with higher than recommended doses. She was diagnosed with type 1 diabetes at the age of 12, but she was often careless with her diet and insulin treatment, omitting most of her fast-insulin doses although rarely the daily basal insulin. Her HbA1C was usually in the 10–12% range, in spite of having access to intensive diabetic education; she skipped most of the scheduled appointments and repeatedly rejected insulin pump therapy. She had developed diabetic non-proliferative retinopathy, with multiple microaneurysms, and mild diabetic cheiroarthropathy, with no other known chronic complications. In a routine visit she was visibly anguished about a lump she had noticed in her left breast in the last few months. It was easily palpable but adhered, painless, rock-hard, and about 3 cm in diameter, with no other palpable lesions in the breasts and armpits. Fine needle aspiration cytology was attempted on the spot, but the lesion was too hard and no sample could be attained; a TruCut core biopsy was performed a week later and the final diagnosis was fibroinflammatory mastitis (diabetic mastopathy). The patient was reassured that this was a benign lesion and that surgery was unwarranted.

The available literature suggest that hormonal therapy in transgender people is not associated with increased risk of any type of malignancy.
Conclusions
Diabetic mastopathy is an unusual metadiabetic complication, typically diagnosed in female diabetic patients with a long history of poor metabolic control (exceptionally in males). It has never been before reported (in our knowledge) in a transgender patient. It is a benign condition usually not requiring surgery, but clinically indistinguishable from breast carcinoma, which may lead to unnecessary anxiety or intervention. Cancer-anxious transgender patients may be reassured that their hormonal therapy is not associated with increased malignancy risk.

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P979

Hypoglycemia: a major problem in diabetics

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Introduction
Hypoglycaemia is the most serious side effect inherent in the search for good glycemic control in diabetic patients, which can be fatal and often cause significant physical and psychosocial morbidity.
Aim
The aim of our study was to estimate the frequency of hypoglycaemia and to determine the factors associated with their occurrence.
Methods
This was a retrospective descriptive study. The study is conducted in 200 diabetic patients at the National Institute of Nutrition of Tunis. Patients underwent careful clinical examination and a standard biological assessment.
Results
We included 200 patients with type 2 diabetes. The mean age was 52.78 ± 14.2 years, 58.5% were female. The mean duration of diabetes progression was 12 ± 8.41 years. Mean HbA1c was 9.9 ± 2.09%. The circumstances of discovery of hypoglycemia were a fictitious dose of insulin therapy in 8% of cases, unstable diabetes in 36%, adrenal insufficiency in 20%, insulin overdose in 18% and in 13% of cases are due a lack of therapeutic education (skipping meals, inadequate physical activity, injection of lipodystrophies, poor management of syringes), and of undetermined origin in 5% of cases. The clinical signs are represented in all patients by neurovegetative signs. Neuroglucopenic symptoms were present in 67% of our patients. Blood glucose levels at the time of hypoglycemia ranged from 0.13 to 0.55 g/l. The immediate evolution after resuscitation and resuscitation was marked by the recovery of the state of consciousness in all our patients.
Conclusion
Hypoglycemia is a diagnostic and therapeutic emergency because of the risk of irreversible neurological damage. It is most often iatrogenic hypoglycaemia caused by the hypoglycemic treatment of the diabetic patient but other causes are possible and to search if necessary. Several factors are associated with an increased risk of hypoglycaemia in diabetics, which leads to caution in determining treatment.

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P980

The influence of the prediabetes phenotype on the efficacy of lifestyle interventions to improve glycemia, insulin resistance and postprandial hyperinsulinaemia

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Three phenotypes of prediabetes are known: impaired fasting glucose (IFG), Impaired glucose tolerance (IGT), and combined IFG/IGT. IFG is associated with impaired early phase and normal second-phase of insulin secretion. IGT is associated with both impaired early and late phase of insulin secretion. Numerous studies have demonstrated efficacy of lifestyle intervention in improving 2-hr oral glucose tolerance and fasting plasma glucose (FPG) in individuals with prediabetes, while other studies have failed to demonstrate improvements in 2-hr oral glucose tolerance and FPG. The aim of this study was to determine the influence of prediabetes phenotype on improvements in glucose homeostasis with resistance training (RT) or low-carb diet.
Methods
Obese prediabetics were treat by resistance training (RT) (IFG = 22, IGT = 24, IFG/IGT = 20; or with low-carb diet (LC) (IFG = 23, IGT = 25, IFG/IGT = 20). RT group (aged 45 ± 5 years.; BMI 34 ± 3.5 kg/m^2) completed a resistance training twice per week (approximately 150 minutes per week) for 12 weeks without diet. Low-carb group (aged 44 ± 3.9 years.; BMI 35 ± 4.2 kg/m^2) achieved low-carb diet for 12 weeks without physical activity. Body weight and waist circumference, fasting plasma glucose, 2-hr oral glucose tolerance, baseline assessments homeostasis model of insulin resistance (HOMA-IR), estimated insulin sensitivity index (ISI) and oral glucose-induced insulin were examined before and after the intervention.
Results
Waist circumference and BMI were decreased in both group with no difference between phenotypes. Fasting glucose did not change ($P > 0.05$) in RT group but it improved in LC group (6.64 ± 0.32 mmol/l vs 5.65 ± 0.41 mmol/l, $P < 0.05$). However, 2-hr oral glucose tolerance in RT group improved in those with IGT (9.34 ± 0.52 mmol/l vs 7.31 ± 0.71 mmol/l, $P < 0.05$) and IFG/IGT (9.86 ± 0.71 mmol/l vs 8.20 ± 0.81 mmol/l). In LC group 2-hr oral glucose tolerance improved in those with IGT and IFG/IGT; FPG improved in those with IFG. There were no significant changes in ISI and HOMA-IR following the RT program but there were following LC program ($P < 0.05$). Oral glucose-induced insulin secretion was reduced only in the LC group (65 ± 11 mU/l vs 29 ± 9.2 mU/l, $P < 0.05$).
Conclusions
Resistance training appears to improve 2-hr oral glucose tolerance in individuals with prediabetes but did not improve FPG. Low-carb diet affect 2-hr oral glucose tolerance and FPG, and postprandial hyperinsulinemia in obese prediabetic individuals. The individualized approach is suggested to clinician's for better treatment of individuals with prediabetes.

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P981

Effectiveness and tolerance of liraglutide and bupropión/ naltrexone: clinical experience

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Introduction
Different pharmacological therapies for obesity have become available in the last years. It is important to know their effectiveness in real-world practice and their acceptance among patients.
Objectives
To analyze the anthropometric changes, daily dosis, side effects and treatment withdrawal in patients treated with Liraglutide or Naltrexone/Bupropion in clinical practice.
Material and methods
Retrospective descriptive study. We analysed the percentage of weight loss, side effects and withdrawal causes in patients treated with Liraglutide or Naltrexone/Bupropion after 1, 3, 6 and 12 months.
Results
Hundred patients were included. Baseline characteristics are shown in TABLE. The daily dosis of Liraglutide (mg) were: 0.6 (1.2%), 0.9 (1.2%), 1.2 (25.3%), 1.8 (36.1%), 2.1 (1.2%), 2.4 (13.25%) and 3.0 (20.48%). Daily dose of Naltrexone/Bupropion (mg) were: 8/90 (11.76%), 16/180 (11.76%), 24/270(17.65%) and 32/360 (58.8%). The % of weight loss were: for Liraglutide −3.4%, −6.1%, −6.9% and −7% at 1, 3, 6 and 12 months ($P < 0.05$ for all); for Naltrexone/Bupropion −4.1% and −5.7% at 1 and 3 months ($P < 0.05$) and −5.6% at 6 months ($P = 0.08$). There were no differences in the % of weight loss between high (>1.8 mg) and low (≤1.8 mg) Liraglutide dose. Withdrawal percentage was: 25.3% with Liraglutide, especially due to economic reasons (28.5%), lack of effectiveness (23.8%) or side effects (19%); 29.4% with Naltrexone/Bupropion especially due to side effects (60%) or lack of effectiveness (25%). Side effects were reported in 52.54% patients treated with Liraglutide, the most common being gastrointestinal effects. One patient had depression symptoms that needed treatment and ceased after Liraglutide withdrawal. 66.7% of patients treated with Naltrexone/Bupropion reported side effects, the most common being nausea, headache, dry mouth or dizziness.

Table 1

	Liraglutide (*N*=83)	Naltrexone/ Bupropion (*N*=17)
Age (years)	52.1±12.8	49.4±13.4
Women	62.4%	83.3%
Hypertension	37.3%	16.6%
Diabetes	4.8%	0%
Pre-Diabetes	38.6%	61.1%
Dyslipidemia	36.1%	11.1%
Obstructive-Sleep-Apnea	25.3%	23.5%
Weight(kg)	101.1±17.4	110.2±20.2
BMI (kg/m^2)	37.2±4.7	41.4±6.3
Waist Circumference (cm)	116.2±14.0	123.6±13.6
Glucose (mg/dl)	95.2±9.9	95.7±10.8

Conclusions
We observed a significant loss of weight after Liraglutide treatment. Weight loss in Naltrexone/Bupropion group was only significant for the first 3 months. Most of patients in Liraglutide group used <3mg/day, mainly for economic reasons. The percentage of withdrawal was relatively high in both groups, especially due to side effects in Naltrexone/Bupropion and to price or lack of effectiveness in Liraglutide group.

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P982

The incidence of pancreatic cancer in diabetic patients

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Introduction
Diabetes mellitus has been claimed to be a risk factor for pancreatic cancer. CA 19-9 is known as a tumor marker for pancreatic cancer upper gastrointestinal tract, ovarian hepatocellular, and colorectal cancers, as well as in inflammatory conditions of the hepatobiliary system, biliary obstruction and in thyroid diseases.
Aim of the study
To evaluate the level of Ca19-9 in diabetic patients and the incidence of pancreatic cancer.
Material and methods
We enrolled in the study 59 subject diagnosed with diabetes. Patients diagnosed with any kind of cancer were excluded. Age, gender CA 19-9, HbA1c were measured.
Results
From a total of 59 patients 61.1% (36) were males and 38.9% (23) were female. Mean age was 56.8±10.6 years old.. Mean value of HbA1c was 8.4% normal value 4.8–6.1% and 40.6% were well controlled HbA1c under 7%; 15.2% were not well controlled HbA1c 7.1–8% and 44.2% were poorly controlled HbA1c over 8%. The average CA 19-9 level was 76.53±467.9 normal value <37 U/ml range (0.6–3608). 89.8% (53) patients had normal value of Ca 19-9 and 10.2% (6) had level over 37 U/ml with only one patient 1.69% diagnosed with pancreatic cancer. Patients with higher level of CA 19-9 were the patients with higher level of HbA1c (average 11.7%) The value of R(Pearson coefficient correlation) is 0.6359 that it means for a moderate positive correlation between level of HbA1c and Ca 19-9. 16.6% of patients with high level of Ca 19-9 had pancreatic cancer.
Conclusion
This study showed that glycemic control influences level of CA 19-9 and it should be interpreted with regard to diabetes status and should be kept in mind as a confounder, therefor maybe its necessary to redefine the normal range of CA19-9 in diabetic patients. Incidence of pancreatic cancer was 1.69%.

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P983

GLP-1 Agonist as an effective add-on basal-bolus therapy in type 2 diabetic patients

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Introduction
Despite basal-bolus regime many type 2 diabetic patients do not achieve good glycemic control. Obesity and a large number of insulin units per day, even in combination with metformin and/or SGLT-2 inhibitors, are challenge in treatment of those patients.
Aim
To assess changes of glycemia, body weight and daily dose of insulin in a group of type 2 diabetic patients treated with basal-bolus scheme (with/without peroral agents), starting with an addition of weekly GLP-1 agonist dulaglutide.
Material and methods
Twenty-two patients (9 female, 13 male) with type 2 diabetes were included. Metabolic parameters (body weight, body mass index /BMI/, HbA1c, fasting glucose, postprandial glucose, daily basal insulin dose, daily bolus insulin dose) were observed in the beggining of the study and 3 months later.
Results
For women: average initial body weight was 111.8±15.5 kg, BMI 43.3±7.1 kg/m^2, HbA1c 8.4±1.2%, C-peptide value range 0.57–1.21 pmol/mL, fasting glucose 9.2±2.2 mmol/l, postprandial glucose 11.3±3.2 mmol/l, daily basal insulin 54.1±28.1 units (range 22–132), daily bolus insulin 62.6±37.9 units (28–150). Three months later patients lost body weight 3.2±2.4 kg (0–7 kg), HbA1c was 7.2±1.0%, fasting glucose 7.3±1.4 mmol/l, postprandial glucose 8.2±1.7 mmol/l, daily basal insulin was lower: 48.4±37.1 units (range 0–120), daily bolus insulin decreased to 45±27.2 units (range 0–80).
Male patients: average initial body weight was 133±19.3 kg, BMI 43.2±6.5 kg/m^2, HbA1c 8.7±1.2%, C-peptide value range 0.42–1.31 pmol/mL fasting glucose 8.2±1.7 mmol/l, postprandial glucose 10.5±2.5 mmol/l, daily basal insulin 97.9±135.4 units (range 13–540), daily bolus insulin 82.9±51.9 units (range 20–200). Three months later patients lost body weight 4.4±4.1 kg (0–13 kg), HbA1c was 7.3±0.8%, fasting glucose 8.0±1.8 mmol/l, postprandial glucose 8.7±1.9 mmol/l, daily basal insulin dose was lower: 53±33.2 units (range 0–120), daily bolus insulin also decreased to 48.8±40 units (range 0–146).
Conclusion
Addition of GLP-1 agonist on basal-bolus regime in type 2 diabetic patients resulted in weight lost in almost all patients, reduction of basal and bolus daily doses, especially in insulin resistant patients, and achieving a better glycemic control.

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P984

The relation between HbA1c, glucose management indicator and average glucose parameters

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Conflicting results of estimated average glucose (eAG) calculated from HbA1c and average glucose values (AG) derived from continuous glucose monitoring (CGM) are a very frequent source of confusion and frustrations in the dialogue with patients. Recently the term glucose management indicator (GMI) has been coined to describe HbA1c estimated from AG. The aim of this presentation is to elucidate the relation between calculated and estimated HbA1c and average glucose values on the basis of existing regression lines. The accepted equation translating eAG to HbA1c is: HbA1c (%) = 0.63 X eAG (mmol/l) + 1.63: (Nathan

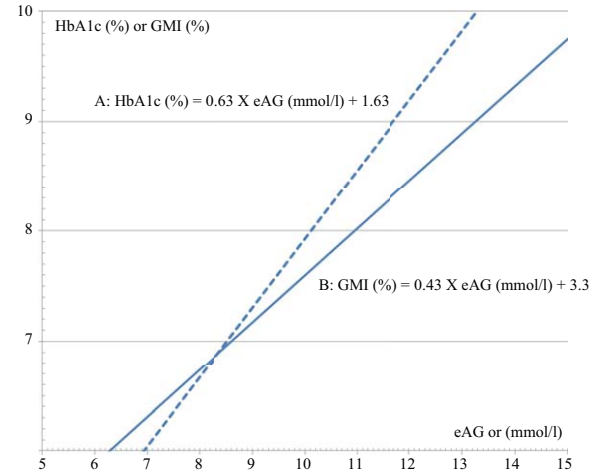

Figure 1

DM *et al*, Diabetes Care,2008; 31: 1473–80). In addition: GMI (mmol/mol) = 4.70587 X AG (mmol/l) + 12.71 (Bergenstal *et al*, Diabetes Care 2018; 41:2275–80). The master equation connecting HbA1c (mmol/mol) and HbA1c (%) is: HbA1c (mmol/l) = 10.93 X HbA1c (%) – 23.5. It follows that: GMI (%) = 0.43 X AG + 3.3. The two lines A: HbA1c (%) = 0.63 X eAG (mmol/l) + 1.63 and B: GMI (%) = 0.43 X AG + 3.3 plotted in the same diagram (figure) cross at a point corresponding to a glucose value of 8.4 mmol/l and HbA1c/GMI of 6.9%. A HbA1c value of 8.5% corresponds to eAG 10.9 mmol/l. A GMI of 8.5% corresponds to AG of 12.1 mmol/l. For HbA1c values higher than 6.9% the eAG value is progressively lower than AG for a similar GMI value. For patient with good glycemic control HbA1c/GMI and eAG/AG is nearly identical.

Conclusion

The present equation translating HbA1c to eAG underestimates AG based on CGM for patients with poor glycemic control. The diagram shown may be valuable when explaining a patient seemingly conflicting HbA1c and GMI results.

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P985

An overview of urinary tract infection in diabetic patients

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Diabetic patients have higher risk of urinary tract infection (UTI). Increasing of infections in patients with diabetes mellitus is conditioned by an immunosuppressive condition resulting from immune damage.

Objective

To give some dates about urinary infection in patients with diabetes mellitus, that are presented for consultation at the service of Endocrinology in the American Hospital, Tirana, Albania

Material

This study was conducted on urine samples from 125 adults diabetic patients that's were presented for evaluation at the American Hospital, Tirana, Albania. In order to quantify the uropathogens, midstream urine samples were collected in sterile leak proof culture bottles and streaked onto diverse bacteriological media. The antimicrobial susceptibility test was performed to determine the resistance/-susceptibility pattern of isolated uropathogens.

Results

Mean age resulted 58.7 years old and S.D. ±21.7. Females were 66.4%. Asymptomatic patients were 26.4% of patients. Based on their medical anamnesis 42.4% of patiens were classified as patient with chronic UTI. Uroculture resulted positive in 58.4%. All patients were with diabetes more than one year. Average HbA1c resulted 8.1%. The predominant isolates were Escherichia coli with 46.5%, Enterococcus faecalis 15%, Staphylococcus aureus 13.7%, Klebsiella pneumoniae 12.3%, Pseudomonas species 8.2%, Proteus mirabilis 2.7% and Citrobacter spp 1.3%. Multi-drug-resistance was observed in 12.3% of all pathogen isolations.

Conclusions

One more time this study revealed that the predominant pathogens of UTI were Gram-negative bacilli, particularly E. coli. Other uropathogens such as S. aureus and Kliebsiella spp. were the second and the third dominant pathogens isolated respectively.

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P986

Weight loss in PCOS - benefits of Metformin and Liraglutide - a single institution experience

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Obesity commonly occurs in PCOS and contributes to increased metabolic risk and low self esteem. Advice on weight loss underpins all management strategies in the obese lady with PCOS but weight loss can remain elusive despite best efforts. We wished to determine how diet advice alone compared to metformin and/or liraglutide in our patients.

Methods

We conducted an observational retrospective anonymized review of patients attending an endocrinology clinic actively seeking management of obesity associated with PCOS. All patients received advice on carbohydrate controlled weight reduction diet from a registered dietician and were encouraged to increase exercise levels. One group of patients opted to follow a diet and exercise program only ($n=12$, mean age 25±7) - 10 declined medication, 2 were intolerant of metformin. A second group of patients also received metformin ($n=31$,age 30.7±7.3). A third and final group of patients were offered and availed of liraglutide therapy ($n=10$, age 36.3±7.2, 7 of these patients also received metformin).

Results

Those patients who received liraglutide were significantly heavier than both other groups – 116.3±21.1 kg versus 86.3±9.7 kg for diet only and 93.0±16.1 kg for metformin. At six month follow up there was no statistically significant weight loss in the diet group while both other groups achieved statistically significant weight loss and reduction in BMI. See Table. 3 of 12 diet patients achieved weight loss > 5% compared to 9 of 10 liraglutide patients and 22 of 31 metformin treated patients.

	Wt Pre (kg)	Wt Post (kg)	*P* value paired t test	BMI Pre (kg/m^2)	BMI Post (kg/m^2)	P value paired t test
Diet	86.25±9.7	83.6±9.3	$P=0.173$	31.9±3.4	30.8±2.9	$P=0.1705$
Met	93±16.1	85.7±17.1	$P<0.0001$	33.4±5.1	30.8±6.0	$P<0.0001$
Lir	116.3±21.1	107.1±23.5	$P=0.046$	41.6±4.2	39.4±6.8	$P=0.0392$

Conclusion

While retrospective studies may contain inherent bias in our group of patients, therapy in the form of metformin and liraglutide with diet and exercise advice was superior to diet & exercise alone. Liraglutide was offered to patients who were older and had significantly higher BMI at first presentation.

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P987

Epidemiological, clinical and biochemical characteristics of metabolic syndrome in adults living in South of Tunisia

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The metabolic syndrome (MetS) is a constellation of physiological and biochemical abnormalities characterized by obesity, hyperglycaemia, elevated triglycerides and decreases in high density lipoprotein cholesterol (HDL-C), and hypertension. The MetS promotes atherosclerosis, and increases the risk of developing diabetes and cardiovascular disease (CVD), as well as rates of mortality. Thus, it has become one of the major public health challenges worldwide. In Tunisia, few studies have described the prevalence of MetS and its related factors, hence restricting the quality of information available on the magnitude of this problem in the country. We studied a retrospective cohort of 602 patients explored in the department of Endocrinology of Sfax (south of Tunisia). The MetS was defined according to the National Cholesterol Education Program–Adult Treatment PanelIII. 66% of patients have a medium level education. The mean age was 58.6 years, sex ratio 3 F/1M, average weight was 82±16 kg, waist circumference was 110±11 cm, and body mass index was 33±5.7 kg/m^2. Hyperglycemia was the most common found in 94.7%. Arterial hypertension and hypertriglyceridemia were less frequent (83% and 70.1% respectivly). 89.7% of our patients have type 2 diabetes. Cardiovascular complications was found in 26% mainly coronary insufficiency in 18% followed by stroke, myocardial infractus and artheritis (7%, 6% and 5% respectivly). 1% of women bave polycystic ovary syndrome.Characteristic features of MetS in patients seen in south Tunisia were found to be similar to those described in the literature. Other more large-scale representative studies would be useful to establish the epidemiology of MetS in Tunisia.

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P988

Effect of high protein diet over caloric expenditure and thermogenesis in individuals with obesity

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Introduction
The caloric expenditure and thermogenesis are very important aspects in the obesity problem, mostly underestimated. The 'Protein Leverage Hypothesis' (PLH) promotes the effect of satiety, delaying the hunger sensation; thus entails the regulation of caloric intake and body weight, as well as, the modification of thermogenic activity and energy expenditure. However, the effect of high protein diet over the physiological components of energy expenditure has not been evaluated.
Objective
To evaluate in adults with obesity the effects of a caloric restriction plan with high protein content (25%) compared with low protein content (10%), over components of energy expenditure and thermogenesis, after 4 weeks of intervention.
Materials and methods
We recruited 47 adults with obesity (BMI $\geq$30kg / m^2) aged 20-50, randomized into two diet groups. Before and after the intervention, anthropometric data were measurement. We estimated of caloric expenditure at rest by indirect calorimetry. Temperature measures in the supraclavicular cavity were recorded for 1 hour with the iButton DS1921H device. Glucose, creatinine and lipid profile were detected. Plasma levels of N^1-methylnicotinamide- (MNA-1) and N^{1}, N^{12}-diacetylspermine were quantified by LC-MS.
Results
At baseline individuals from both groups showed no differences between them. After the intervention, significant reduction in body weight, BMI and waist circumference was observed in both groups ($P<0.0001$, $P=0.003$ and $P<0.0001$, respectively). In the diet group with high protein content there was a significant decrease in the levels of MNA-1 ($P=0.0001$), and increase in the concentrations of N^{1},N^{12}-diacetylspermine ($P=0.03$). It was also observed that the temperature of the supraclavicular cavity decreased significantly ($P<0.01$). When comparing the deltas of change of both groups, a lower calorie intake was observed in the group of high protein content. However, no significant changes in caloric expenditure were observed.
Conclusions
These preliminary data suggest that the diet rich in proteins induce major changes in the components of energy expenditure favoring weight loss. The changes observed in the temperature of the supraclavicular cavity support that the protein favors thermogenic activity. And the lower caloric intake in the high protein group reaffirms the idea of promoting the effect of satiety.

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P989

Metformin and Vitamin B12 deficiency: evaluation of vitamin B12, homocysteine and methylmalonic acid levels in type 2 diabetics

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Introduction
The American Diabetes Association guideline states that the long-term use of metformin may be associated with biochemical vitamin B12 (B12) deficiency and periodic measurement should be considered, although isolated serum B12 measurement has low sensitivity and specificity. Homocysteine (Hcy) and methylmalonic acid (MMA) are more sensitive biomarkers, the latter being more specific.
Objectives
To estimate B12 deficiency in type 2 diabetics (DM2) taking metformin according to the serum levels of B12, Hcy and MMA and correlation with duration of diabetes, exposure and doses of metformin, anemia and neuropathy.
Material and methods
Included DM2 taking metformin (MET) and DM2 control group not taking metformin (nMET). Blood count, B12, Hcy and MMA were measured. Neuropathy was assessed through the Michigan Neuropathy Screening Instrument (MNSI).
Results
A total of 56 patients were studied: 64.3% males, with mean age of 63.6$\pm$10.5 (38-83 years) and 13.8$\pm$8.4 years of mean duration of diabetes. Acid suppression drugs in 32.1%, A1C 7.7$\pm$1.2%. MET group was composed of 40 and NMET by 16 patients. MET patients were under metformin for 10.7$\pm$6.5 years, with a current dose of 2073$\pm$583 mg. MET patients had sufficient but significantly lower levels of B12 (367.4$\pm$166.5 vs 544.0$\pm$429.9, $P=0.035$). The prevalence of B12 deficiency ($\leq$211 pg/mL) was 12.5% in MET and 6.3% in nMET ($P=0.662$). Combined low and borderline B12 levels ($\leq$246 pg/mL) was 25% in MET and 6.3% in nMET ($P=0.150$). Although there were no statistically significant differences, MMA elevation (>32 ug/L) was higher in MET (23.1% vs 14.3%), but combined elevation of Hcy ($\geq$15 µmol/L) and MMA was lower (12.1% vs 14.3%). Both in the analysis for all patients and in the subgroup with eGFR >45 mL/min/1.73m^2, MMA levels was correlated with duration of DM2 ($r=0.439$, $P=0.010$, and $r=0.406$, $P=0.029$, respectively) and exposure to metformin ($r=0.454$, $P=0.026$, and $r=0.406$, $P=0.026$, respectively). No statistically significant correlations were found between B12, Hcy or MMA with age, doses of metformin, A1C, hemoglobin or MNSI scores.
Conclusion
Patients taking metformin had lower levels of B12, as already described in other studies. The results shows that B12 should be monitored in these patients. The absence of significant differences between the groups for Hcy and MMA assays may be due to the limited size of the sample. Further studies are needed to identify the risk factors for B12 deficiency and the real contribution to the development of anemia and neuropathy.

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P990

What is the factor that most influences perinatal outcomes in pregnant women with Gestational Diabetes Mellitus: Country of origin or previous Gestational Diabetes?

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Introduction
Gestational Diabetes Mellitus (GDM) is one of the pregnancy diseases with the highest rate of complications, influenced by several factors. Its prevalence has increased, with a prevalence of 7.2% in Portugal.
Objective
Characterize pregnant women with GDM and evaluate the perinatal outcomes according to the country of origin and previous GDM.
Material and methods
Cross-sectional and retrospective study. We collected clinical data and perinatal outcomes of 784 pregnancies followed at the endocrinology and diabetes clinic, from a central hospital, between 2012 and 2016. We excluded 43 cases due to lack of data or twin pregnancies. They were distributed by country of origin considering Portugal and 11 geographic regions according Statistics Division of the United Nations. The data were analyzed using SPSS software, differences were considered statistically significant when $P<0.05$. Results were presented as mean$\pm$standard deviation.
Results
In this population, mean age was 32.9$\pm$6.2 years and BMI was 27.0$\pm$5.7kg/m^2. Fasting glycemia in the first trimester was 87.1$\pm$12.3 mg/dL. Oral glucose tolerance test (OGTT) was performed in 70.4% of pregnant women. Previous GDM (pGDM) and previous macrosomia occurred in 15.5% and 8.2% of cases, respectively. Insulin therapy was used in 52.0% and associated to higher BMI (64.3% were overweight or obese, $P=0.001$) and pGDM (Odds ratio (OR) 1.8; 95%confidence interval (CI) 1.2–2.7, $P=0.005$). The gestational age at birth was 38.3$\pm$1.6 weeks, birthweight was 3147.9$\pm$529.4 g and 3.6% of newborns were macrosomic. Previous macrosomia and pGDM were related to macrosomia, with a relative risk of 6.3 (95%CI 3.0–13.1, $P=0.001$) and 2.7 (95%CI 1.2–5.8, $P=0.01$), respectively. Neonatal morbidity occurred in 23.6% and depended on mother's BMI ($P=0.027$) and pGDM ($P=0.006$) and was not different between regions. Hyperbilirubinemia was the most frequent neonatal morbidity in 18.2% of cases. We found statistically significant differences between geographic regions in fasting glycemia of OGTT (the highest value in Middle Africa women: 93$\pm$15.3 mg/dL, $P=0.001$), in BMI (the highest value in Middle Africa women: 28.4$\pm$5.3, $P=0.04$), in occurrence of hydramnium (the highest frequency occurred in Southern Asia women with 14.3%, $P=0.002$) and in birthweight (newborns of Western Europe women had a higher weight 3550.0$\pm$869.1 g, $P=0.009$).
Conclusion
Based on the analysis performed, the country of origin didn't influence the majority of perinatal outcomes and previous GDM was the factor that most influenced these results. Pregnant women with previous DMG may benefit from targeted interventions to improve outcomes.

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P991

Neuroimaging in the diagnosis of neuroplasticity in patients with diabetes mellitus

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The goal was to study neuroplasticity in patients with diabetes mellitus using neuroimaging techniques. We examined 80 patients with diabetes mellitus type 1 and 2. All were conducted general clinical examination, neuropsychological testing - MoCa test, test 12 words. All patients underwent continuous glycemic monitoring and HbA1c assessment. An MRI study was also performed on Siemens 1.5 T, the protocol included a standard examination of the brain, a proton spectroscopy, and functional MRI at rest and with paradigms. As a result, changes in the metabolites in the hippocampus were found in patients with diabetes mellitus type 1 and in the temporal and frontal areas in patients with type 2 diabetes mellitus. Resting fMRI revealed many artifacts, however, quiescent networks were identified. When conducting the exercise with a load, zones of activation were identified for various stimuli, often a decrease in demand for a task.

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P992

IN-FOCUS France: an epidemiological survey on severe hypertriglyceridaemiae assessing the comparative burden of illness of familial chylomicronaemia syndrome (FCS) and multifactorial chylomicronaemia syndrome (MCS)

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Background
Familial chylomicronaemia syndrome (FCS) is a rare, inherited disorder characterised by impaired clearance of triglyceride (TG)-rich lipoproteins from plasma, leading to severe hypertriglyceridaemia (HTG), which have major effects on both physical and mental health, and a markedly increased risk of acute pancreatitis. A large overlap in the phenotype between FCS and multifactorial chylomicronaemia syndrome (MCS) contributes to the inconsistency in how patients are diagnosed and managed worldwide. To date, there have been no systematic efforts to characterize and compare the impact of chylomicronemia on FCS and MCS patients' lives. In particular, the impact of FCS and MCS on the burden of illness (BoI) and quality of life (QoL) has not been fully described in the literature.
Methods
IN-FOCUS was a comprehensive web-, paper- and phone-based research survey of patients with either FCS or MCS, focused on capturing the BoI and impact on QoL associated with FCS and MCS. Forty-three (43) patients from France participated, twenty-two (22) of whom were diagnosed with FCS and twenty-one (21) were diagnosed with MCS. Patients described multiple symptoms spanning across physical, emotional and cognitive domains.
Results
Nearly all patients reported a major impact on BoI and QoL, with a slightly larger impact reported on each item in the FCS group. The difference between groups was statistically significant regarding the impact of the disease on patients' career choice and employment status which was reported as being significant for 33.3% of MCS patients, but for as many as 81.8% of FCS patients. In terms of symptoms and comorbidities, there were significant differences between both groups most notably in the incidence of cutaneous lesions (31.8% in the FCS group vs. 0% in the MCS group), pancreatic pain (45.4% in the FCS group vs. 9.5% in the MCS group), and chronic hypertriglyceridaemic pancreatitis (40.5% in the FCS group vs. 14.6% in the MCS group). Moreover, 59% of FCS patients had been hospitalized for acute pancreatitis on average 10 times in their lifetime, whereas 14.3% of MCS patients had been hospitalized for the same, on average only slightly over 1 time in their lifetime.
Conclusion
Both MCS and FCS imparts a considerable burden across multiple domains, with a significantly higher reported burden for FCS over MCS. The results were consistent with previous research findings.

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P993

Abstract Unavailable.

Environment, Society and Governance

P994

Effect of octyl-phenol and bisphenol A on calcium signaling in cardiomyocyte differentiation of mouse embryonic stem cells

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Endocrine-disrupting chemicals (EDCs) have similar structures with steroids hormones, which can interfere with hormone synthesis and normal physiological functions of male and female reproductive organs. Sex steroid hormones influence calcium signaling of the cardiac muscle in early embryo development. Progesterone (P4) has been reported to reduce blood pressure. To confirm the effect of P4, octyl-phenol (OP) and bisphenol A (BPA) on early differentiation of mouse embryonic stem cells (mESCs) into cardiomyocytes, P4, OP and BPA were treated at two days after attachment and media were replaced every two days. In addition, mifepristone (RU486) is a synthetic steroid that has an affinity for progesterone receptor (Pgr) and was treated for one day starting on day 11. To investigate the calcium signaling, the expression of calcium channel gene and contraction-related genes was analyzed. Beating ratio was decreased in P4, OP and BPA treatment. The *Pgr* mRNA level was significantly increased in P4, OP and BPA-treated group. However, the mRNA level of calcium channel gene, Trpv2, was significantly decreased in the P4, OP and BPA-treated group. In addition, expressions of contraction-related genes such as *Ryr2, Cam2 and Mlck3* were significantly decreased in the P4, OP and BPA-treated group. Interestingly, treatment of RU486 rescues altered calcium channel gene and contraction-related genes. P4, OP and BPA treatments resulted in the reduction of intracellular calcium level. Taken together, these results suggest that OP and BPA may impact on the inhibition of cardiomyocytes differentiation of mESCs, results in disruption of cardiomyocytes differentiation of mESCs.

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P995

Second-phase validation of developmental toxicity test using embryoid body's area

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The embryoid body test (EBT) is a developmental toxicity test method that assesses the half inhibitory concentrations of substances in the area of embryoid bodies (EBs), and in the viability of mouse embryonic stem cells (ESCs) and fibroblasts (3T3 cells). In the previous pre-validation study evaluated the predictive accuracy of the EBT using 26 coded test substances and highly accurate (above 80%) when substances were classified using the predictive model. EBT used two same endpoints as EST, the half inhibition concentrations for cell viability of mouse ESCs (IC50 E14) and 3T3 fibroblasts (IC50 3T3), but replaced the half inhibition concentration for cardiac differentiation (ID50 CM) with the half inhibition concentration for EB area (ID50 EB). We used the

hanging drop method to form an embryoid bodies. In order to verify the proposed EBT method in this study, inter-laboratory reproducibility (5 substances in common) and predictive capacity (10 substances in each laboratory) tests were performed. To ensure reliability of the study results, the tests were conducted using identity-coded test substances. The results of statistical analysis of the inter-laboratory reproducibility test indicated that reproducibility accuracy 87%, sensitivity 78%, and specificity 100%. The results of statistical analysis of the predictive capacity test indicated that the lead laboratory had reproducibility accuracy 80%, sensitivity 86%, and specificity 67%. Participatory laboratory 1 had reproducibility accuracy 80%, sensitivity 71%, and specificity 100% and participatory laboratory 2 had reproducibility accuracy 80%, sensitivity 86%, and specificity 67%. The results of the intra- and inter-laboratory 2tests were highly accuracy 83%, sensitivity 80%, and specificity 89% when substances were classified using the predictive model. EBT can accurately classify various embryotoxicants in a short time with less effort and greater validation.

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P996

When do Greeks seek information on obesity and diet?

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Introduction
Internet users perform health information-seeking searches triggered by personal symptoms or diseases. Such searches may provide information - albeit indirectly - on disease patterns and epidemiology (PLoS One. 2014, 9:e109583, PNAS 2016; 113:6689-94). It was recently reported that in Asia (more particularly in Taiwan), online searches for obesity and diet (indirectly reflecting corresponding health-seeking behaviors) at times of financial crisis (recession) were negatively related to the country's economic indicators (JMIR Public Health Surveill 2018; 4: e37).
Purpose
The assessment of web searches in Greece on obesity/diet in relation to the country's financial situation (now on a slow road to recovery from its sovereign debt crisis).
Method
Relative search volumes (RSVs or Google Trends Index) were collected online from Google Trends for 2011–2018 with the search terms 'obesity + diet' in English & Greek. For the same time period, the course of the composite Economic Sentiment Indicator (ECI; calculated from surveys according to standardized Eurostat methods) by the Hellenic Foundation for Economic and Industrial Research (IOBE) was noted. Autocorrelation coefficients (ACFs) were assessed, the time series values of the RSVs and ECI were normalized, and the cross-correlations (CCFs) of the RSVs against the ECI were calculated with an autoregressive integrated moving average (ARIMA). Finally, the seasonality of the searches was evaluated with the Kruskall Wallis test. The statistical significance was set at $P<0.05$.
Results
Online searches had annual periodicity, but after the normalization of the time series, the CCFs of RSVs vs ECI values were not statistically significant. More internet searches for 'obesity + diet' were in the spring compared to other seasons ($P<0.05$).
Discussion
In Greece, web searches on obesity and diet – unlike in other countries – were not related to the economic climate but were more prone to calendar effects, obviously reflecting differences in the country's climate/environment and the social/cultural background of its inhabitants.

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P997

Influence of structure education program on glycemic control of patients with type 1 diabetes and depression

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Introduction
In patients with type 1 diabetes (T1D), depression increases the risk for persistent hyperglycemia, diabetes complications and mortality. Most results demonstrated that depression is associated with nearly all important medical and psychosocial outcome parameters of T1D. Also, it has been demonstrated that poor diabetes self-care can result from patients' lack of knowledge or existing psychosocial issues, primarily depression. The aim of the study was to determine: the presence of depressionin patients with T1D and its impact on the level of HbA1c; impact of structured education program on the level of patients knowledgeabout T1D and level of depression.
Methods
The study included 38 patients with T1D. For assessment of the level of depression the Zung Self-Rating Depression *Scale (ZSDS)* and Beck's Depression Assessment Scale (BDI) was used, as well as questionnaire on knowledge about diabetes and self–control. Structureeducation program-'Düsseldorf model' of 5 day duration was applied and conducted in the day hospital Clinical centre of Banjaluka. All patients had HbA1c measured at the beginning of the education and at 3, 6, 9 and 12 month follow-up.
Results
Based on the ZSDS, 36 patients (94.7%) had depression, 20 (52.6%) had clinically significant level of depression, 16 (42.1%) showed mild symptoms of depression and 2 (5.2%) patients showed no symptoms of depression ($P<0.001$). In the group with depression ofdiabetic patients, 65% had unsatisfactory level of glycoregulation (HbA1c 9.8%). After education, HbA1c levels decreased by 1.8% after 6 months, and 1.2% after 12 months compared to initial levels ($P<0.005$). Results of test knowledge about T1D hasshown that patients improved their knowledge for 36.78%($P<0.005$) after education. BDI showed a score of 57 at thebeginning of examination and score was reduced to12 at the end of examination ($P<0.005$).
Conclusion
Up to now, no single treatment that consistently leads to better medical outcomes in patients with both depression and T1D has been clearly identified. Structured educational program and functional insulin therapy are efficient in improving glycemic control in patients with T1D and depression. It motivates patients in achieving better glycaemic control and beter deprresion score. Thus, the main role of diabetes team is to assess the disease course, to educate and provide psychosocial support in order for the patient to make decisions about their daily self-care and self-control.

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P998

Evaluation of patient satisfaction in an endocrinology and metabolism diseases center

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Introduction
In our country, some health institutions are allowed to constitute additional service buildings/centers in order to increase the accessibility to outpatient services and decrease the crowdiness in hospitals. We aimed to investigate the satisfaction of the patients evaluated in our endocrinology and metabolism diseases center-ENDOOTEM (Endocrinology-Nuclear Medicine-Diabetes-Obesity-Osteoporosis-Thyroid Diagnosis and TreatmentCenter)- which serves as a part of our university hospital since 2007.
Methods
Patients who were examined in our center between September 2018-January 2019 were asked to participate in satisfaction survey. 'Satisfaction surveys application guide' published by Ministry of Health of our country, satisfaction survey recommended by 'American Association of Family Physicians-AAFP' and PQ8-18 survey developed in 1994 were modified to create our own satisfaction survey.
Results
1387(58.6%) female and 979 (41.4%) male patients completed the questionnaire. The question of 'Are you satisfied with our center in general?' was answered as yes by 1374 (58.1%), partially by 625 (26.6%) and no by 353 (14.9%) patients. There were 1526 (64.5%) patients who thought that the doctor spent enough time for his/her illness and 368 (15.6%) patients who thought he/she partially spent enough time. Whether the doctor was polite and respectful was answered as yes by 1800 (76.7%), partially by 335 (14.3%) and no by 213 (9.1%) patients. There were 1930 (82.0%) patients who were completely or partially pleased with the attitude of the staff and 1988 (84.5%) patients who stated that his/her personal privacy was taken care of. Waiting rooms were not enough according to 1406 (59.4%) and not comfortable according to 1140 (48.2%) patients. The main problems were defined as difficulty of making appointment by 990 (41.8%),

waiting for a long time for evaluation of results by 1056 (44.6%), waiting for a long time for examination dates by 734 (31.0%), difficulty in transportation and car parking by 573 (24.2%) and not being able to make appointment for the same doctor by 472 (19.9%) patients. 1695 (72.2%) patients declared that they wanted to continue the follow-up in our center.

Conclusion

Majority of patients were satisfied with the services, the physicians and the staff working in our center. However, the difficulty in making appointments and physical conditions seem to be the most important problems. These results suggest that specialized centers may increase the quality of health services and the number of such centers should be increased. Nevertheless, it is important to provide the proper physical conditions before opening a specialized health center.

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P999

Low doses of persistent organic pollutants (PFOA and PCB153) increase the tumor aggressiveness of hormone-dependent cancer cells

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Persistent organic pollutants (POPs) are lipophilic chemicals that chronically accumulate in the body during lifetime from fetal life. Some POPs alter the endocrine metabolism and are considered as endocrine disrupting chemicals (EDCs). Human exposure to EDCs, even at low doses, raises some serious concerns for human health because they can participate in hormone-dependent cancer initiation and progression (prostate, breast, testis). These mostly non-metabolizable molecules are found in many daily products such as food preservatives and packaging, pesticides or residues and can accumulate in fat deposit of living organisms. A major scientific issue is thmus to be able to provide relevant tools for predictive analysis and to decipher more precisely biological mechanisms to evaluate EDCs risks. The aim of this work is to study the effects of four EDCs (Aldrin, BDE28, PCB153, PFOA), previously detected in the plasma of patients, on the aggressiveness of two human hormone-dependent cancer cell lines DU145 and MCF7, respectively for prostate and breast cancer. Each cell line was exposed to increasing doses of EDCs (10^{-12}M to 10^{-6}M) up to 72 h. Using videoimaging technology (Incucyte), we monitored proliferation, cytotoxicity and collective migration. We also assessed individual migration using Boyden chamber assays. Interestingly, we unraveled a pro-proliferative effect, with no cytotoxic effect, for PFOA and PCB153 at very low concentration (10^{-12}M) in both cell types (DU145 and MCF7), while the same effects were observed only at high concentrations (10^{-6}M) for aldrin and BDE28. We were also able to measure an increase in individual migration after PFOA or PCB153 exposure at the same concentration. To decipher the mechanisms implicated in this effect, we performed a human phospho-proteome which revealed a potential involvement of the PI3K-AKT-mTOR pathway in MCF7 cells. Our results demonstrate that PFOA an PCB153, at very low concentration, increase the aggressiveness of prostate and breast cancer cell lines suggesting that endocrine disruptors are potentially implicated in the progression of cancer during late stages of disease.

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P1000

***In vitro* effects of the endocrine disruptors DEHP, DBP and BPA on INSL3 receptor (RXFP2)**

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Introduction

Epidemiological and *In vivo* experimental studies reveal reprotoxic effects of endocrine disruptors (phthalates (DBP, DEHP) and bisphenol A (BPA)). An inverse association was found between the concentration of these endocrine disruptors and the concentration of INSL3. INSL3, a relaxine peptide, is involved in reproductive function, *via* its cognate receptor, RXFP2. The aim of this study was to characterize the involvement of RXFP2 in the effects of these endocrine disruptors.

Methods

We used HEK293 cells transiently transfected with hRXFP2 to investigate the impact of the endocrine disruptors on RXFP2 activity. Receptor activity was analyzed by measuring intracellular cAMP production.

Results

We first checked that the different PEs tested did not induce cellular toxicity (MTT test). DEHP and DBP at concentrations between 10^{-10}M and 10^{-4}M increased the action of INSL3 by 40%. In the same way, BPA between 10^{-9} and 10^{-5}M potentiated the response to the hormone by 10 to 25%. This effect was specific to RXFP2 because they did not act on the adenylate cyclase (cAMP synthesis) or on phosphodiesterases (cAMP degradation). The analysis of dose-response curves showed that DEHP, DBP and BPA increased the potency and/or efficacy of INSL3. These compounds also increased the constitutive activity of RXFP2 by about 20%. DEHP, DBP and BPA could act as agonists with positive allosteric modulation.

Conclusion

These findings suggest that RXFP2, as others G protein–coupled receptors, may be involved in the mode of action of DEHP, DBP and BPA in experimental conditions.

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P1001

Halogenous derivatives of Bisphenol A inhibit the human FSH receptor activity

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Numerous epidemiological studies link exposure to Bisphenol A (BPA) to reproductive function anomalies. Our team recently showed that BPA inhibits the action of Follicle Stimulating Hormone (FSH) on its receptor (FSHR). Water decontamination is achieved by chloration, which leads to the formation of chlorinated derivatives of Bisphenol A (Cl_XBPA), that may be found in natural environments and biological liquids or organs. In the presence of bromine, the formation of brominated derivatives of BPA (Br_XBPA) is also expected. One to four chlore or bromine atoms may link to the BPA molecule. Our work aimed at determine precisely the effects of Cl_XBPA and Br_xBPA on the activity of the FSHR. We used a CHO cell line, which endogenously and stably express the human FSHR. The activity of the receptor is assessed by measuring the cyclic AMP (cAMP) production. Cl_XBPA compounds were synthesized with sulfuryl chloride, and Br_XBPA with Br_2, and purified by LC/MS/MS. First, we verified the absence of cell toxicity of the compounds by an MTT test. BPA at the concentration of 10^{-7} M reduces the production of cAMP stimulated by FSH by roughly 40%. Likewise, Cl_XBPA diminish by 30% the response of the FSHR to FSH, without altering the basal activity of the receptor, suggesting a negative allosteric effect. Cl_4BPA (10^{-8} M) is the most powerful negative modulator of the FSH response, followed by Cl_3BPA (10^{-7} M) and Cl_2BPAs and Cl_1BPA (10^{-5} M). In the same way, Br_XBPA have an inhibiting effect on response to FSH, with up to 30% reduction. They have no effect on the basal activity of the receptor, then again suggesting a negative allosteric effect. These results show for the first time that, like BPA, halogenous derivatives of BPA can be considered as endocrine disruptors and may have reprotoxic effects that need better characterization.

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P1002

Observational study on the cardio-metabolic effects of a night shift on internists

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Introduction
Shift work has been associated with increased cardiovascular morbidity and mortality. Several studies have demonstrated that shift work has an effect on cardiovascular and metabolic health. Most of these studies have compared different groups of shift workers to nonshift workers. By contrast, the present work aimed to evaluate the cardio-metabolic effects of night shifts on the same group of internists as they changed type of duty. In particular, we focused on blood pressure and dipping status, as well as the levels of glucose, insulin, cortisol, and proinflammatory mediators.
Methods/design
A total of 14 internists working rotating shifts in a teaching Hospital were included in the study. Subjects with children aged less than 3 years and/or subjects with history of diabetes and cardiovascular disease were excluded from the study. Medical history, general and anthropometric parameters were collected at baseline. Then, since internists worked either a day shift (from 0800 h to 1600 h) or a night shift (from 1600 h to 0800 h), we scheduled a first 24-hour ambulatory blood pressure monitoring (ABPM) starting at 8 am on the work day with the day shift and a blood sampling the day after, at 8 am (at fasting). Then, the same subjects underwent a second 30-h ABPM starting at 8 am on the work day with the night shift and ending at 1400 h after the night shift. In addition, a blood sample was taken at 8 am after the night shift (at fasting), in order to measure glucose, insulin, cortisol, CRP, and proinflammatory mediators. During the night shifts, the number of admissions, calls, and the total amount of steps were recorded.
Results
Among the internists recruited, the ratio M:F was 1:1. On average, the age of the participants was 38 ± 3 years, their BMI was 24 ± 0.8, and they had been working for 9 ± 2 years. Our preliminary data show that blood pressure dipping status was significantly impaired when comparing the work day with the day shift to the work day with the night shift, being $14.13 \pm 1.39\%$ and $4.30 \pm 1.53\%$, respectively ($P < 0.001$). Also the dipping status of the resting period after the night shift was significantly impaired as compared to that after the day shift, being $6.86 \pm 2.77\%$ and $14.13 \pm 1.39\%$, respectively ($P < 0.05$).
Conclusion
Our preliminary data suggest that night shifts have significant effects on the cardio-metabolic health of workers.

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P1003

Anthropometric outcomes of shift work in midwives

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Introduction
The twenty-four hour nature of healthcare demands many nurses and midwives work in shifts. However night work shift is associated with adverse health outcomes like higher risks of obesity; and an unhealthy diet may be a contributing factor.
Methods
A descriptive, cross-sectional study, carried out for one month, about midwives in delivery room in five university hospitals in Tunis. For this population there is no worker on the day but rather two working modes: 12 hours and 24 hours. We included 50 midwives divided in two equal groups G12h and G24h. Anthropometric parameters and dietary intake was assessed in the two groups. The aim was to investigate the impact of shift work on anthropometric parameters and to compare the feeding behavior in the both groups, and this during the day of the night work (D 0), the day before ($D-1$) and the day after day care ($D+1$) as well as the anthropometric profile of the participants in each group. Data were analyzed with SPSS20.0 software.
Results
The total energy intake was higher than the recommendations in the majority of cases and this especially the day of the night work (86%) without significant difference between the two groups but with a significant correlation with the seniority in the post ($P = 0.001$). Comparative anthropometric data before and after night work showed an increase in overweight of 33% (an equal distribution between the 2 groups G12 G24) and the appearance of an obesity in 24% of which 4% was classified stage III.
Conclusion
Food disruptions during night work, wich are a major issue regardless of mode of work, can be a factor of anthropometric changes and development of obesity in this population.

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P1004

Evaluation of weight and nutritional diaries of students of public schools in a Brazilian town

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Between 1970–1975 brazilian children with overweight were 8% and 11%, and obesity 2% and 3% for girls and boys, respectively. In 2008 overweight was 32% and 34%, and obesity 12% and 17% for girls and boys, respectively. In this study we have evaluated the nutritional profile of public school students in our town. A cross sectional observational study was developed in 2017. Mean height (3 determinations) was ascertained in the morning by trained physical educators in 1115 randomized students aged 9–10 years old. BMI (kg/m^2) obtained from 461 boys and 497 girls were stratified by the 2007 WHO BMI Z scores. Students received two Qualitative Nutritional Diaries. Teachers were trained to fill in the diaries by a video prepared by us. Essentially, explained that every time children ate they should trace a small dash in front of the name of the respective food in the roll of the diary. Each signed dash meant that they consumed the food in that moment, no matter the quantity. Nutritional diaries from 623 (1246 diaries) children were computed together (sum of dashes traced of each food in each diary). Overweight was 24.8% and 23.2%, obesity 15.9% and 21.7%, and severe obesity 2.6% and 6.5% in girls and boys, respectively. Low body weight was 1.2% in girls and 0.9% in boys. Expected reportedly low input of data into diaries was evidenced by water consumption which had 1132 dashes traced (dt), or 0.91 dt/diary (dt/d). Fresh fruit juice 0.2 dt/d. Sugar sweetened beverages 0.5 dt/d. Diet soda 0.1 dt/d. Coffee 0.2 dt/d. Milk/yogurt/cheese consumption 0.7dt/d. Main brazilian carbohydrates sources (80–110 kcal/100 g) 1.0 dt/d. Roasted/cooked/fried meat 0.6 dt/d. Processed meat 0.3 dt/d. Eggs 0.1 dt/d. Salads/vegetables 0.6 dt/d. Fruits 0.3 dt/d. Butter/cream/cheese/mayonnaise 0.4 dt/d. Highly processed industrialized foods (220–580 kcal/100 g) 1.7 dt/d. Snacks and hamburgers 0.4dt/d. Brazilian homemade whole fruit desserts (90–250 kcal/100 g) 0.2 dt/d.
Conclusions
Prevalence of overweight and obese children in our town was similar to national data of 9 years earlier, suggesting that the group of *vulnerable* children to excessive weight gain has been attained completely. Severe cases, however, have increased sharply, indicating that this *group* might be under continued and/or stronger obesogenic factors. High consumption of highly caloric & processed industrialized food and consumption loss of less caloric cultural cooking was evidenced. Physical activity has been evaluated separately. These are the initial steps towards an obesity preventive task force in our school children.

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P1005

Genetic associations of vitamin D increase after supplementation

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Apart from the crucial effects of vitamin D on bone health, vitamin D deficiency has been associated with various chronic conditions such as metabolic or reproductive disturbances. The polycystic ovary syndrome (PCOS) represents the most common endocrine disorder among women of reproductive age. Women affected by PCOS frequently suffer from oligo- or anovulation as well as from obesity and insulin resistance. There is accumulating evidence showing an association of vitamin D status with pathogenesis, signs and symptoms of PCOS, results from RCTS are, however, inconsistent. Genome wide association studies (GWAS) identified common genetic determinants of vitamin D insufficiency. Several genetic loci are located near genes which are involved in the metabolism of vitamin D. Genetics may further play a role in the body's response to vitamin D after vitamin D supplementation. However, only a few studies have examined the impact of genetic variation in response to vitamin D intake so far. Aim of this study was to investigate genetic variants of vitamin D metabolizing genes in

relation to baseline vitamin D levels (25-hydroxycholecalciferol, 25(OH)D) as well as vitamin D increase after vitamin D intake. We investigated 10 selected SNPs in two intervention studies (Vitamin D RCTS in women with PCOS and healthy women (RCT1), hypogonadal men and eugonadal men (RCT2) $n=530$), one prospective cohort study of osteoporosis patients with vitamin D intake (VitaGEN study, $n=41$) and one prospective cohort study of healthy individuals with one cardiovascular risk factor (BioPersMed study, $n=963$). The A-allel of GC_rs7041, the T-allel of GC_rs4588, the C-allel of GC_rs1155563 as well as the G-allel of VDR_rs2228570 were found, to be associated with lower baseline 25(OH)D levels in the 2 vitamin D RCTs according to a gene dose effect. VDR_rs2228570 was further confirmed in the BioPersMed replication study, whereas the other 3 polymorphisms showed no association. Remarkably, VDR_rs10783219 shows twice a borderline association ($P\leq0.1$) in relation to vitamin D increase after supplementation in the RCT studies as well as in the VitaGEN study. Even not statistically significant, VDR_rs10783219 may be worth of further investigation in prospective studies.

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P1006

Telemedicine in the management of acromegalic patients

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Background

In acromegalic patients, quality of life reduction and neuropsychological impairment are common, in addition to well-known complications related to the pituitary adenoma and to the GH/IGF-I excess. Acromegalic patients need a lot of outpatient visits and a multidisciplinary approach during the management of the disease and its comorbidities. Aim of the project is to analyze the role of an electronic health device (eHD) with remote monitoring in management of acromegalic patients.

Materials and methods

In agreement with Philips, Pfizer and the Department of Management Engineering of the Politecnico of Milan, we provided an eHD, running a web application (Motiva by Philips) to 30 acromegalic patients in regular follow-up at our Institution, for a pilot project of 6 months. The project asked to every patients to periodically fulfill a series of questionnaires investigating compliance to medical therapy (daily or monthly depending on therapy), neuropsychological settings (every three months), quality of life (QoL, monthly) and disease specific symptoms (weekly).

Results

30 patients (13 Male, mean age 56.9 ± 13.2) received the tablet, 7 (23%) patients were in remission, 14 (47%) in treatment with somatostatin analogue and 9 (30%) with pegvisomant. Two patients abandoned the project for concomitant medical problems. Up to now, we are able to report preliminary data on the acceptance and use of the device and on adherence to the therapy, waiting for the end of the project in all patients. Three months after the start, data showed a high response rate to questionnaires (74%), especially to the disease-specific one. Adherence to therapy was 97.3%; in particular, only 4 patients (12%) declared they forgot or refused the therapy in more than one occasion. Patients demonstrated good adherence to the program, quickly reporting problems in the use of the device. At the end of the study, compliance improved to 98%. Five patients (17%) reported a better compliance to therapy, confirmed by an improved biochemical control.

Conclusions

Telemedicine may be a support for comprehensive management and follow-up of chronic patients. Our data showed that an eHD could be useful in the management of acromegalic patients, improving compliance to therapy. Moreover, these devices allow us to study aspects of difficult examination with regular outpatient visits, such as neuropsychological comorbidities or QoL.

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P1007

Seasonality of hyponatremia in hospitalized medical patients – data from a nationwide cohort study

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Introduction

Hyponatremia is the most prevalent electrolyte disturbance in hospitalized patients. Seasonal variation with higher incidence of profound hyponatremia during summer months has been described for patients in the emergency department setting. Whether this observation is also true among medical inpatients is unknown. This study aimed at analyzing the seasonal incidence of hyponatremia as well as sex and age specific differences among medical inpatients.

Methods

Medical inpatients diagnosed with hyponatremia between January 2009 and December 2015 using prospective administrative data were included in this nationwide cohort study. The primary outcome was the monthly alteration in hyponatremia incidence. Secondary outcomes were the impact of outdoor temperature on hyponatremia incidence and differences among sex and age groups.

Results

Of the 2,426,722 medical inpatients included in this study, 84,210 were diagnosed with hyponatremia, of whom 61% ($n=51,262$) were female. There was a strong seasonal variation in the incidence of hyponatremia. While the highest overall incidence of hyponatremia was observed in July (9.2%, $n=8,976$), it was lowest in December (5.5%, $n=6,530$). The overall incidence of hyponatremia in men was lower by 37% (OR 0.63 [95% CI 0.62 to 0.64]) compared to women. Sex-specific difference was most pronounced in the warmest month of July (mean temperature 20.1°C, OR 0.57 [95% CI 0.54 to 0.59]). The strongest association between seasonality and hyponatremia was seen in elderly female inpatients admitted during summer.

Conclusions

The incidence of diagnosed hyponatremia in medical inpatients increases during summer months with higher outdoor temperature. Association between seasonality of hyponatremia and outdoor temperature was most pronounced in elderly female inpatients.

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P1008

Abstract Unavailable.

Interdisciplinary Endocrinology 2

P1009

Decreased hepatic detoxification potential in males - consequences of androgen excess in fetal life

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Introduction

Altered intrauterine endocrine environments can 'programme' adverse health outcomes. Linkage between altered androgen exposure *in utero* and adverse

offspring health is robust. For example, increased maternal androgen concentrations and PCOS in female offspring and dyslipidaemia in male offspring. We hypothesised that the liver was a major target for androgenic programming *in utero* and hepatic dysfunction would be present in offspring. We therefore examined the hepatic transcriptome and proteome in a non-biased approach, to understand if key hepatic functions are altered by prenatal androgens, and identify circulating biomarkers in adolescence, indicative of prenatal androgenic excess.

Methods

Ovine fetuses were directly injected with 200 µl testosterone propionate (PA; 20 mg) or vehicle control (C), under ultrasound guidance at day 62 and 82 of gestation. Male fetuses were studied at day 90 of pregnancy (C, $n=11$; PA, $n=6$) and adolescents at 6 months postnatal age (C, $n=14$; PA, $n=14$). Hepatic transcriptome and proteome were determined using Illumina RNA sequencing and liquid chromatography-mass spectrometer (LC-MS/MS). Plasma proteins and analytes were measured using LC-MS/MS, ELISA or benchtop biochemistry autoanalysers. Statistical analysis between C and PA groups was performed using pairwise comparisons, with false discovery rate correction, accepting $P<0.05$ as significant.

Results

In fetal livers of PA males there was downregulated expression of transcripts involved in bile acid, bilirubin and xenobiotics export (*ABCC2*) ($P<0.05$). This was maintained in the transcriptome data from livers of adolescent PA males ($P<0.05$). However, in adolescence there was also altered expression of genes/proteins involved in liver damage and fibrosis. Data predicted increased oxidative stress and altered reactive oxygen species handling with downregulated phase II detoxification (*GSS, GSTM1, GSTM4, GSTO1*) (all $P<0.05$) and decreased protection against reactive oxygen species (*GPX4, GSR, PRDX5, XDH*) (all $P<0.05$). This was associated with increased expression of genes associated with liver fibrosis (*COL4A1, COL4A5, COL4A6, COL18A1, COL27A1, FGF7, FGFR2, FGFR3, SMAD3, SMAD7, TGFBI*) (all $P<0.05$). Plasma analysis of adolescent males revealed decreased levels of antioxidant enzymes (CAT, SOD3, GPX3) (all $P<0.05$) and increased circulating bilirubin and collagens (COL1A1, COL1A2, COL5A1) (all $P<0.05$).

Conclusions

This is the first study documenting that direct fetal male androgen overexposure results in decreased hepatic detoxification capacity, with potential for liver damage and fibrosis. In addition to mechanistic understanding of the journey from *in utero* androgenic overexposure to adolescent hepatic health issues, we observed the echoes of hepatic alterations reflected in the circulation, providing utility for biomarker development.

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P1010

Noonan syndrome: about three cases

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Introduction

Known to be 'male Turner syndrome', Noonan syndrome (NS) classically associates short stature, facial dysmorphism, and congenital heart disease. It is an autosomal dominant disease with an incidence of 1: 1,000 to 1: 2,500. We report 3 observations of NS.

Observations

Case 1: A 7-year-old female patient was admitted for a growth delay. On examination, she had a dysmorphic syndrome suggestive of NS: facial dysmorphism with triangular face, hypertelorism, low implanted ears, webbed neck, enlarged chest and small hands. Cardiac ultrasound was normal. Dynamic tests confirmed a partial GH deficiency. The causal mutation has not been identified.

Observation 2: A newborn was admitted for prematurity, intrauterine growth retardation and neonatal respiratory distress. The patient had a dysmorphic syndrome with an erased forehead, hypertelorism, low implanted ears with congenital lymphedema. NS was suspected. Cardiac echocardiography was indicated, but the child presented a cardiopulmonary arrest at the 6th day of life. A mutation of PTPN11 gene has been found.

Observation 3: A 7-year-old female patient was admitted for a stature delay. On examination, she had a dysmorphic syndrome suggestive of NS: a triangular face with curly hair, hypertelorism and low implanted ears. Cardiac ultrasound was normal. Dynamic tests confirmed a complete GH deficiency. The causal mutation has not been identified.

Discussion

The initial diagnosis of NS is based on the clinical presentation. In the neonatal period, there may be asymmetrical ptosis and the ears may be thick, wide and angulated posteriorly. As childhood progresses, the appearance of the face becomes longer and takes a more triangular shape. Asymmetric bilateral ptosis and hypertelorism become more apparent. The hair can be unusually curly. Facial features tend to normalize in late adolescence and it can be very difficult to recognize adults with NS from facial features alone. More than 80% of patients have cardiovascular abnormality. Pulmonary stenosis is the most characteristic lesion of NS. Our second patient would most likely have a cardiopulmonary malformation. Since the identification of the responsible genes, it has become possible to use genetic tests to establish the diagnosis. In some centers, testing will be limited to the PTPN11 gene, but since it can only diagnose half of the cases of NS, it is best to use a panel of genes if possible. The causal mutations are unknown in 30% to 40% of cases which was the case of the 1st and the 3rd observation.

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P1011

The prevalence of oral glucocorticoid use in doses associated with risk of tertiary adrenal insufficiency

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Objective

Patients who receive ≥ 5 mg prednisolone per day, for more than 2–3 weeks, are at risk of developing glucocorticoid (GC) induced adrenal insufficiency (tertiary adrenal insufficiency, 3° AI). The aim of this study was to a) determine the prevalence of GC use in doses that are associated with development of 3° AI, b) assess prescription pattern of short and long-term GC treatment in adults and children, and c) investigate the indication for the GC treatment.

Methods

This was a retrospective cohort study where dispensed GC prescriptions were obtained from the Swedish Prescribed Drug Register. Individuals who had received a prescription of ≥ 5 mg prednisolone (or equivalent dose of other GC) daily, for more than 21 days, from 1 January 2007 to 31 December 2014, were included. Information on underlying diseases was obtained from the Swedish National Patient Register and the Västra Götaland's regional healthcare database. The patients were divided into four groups according to the length of the GC treatment: 1. *Single-occasion users* (one prescription). 2. *Occasional users* ($>$ 1 prescription but $<$ 300 tablets/year). 3. *Medium-term users* ($>$ 300 tablets/year for 0-2 years in a row) and 4. *Long-term users* ($>$ 300 tablets/year for $>$ 2 years in a row).

Results

Of 1,585,335 inhabitants in the region of Västra Götaland, 223,211 had received a prescription of oral GCs (women 55.6%). The mean age was 48.4 ± 24.2 (range 0.1–107) years. A total of 118,456 (53.1%) were single-occasion users, 69,036 (30.9%) were occasional users, 27,831 (12.5%) were medium-term users and 7,888 (3.5%) were long-term users. The overall prevalence of oral GC use was 14.1%; 7.5% for single-occasion users, 4.4% for occasional users, 1.8% for medium-term users and 0.5% for long-term users. The highest prevalence rate (27.4%) was found in men aged 80–89 years, and lowest (7.5%) in men 10–19 years of age. Prevalence in children 0–9 years was 10.6%. The most frequently used GCs were betamethasone (53.8%) and prednisolone (45.3%). COPD and asthma were the most common indications for treatment (17.2%), followed by allergy (12.5%), neoplasms (11.5%) and skin disorders (10.1%). Allergy was the most frequent indication in children and adolescents (0–19 years).

Conclusion

Between the years 2007 and 2014, every seventh individual received treatment with oral GC in doses that are associated with a risk of developing 3° AI. The highest prevalence was seen in the elderly where every forth individual received GC treatment.

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P1012

The association between retinol-binding protein 4 and prediabetes in obese patients with non-alcoholic fatty liver disease

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Background
Retinol-binding protein 4 (RBP4) is known as an acute phase inflammatory reactant, associated with insulin resistance. Increased levels of this novel adipokine is observed in obesity, type 2 diabetes mellitus, metabolic syndrome (MetS) and cardiovascular diseases, as well as in nonalcoholic fatty liver disease (NAFLD), but some of these data remain controversial. The aim of this study was to evaluate the relationship between RBP4 and prediabetes in obese patients with NAFLD.
Subjects and methods
A total of 79 obese patients with ultrasound based diagnosis of NAFLD were included. All subjects were divided into 2 groups: 1) without carbohydrate disturbances ($n=41$), and 2) with prediabetes ($n=38$). Serum RBP4 was measured using ELISA method.
Results
The obese NAFLD patients with prediabetes had significantly higher levels of RBP4 compared to those patients without carbohydrate disturbances (78.55 ± 35.74 vs. 65.30 ± 32.25 μg/ml, $P=0.041$), as well as patients with MetS than patients with less than 3 MetS components ($P=0.019$), and patients with dyslipidemia compared to patients without lipid abnormalities ($P=0.013$). There was weak to moderate positive correlation between RBP4 levels and visceral adiposity index, glucose, insulin and HOMA-IR, and moderate negative correlation with Quicki index ($P<0.05$–0.001). RBP4≥61 μg/ml compared to those with lower values, have about 3.5-fold higher risk of prediabetes (OR 3.544, 95% CI 1.385–9.072, $P=0.008$ and OR 3.522, 95% CI 1.293–9.596, $P=0.014$, individually and in the group plan respectively). RBP4≥55 μg/ml in creased the risk for MetS approximately 3.1 times (OR 3.148, 95% CI 1.178–8.414, $P=0.022$). In the group plan, the regression equation kept thisvalue, lost statistical significance but retaining the risk predictive value (OR 2.988, 95% CI 0.499–17.882, $P=0.230$).
Conclusions
RBP4 is associated with increased risk for prediabetes and MetS in obese patients with NAFLD.
Keywords: Retinol-binding protein 4, nonalcoholic fatty liver disease, prediabetes, obesity, metabolic syndrome

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P1013

Burden of hyponatremia on clinical outcomes in hospitalized adult medical inpatients

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Background
Hyponatremia is the most prevalent electrolyte disorder in hospitalized adult medical patients and is associated with a significant healthcare resource burden. However, evidence remains scarce whether hyponatremia is a marker of disease severity or whether it has an independent effect on clinical outcomes.
Methods
In this nationwide cohort study, we analyzed medical inpatients with hyponatremia diagnosed between January 2009 through December 2015 using prospective administrative data. Hyponatremia patients were matched (1:1) to a non-hyponatremia cohort using propensity score matching. We used multivariate regressions models to assess differences in in-hospital mortality, intensive care unit (ICU) admission, length of hospital stay, and 30-day readmission rates.
Results
Among 2,426,722 medical inpatients, 83,871 (3.5%) were diagnosed with hyponatremia and propensity-matched with 83,871 patients without hyponatremia. We found no difference for in-hospital mortality (odds ratio [OR] 1.02, 95% confidence interval [95% CI]: 0.97–1.06, $P=0.459$), however a higher risk for ICU admission (OR 1.19, 95% CI: 1.15–1.22, $P<0.001$). The diagnosis of hyponatremia was associated with a prolonged length of hospital stay by 1.37 days (95% CI: 1.28–1.47, $P<0.001$). 30-day readmission rates were not significantly different between both groups (OR 1.02, 95% CI: 0.99–1.05, $P=0.170$).
Conclusion
Hyponatremia is an independent risk factor for increased ICU admission and length of hospital stay and therefore represents a potential target for intervention to reduce healthcare burden for a large population of hospitalized hyponatremic patients.

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P1014

Characterization of type 1 angiotensin II receptor activation induced gene expression changes in rat vascular smooth muscle cells

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Angiotensin II (AngII) mainly acts through type 1 angiotensin II receptor (AT1R) to promote a broad variety of biological effects. The vascular smooth muscle cells are one of the main target of AngII and its stimulation activates numerous signaling pathways which could result in gene expression changes in these cells. We carried out Affymetrix GeneChip experiments to analyze the effects of AngII stimulation on gene expression. More than 200 genes were upregulated in response to AngII stimulation of primary rat vascular smooth muscle cells in our experimental setup. We have selected several genes (i.e. Lmcd1, HbEGF, DUSP5, DUSP6, and DUSP10) to further investigate the kinetics of the gene-expression changes, and the possible signal transduction processes which lead to the altered expression changes after AngII stimulation. The results of the quantitative PCR measurements confirmed the AngII-induced upregulation of the investigated genes. The maximal induction of the most genes appeared two hours after the AngII stimulation. Our data show that the upregulated genes can be stimulated through several signal transduction pathways. We also examined the role of epidermal growth factor receptor (EGFR) transactivation in the upregulation of the investigated genes. According to our data the EGF receptor transactivation is not critical in response to AngII stimulation since knock-down of EGF receptor did not alter the AngII induced gene expression changes. Our pharmacological approach revealed that dasatinib, which is a potent inhibitor of ABL and Src family soluble tyrosine kinases, can significantly inhibit several gene expression changes. Interestingly, when we applied ABL kinase inhibitors, which have less potency toward Src tyrosine kinases such as imatinib or nilotinib did not evoke similar effects as dasatinib. Our data can help to understand the details of AngII-induced long term effects and the pathophysiology of AT1R, moreover it can help to develop potential interventions in symptoms when this receptor over functions such as vascular remodeling or atherosclerosis. This work was supported by the National Research, Development and Innovation Fund (NKFI K116954 and NVKP_16-1-2016-0039).

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P1015

Advanced glycation end-products and chronic inflammation in adult survivors of childhood leukemia treated with hematopoietic stem cell transplantation: possible role in the pathogenesis of cardiovascular late effects

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Cardiovascular (CV) diseases significantly contribute to the mortality excess observed in survivors of pediatric acute lymphoblastic leukemia (ALL) who received hematopoietic stem cell transplantation (HSCT). The study explores advanced glycation end-products (AGEs) levels, inflammatory status and lipid profile in a cohort of ALL survivors, in order to investigate their potential role in the pathogenesis of CV late effects. Inclusion criteria were: a) previous diagnosis of ALL at age <18 years, treated with HSCT conditioned with total body irradiation (TBI), b) age >18 at the time of the enrollment; c) off-therapy for at least 5 years. Radiotherapy other than TBI, pre-existing heart disease, glucose metabolism impairment, body mass index >25, smoking or treatment with cholesterol lowering medications were exclusion criteria. Eighteen survivors were included and 30 age-matched healthy subjects worked as controls. Age at the time of the study was 27.5 ± 4.8 years for ALL survivors and 26.7 ± 3.2 years for controls (mean $\pm$ s.d.). ALL survivors had higher levels of triglycerides (189.38 ± 147.40 vs 84.97 ± 37.28 mg/dl, $P<0.01$) and Apo B (105.80 ± 20.47 vs 80.81 ± 13.54 mg/dl, $P=0.001$). Also the total cholesterol (Chol)/HDL Chol (4.25–1.09 vs 3.17–0.45, $P<0.02$) and Apo B/Apo A-1 (0.73–0.15 vs 0.48–0.09, $P<0.001$) ratios were higher in survivors. High-sensitivity C-reactive protein levels (2.32–1.70 vs 0.88–1.09 mg/dl, $P<0.05$), IL-1β (7.04–1.52 vs 4.64–2.02 pg/ml, $P=0.001$) and IL-17 (37.44–3.51 vs 25.19–6.34 pg/ml, $P=0.001$) were higher in ALL survivors than in the control group. AGEs plasma levels in ALL survivors were markedly higher than in heathy subjects (2.15–2.21 vs 0.29–0.15 pg/ml, $P<0.01$). In ALL survivors an increased GSSG/GSH ratio (0.085–0.07 vs 0.041–0.036, $P<0.05$) was also observed. Despite slight alterations of the lipid profile, adult survivors of childhood ALL who received HSCT with TBI have very high levels of AGEs and evidence of chronic inflammation. It can be hypothesized that the oxidative stress induced by exposure to chemotherapy or radiotherapy leads to the formation and accumulation of AGEs, which in turn could induce inflammation, reduce antioxidant defenses and enhance the production of reactive oxygen species (ROS). By this way the oxidative stress might be self-perpetuated after the end of cancer therapies. These alterations could contribute to the increased risk of CV diseases that has been reported in transplanted ALL survivors.

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P1016

Differential impact of body mass index on bone and breast density in post-menopausal women and potential implications for the risk of breast cancer

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Introduction
Women with a high breast density have an increased risk of breast cancer, which prevalence increases after menopause in obese subjects. Breast density can be calculated on mammograms as the proportion of dense tissue (percent mammographic density-PMD). Several factors may influence the PMD, including age, menopausal status, body mass index (BMI), and bone mineral density (BMD) taken as an index of overall estrogen exposure. However, conflicting data have been reported, possibly due to the heterogeneity of large populations. We aimed to determine which factors influence PMD in a series of postmenopausal women at a single center, excluding those with early menopause (<40 yrs).
Methods
A hundred of post-menopausal women (median age 61 yrs-old, range 50-83) was studied in the last year. The median age at menopause was 50 yrs (42–57), median BMI was 27.5 kg/m^2 (17.58–41.62) and 36 patients (36%) were obese (BMI >30 kg/m^2). PMD was calculated on bi-dimensional mammographic projections of the left breast. Lumbar, total and neck femoral BMD (g/cm^2) was evaluated by MOC-DEXA (Lunar, GE). Non-parametric statistical analysis (Spearman correlations, Wilcoxon-test) was performed (JMP 11.0, SAS, USA).
Results
A significant negative correlation was found between BMI and PMD ($P=0.0026$; $\rho=-0.298$), but PMD was not significantly influenced by age, age at menopause, duration of menopause or BMD on the whole series. In contrast, a significant positive correlation was found between BMI and BMD ($P<0.0001$ and $\rho>0.40$ at all bone districts). PMD tended to be lower in obese women ($P=0.068$ *vs* non-obese) but the degree of obesity (BMI) did not appear to significantly influence PMD or BMD in this group. In contrast, the differential impact of BMI on PMD ($P=0.0026$, $\rho=-0.370$) and BMD at any bone district was confirmed in non-obese women, in particular at the total femoral site ($P<0.0001$, $\rho=0.483$). In addition, the non-obese group was characterized by a significant negative correlation between PMD, patient's age ($P=0.0086$, $\rho=-0.326$) and menopause duration ($P=0.002$, $\rho=-0.319$).
Conclusion
BMI has a differential impact on PMD and BMD after menopause, probably accounting for some conflicting data in the literature. Increased estrogen exposure, increased breast adiposity and long-term persistence the fibro-glandular breast tissue may contribute to the increased risk of breast cancer after menopause in obese women, suggesting a complex interplay between endocrine and paracrine factors.

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P1017

Diagnosis announcement procedure in rare endocrine diseases: a survey of the French National Healthcare Network for Rare Endocrine Diseases (FIRENDO)

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Context
Diagnosis announcement of a chronic disease is a crucial moment for patients as well as for their families and an important step of the management of severe conditions like rare endocrine diseases. It is considered as an 'eternal minute', marking the end of a time of life when the disease was absent. Little is known on how diagnosis is communicated to patients and families. FIRENDO as defined by the National Plan for Rare Diseases aims at promoting education, care and research on rare endocrine diseases. Patients associations are FIRENDO active members and listed as a main subject diagnostic announcement and its consequences on disease management.
Objectives
The aim of this study was to characterize for the first time the experience of patients and/or their parents around the announcement of diagnosis, and to define their needs in order to ensure optimal quality of care.
Methods
A quantitative self-administered survey on diagnosis announcement procedures in rare endocrine diseases was launched in April 2017 under the auspices of the

FIRENDO thematic working group in collaboration with its partnering patient support groups. The questionnaire was designed by 2 adult and 2 pediatric endocrinologists, 2 psychologists and 1 biologist, all experts in rare endocrine diseases, and revised by patient support groups' representatives; it was made available on the FIRENDO network website and spread mainly by email to members of the 16 patient support groups affiliated to the network, with electronic links on their respective websites.
Results
Questionnaires were filled by 391 patients and 223 parents (median age of patients: 39 years). The following conditions were represented by 30 answers or more: Addison's disease, classical forms of Congenital Adrenal Hyperplasia (CAH), Silver-Russel syndrome, Cushing's syndrome, acromegaly and craniopharyngiomas. The analysis revealed that some modalities of announcement were considered as favorable by patients: the physician's empathy, availability and use of clear terms, presence of family at the time of announcement. However, a lack of psychological care and information documents was reported as well as some inadequate procedures like postal mail announcements.
Conclusion
This work confirmed that better knowledge of the patient's experience is useful for improving the diagnosis announcement of rare endocrine disorders. The main recommendations derived from the survey were the need for several announcement visits, and informing on patient support groups and reference centers; the ban of impersonal announcement and the usefulness of a written accompanying document.

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P1018

MicroRNAs regulate aldosterone signaling by post-transcriptional control of mineralocorticoid receptor expression

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The Mineralocorticoid Receptor (MR), a hormone-activated transcription factor that mediates sodium-retaining action of aldosterone, is highly expressed in the distal nephron in which large variations in extracellular fluid tonicity are generated by the cortico-papillary gradient. However, mechanisms regulating MR expression remain sparse. We recently showed that extracellular tonicity modulates renal MR expression through posttranscriptional mechanisms (Viengchareun, Mol Endocrinol, 2009) involving recruitment of RNA-binding proteins, which modulate the half-life time of MR transcript. Indeed, hypertonicity compromises MR signaling through Tis11b-mediated MR mRNA degradation (Viengchareun, J Am Soc Nephrol, 2014), while HuR favors MR mRNA stability (Lema, Cell Mol Life Sci, 2017) and edits MR transcript (Lema, Sci Rep, 2017), thus enhancing renal MR signaling under hypotonicity. Herein, we showed that MR transcript is also targeted by microRNAs (miRNAs), which represent another class of posttranscriptional regulators. We first demonstrated that expression of miR-324-5p increases under hypertonicity ($\times$1.5) in the differentiated cortical collecting duct KC3AC1 cells, but also in mouse kidneys ($\times$4) under conditions mimicking extracellular distal hypertonicity (furosemide exposure). Next, we showed that miR-324-5p functionally interacts with MR 3'-untranslated region (3'-UTR). Indeed, miR-324-5p mimics, leading to miRNA overexpression in transfected HEK293T cells, significantly decrease in a dose-dependent manner the luciferase activity of a reporter plasmid in which the MR 3'-UTR was cloned downstream of the luciferase reporter gene. Stable clones of KC3AC1 cells, overexpressing inducible miR-324-5p, are currently generated using lentiviral strategy to further investigate functional consequences on aldosterone signaling and sodium transport. Moreover, we showed that miR-324-5p is secreted into the apical compartment of KC3AC1 cells, suggesting that this miRNA may also act in a paracrine and/or endocrine manner on other cell types. We have also performed pilot experiments that conclusively demonstrate the feasibility to quantify this miRNA in urine samples of humans and mice subjected to osmotic stress (hypertonicity or hypotonicity). As a result, we set up a collaboration with the Clinical Investigation Center of Poitiers Hospital to get plasma and urine samples of well-characterized patients presenting with cardio-renal pathologies such as diabetic nephropathy. Thus, miR-324-5p might represent a promising new biomarker or a novel therapeutic target for renal dysfunction. Collectively, we demonstrate for the first time that renal MR expression is post-transcriptionally regulated by both RNA-Binding Proteins and miRNAs. Such regulatory mechanisms could lead to new pharmacological perspectives of modulating aldosterone signaling during the management and follow-up of cardio-renal pathologies.

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P1019

SOAR Study: New approaches to managing social skills deficits in Turner Syndrome

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Background
Turner Syndrome (TS) is a sex chromosome aneuploidy (45,X) associated with social skill difficulties. The 2016 Cincinnati clinical care guidelines recommend that the Program for the Education and Enrichment of Relational Skills (PEERS) social skills intervention is piloted. PEERS has previously been used in face to face interventions with male adolescents with autism spectrum conditions. This pilot project will be the first to examine the feasibility and acceptability of the PEERS protocol online.
Methods
The PEERS program has been piloted with 7 young women with TS (classic, mosaic and variant karyotypes) between the ages of 17 and 20 with a verbal IQ above 70. Participants were screened using the Strengths and Difficulties Questionnaire (SDQ) Peer Scale and the Social Competence with Peers (SCP) questionnaire to measure deficits in social performance (parent report). The PEERS screening interview assessed motivation to improve social competence (young person and parent). Participants scored in the abnormal range on the SDQ peers scale ($t_{(6)}=4.66$, $P=0.003$) and on the SCP ($t_{(6)}=-4.02$, $P=0.007$) compared to female population norms. The young women and their parents were highly motivated to improve their daughter's social functioning. The PEERS program consists of 14 weekly lessons and runs two concurrent groups; one for the young women and one for parents. The young person lessons are structured to provide didactic instruction as well as social skill rehearsal. In order to broaden the reach of the program PEERS has been modified to be delivered primarily online. Face to face sessions took place at the start, middle and end of the program. All other sessions were conducted online using Adobe Connect Meetings. The pilot used an uncontrolled study design with multiple-case tracking. The primary outcome measure assessed social performance at 9 time-points (3 pre-pilot, 3 during pilot, 3 post-pilot). Secondary outcome measures assessed pre-post changes in social knowledge, social cognition, anxiety, self-esteem, autistic symptomatology and evaluated intervention acceptability.
Results & discussion
The outcomes of this small scale pilot will be used to adapt the programme based on feedback and estimate the sample for a future randomised controlled trial. Should the online model of delivery prove acceptable to families, this will substantially broaden the accessibility of social skills interventions in a cost-effective way to more young women with TS and other rare genetic disorders.

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P1020

Circulating miRNAs expression profile in *in vitro* muscle cell model exposed to cortisol excess

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Cushing's Syndrome (CS) is associated with a severe myopathy mainly affecting type 2 muscle fibres, with a higher prevalence in male subjects. The excess of glucocorticoids (GC) levels represents the most common cause of myopathy due to an alteration of protein metabolism. The non-coding post-transcriptional gene regulators muscle-specific microRNAs (miRNA) control muscle development and differentiation but when dysregulated lead to skeletal muscle (SM) disorder. The aim of the current study was to investigate circulating miRNAs expression profile during SM wasting in mouse differentiated C2C12 cell line, in a condition of cortisol excess. To mimic a CS condition in vitro, and particularly a condition resembling a pituitary-dependent CS with increased ACTH and cortisol, mouse differentiated C2C12 cells have been treated with ACTH at $2.2*10^{-11}$M

(corresponding to 100 pg/mL patients' serum levels), hydrocortisone (HC) at $1.4*10^{-6}$M (corresponding to 300 ng/mL) and in combination for 12 h. In order to confirm that 12h of drug treatment were able to induce SM wasting, gene and protein expression of *Atrogin* and *Murf* were evaluated by RT-qPCR and Western Blot, respectively. Circulating miRNAs expression profile miScript miRNA was evaluated by PCR arrays. The results of the study demonstrated that 12h of HC treatment at $1.1*10^{-6}$M was sufficient to induce a condition resembling muscle wasting in C2C12 cell line prompting a significant increase of *Atrogin* gene ($P=0.01$) and ATROGIN protein expression compared to the control and compared to ACTH treatment ($P=0.001$) and a non-significant increase of *Murf* gene ($P=0.07$) and MURF protein expression. Circulating miRNA microarray analysis demonstrated that in C2C12 treated for 12 h with HC, miR 133a-3p ($P=0.006$), miR 122-3p ($P=0.018$) and miR 200b-3p ($P=0.044$) were significantly up-regulated compared to the control. Conversely, C2C12 treated for 12 h with ACTH did not show any change in miRNA expression profile. The preliminary results of the current study demonstrated that 12h of treatment with HC is sufficient to induce a condition resembling muscle wasting in C2C12 by means of an up-regulation of main miRNAs known to be involved in the development of myopathies. In conclusion, the up-regulation of specific miRNAs might potentially be used as marker or predictive factors for the development of GC-induced myopathy in patients with CS.

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P1021

MAMLD 1 gene mutation and 46 XY sex development disorder: a case report

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Introduction
46 XY sex development disorders are a group of rare congenital conditions in which chromosomal, gonadal or anatomic sex is atypical. Less than 20% of cases have a precise genetic diagnosis. We report here the case of a patient suffering from a 46 XY sexual development disorder secondary to the MAMLD 1 gene mutation.
Observation
The patient is a nine month infant who was admitted for abnormalities of the external genital organs. The physical examination, revealed a 1.5 cm micropenis with posterior hypospadias, and normal positioned gonads. Blood karyotype showed 46 XY chromosome formula with a positive SRY gene. Exocrine testicular function was found to be normal with an AMH level of 236.9 ng/ml, while endocrine function assessments are planned. The genetic study revealed a new mutation of the MAMLD 1 gene (c.G 2217 A:p.W739X). The patient has benefited from a cure of hypospadias and bifurcated scrotum, as well as several courses of medical micropenis therapy (cutaneous dihydrotestosterone treatment).
Discussion
The MAMLD 1 gene is located at the position 28 of the long arm of the X chromosome. This gene's mutation is responsible for the fetal Leydig cells function alteration during the critical period of sexual development. At birth, it leads to a 46 XY sexual development disorder. Therefore, testicular function is most often conserved during infancy, but it needs surveillance as it may deteriorate in long term.

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P1022

Influence of type 2 diabetes on androgen levels in women with Alzheimer's disease

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Introduction
Alzheimer's disease (AD) is a neurodegenerative disease that is manifested by progressive loss of cognitive function. Neuroactive steroids and their metabolites have an important regulatory role in the nervous system, affect neuronal plasticity, response to stress, learning and memory and have a neuroprotective effect. One of the not fully elucidated risk factors for AD is impaired glucose tolerance/type 2 diabetes (T2D). It is well known that lower androgen levels contribute to the development of metabolic syndrome and T2D in males. In females, on the contrary, insulin resistance and T2D are associated with an excess of androgens. In previous studies, we have constructed a predictive model for the classification of AD patients based on levels of circulating steroids and their polar conjugates. We found lower androgen levels in AD patients regardless of sex.
Aim
The aim of this study was to examine whether the presence of T2D affects steroid hormone levels in female AD patients.
Methods
We compared the spectrum of steroid hormones in 3 groups of women: 1. women with AD and without T2D ($n=10$, median age 78 years), 2. women with AD and T2D ($n=10$, median age 78 years), 3. women without AD and without T2D ($n=10$, median age 77 years). The data were processed by GLM ANOVA and multidimensional regression using O2PLS method (Statgraphics 18×64, SIMCA v. 12.0).
Results
T2D-only women had higher androgen levels compared to women with AD and T2D (conjugated 7α-hydroxy-dehydroepiandrosterone, $P=0.02$, conjugated 7β-hydroxy-dehydroepiandrosterone, $P=0.0008$, 5-androstene-3β,7β,17β-triol, $P<0.001$, conjugated 5-androstene-3β,7α,17β-triol, $P<0.001$; 5α-androstane-3α,17β-diol, $P=0.02$). These results were confirmed by multidimensional regression analysis, which also found significantly higher levels of testosterone in T2D-only group compared to the other two groups. Between the two groups of patients with AD there were found no significant T2D-dependent differences in steroid hormone levels.
Conclusion
T2D in women increases androgen levels, but in AD patients these differences are not significant enough to affect the model for the classification of AD patients based on the circulating steroid hormones.
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P1023

The Miller-McKusick-Malvaux syndrome: a rare cause of short stature

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The Miller-McKusick-Malvaux (3M) syndrome is a primordial growth disorder characterized by low birth weight, reduced birth length, severe postnatal growth restriction, a spectrum of skeletal anomalies, facial dysmorphism and normal intelligence. Mutations in the *CUL7* gene (6p21.1) are most often responsible for 3M syndrome (67% of cases). Other causal mutations include those in the *OBSL1* gene (2q35), in 28% of cases, or the *CCDC8* gene (19q13.33), in 5% of cases. The precise mechanisms leading to growth failure in 3M syndrome remain unclear. Recurrent mutation in Maghreb patients was reported. It is a frameshift deletion (c.4451_4452delTG) in exon 24. We report two Tunisian 3M syndrome patients. The first patient is a 4 year-old girl. She is born from two healthy cousin parents from induced twin pregnancy. She had an intrauterine growth restriction with low birthweight (1820<3p) and length (40 cm:<3P) and normal head circumference pc (34 cm). Her face was triangular with pointed chin, prominent forehead and malar hypoplasia. The nose was short with upturned nares. She had full fleshy lips, long philtrum, dysplastic ears, prominent heels, unique transverse palmer crease and short neck and thorax. Molecular analysis confirmed the diagnosis showing the Maghreb mutation in homozygous state. The results of her endocrine evaluation, which included thyroid function, GH (2.2 ng/ml), IGF1 (90 ng/ml) and catapressan stimulation test were normal. Nevertheless, she have received recombinant human GH (rhGH) treatment from the age of 2 years. She gained 19 cm and 4 kg in 2 years. The second patient is a 3-year-old boy. He was referred to us for pre and postnatal growth restriction. He had already have prenatal caryotype because of intrauterine growth restriction. No chromosomal anomalies were diagnosed. At birth he had low birth weight and lengh, bilateral hip dysplasia, hyperextensible joints, proeminent heels and a short chest. He showed facial dimorphism: a triangular face and a hypoplasic midface and proeminent forehead. At the age of three years, he is 74 cm (-4DS) tall. He has growth normal mental development. The bone x ray showed a distal phalange hypoplasia. Molecular investigation for the maghreb mutation was normal. Endocrinological investigations: IGF1 = 92 ng/ml (13–143 ng/ml), GH = 3.62 ng/ml and the hypoglycemic GH stimulation revealed a total GH deficiency. The patient received (rhGH).
Conclusion
Nowadays GH treatment outcomes for 3M syndrome appear controversial, but based on the successful height increase in our case significant individual variation in relation to GH response in 3M syndrome should be considered.

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P1024

Association of the Period3 clock gene polymorphism with adrenocorticotropin-stimulated cortisol levels among patients with autoimmune thyroid disease

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Background
Immune function and responses are tightly regulated by the circadian clock system and hypothalamic-pituitary-adrenal (HPA) axis. Accumulating evidence supports that there is a strong mutual relationship between these two regulatory systems at multiple levels. Recent publications suggest that the clock system may also regulate glucocorticoid release from adrenal glands by altering the sensitivity of the adrenal cortex to adrenocorticotropic hormone (ACTH).
Aim
To investigate the influence of a polymorphism in clock gene Period3 on adrenal cortisol response to ACTH in patients with autoimmune thyroid disease (AITD).
Methods
A total of 72 unrelated patients with AITD [Graves' disease (GD), 37; Hashimoto's thyroiditis (HT), 35] who were genotyped for Period3 rs2797685 (G/A) polymorphism in a previous study were included. A standard dose (250 μg) ACTH (1-24) stimulation test was performed. Basal serum ACTH levels and serum cortisol concentrations before and 30 and 60 minutes after intravenous injection of ACTH (1-24) were measured by ELISA.
Results
Free thyroid hormone levels were normal in all participants at the time of the ACTH (1-24) stimulation test. The mean basal serum ACTH levels and serum cortisol measurements before and after ACTH (1-24) stimulation test were not significantly different between GD and HT groups. No association was observed between genotypes of the studied polymorphism and serum levels of these parameters in GD, HT and overall AITD groups.
Conclusion
Period3 rs2797685 (G/A) polymorphism was not determinative for ACTH-stimulated cortisol release in patients with AITD. Although linkages between circadian clock system and the HPA axis has been identified, further studies with different clock genes are needed to elucidate the physiologic as well as pathologic inter-communications between these two systems.

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P1025

In vitro study of Orexin alpha effects on factors involved in atherosclerosis: a dual role?

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Introduction
Malnutrition in neonates and children has been associated with adult-onset diseases such as obesity and atherosclerosis. Infants breastfeeding exhibit a different pattern of orexin-α secretion compared to formula-fed or infants on parenteral feeding. Given the protective role of maternal milk in the onset of metabolic syndrome and atherosclerosis in later life, we hypothesized that orexin-α may be involved in this process. We studied *in vitro* the effect of orexin-α on cell proliferation and expression of factors involved in atherosclerosis process in human aortic endothelial cells (HAECs).
Methods
HAECs were incubated with orexin-α at concentrations of 40 ng/ml, 200 ng/ml and 400 ng/ml for 6, 12, 24 and 48 hours. MTS assay was performed to evaluate cell viability/proliferation. The expression of MCP-1, MMP-2, MMP-9, TIMP-1 and TIMP-2 mRNA was measured by real-time qPCR. Orexin-α receptor and MMP-2 protein expression was evaluated by Western blot. Finally, the expression of TIMP-1 protein was studied using an enzyme immunoassay.
Results
Western blot analysis in HAEC cells, revealed very low orexin-α receptor protein level. Incubation of cells with orexin-α for 24 h induced a dose-dependent decrease in TIMP-1 protein expression (200 ng/ml and 400 ng/ml, $P<0.05$) with stronger suppression exerted at the lowest concentration (40 ng/ml-$P<0.01$). However, this was not demonstrated at mRNA level. Incubation of HAECs with orexin-α for 6 h resulted in a decrease in MMP-2 expression at mRNA level (all concentrations-$P<0.05$), and dose-dependently at protein level (400 ng/ml-$P<0.05$), while incubation of cells for 24 h increased dose-dependently MMP-2 mRNA (400 ng/ml-$P<0.05$) and protein levels (200 ng/ml $P<0.05$ and 400ng/ml, $P<0.01$). Incubation of HAECs with orexin-α at the highest concentration of 400 ng/ml for 6 and 12 h decreased significantly MCP-1 mRNA levels ($P<0.05$), while incubation for 24 and 48 hours promoted a significant increase of MCP-1 expression ($P<0.05$). Incubation of cells with orexin-α (400 ng/ml-6h) resulted in significant reduction ($P<0.05$) of MMP-2/TIMP-1 ratio while this ratio was significantly induced ($P<0.01$) after 24 h of incubation.
Conclusion
According to our findings, orexin-α may have an equivocal role in atherosclerosis process/plaque stability with its effects depending mainly on incubation duration. Short incubation period of 6 or 12 hours could promote beneficial effects exerted via reducing the expression of MCP-1 and MMP-2/TIMP-1 ratio. In contrast, longer incubation duration of 24–48 hours could result in detrimental effects, by inducing factors involved in atherosclerosis process and plaque instability (MCP-1, MMP-2/TIMP-1). Further investigation is warranted in order to shed light in the mechanism of action of orexin-α in human aortic endothelial cell.

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P1026

Glucocorticoid receptor alpha and betaexpression, serum cortisol and cytokine levels in critical illness

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Purpose
HPA axis activation resulting in increased cortisol production by the adrenals is a crucial part of the response to critical illness. The action of cortisol may also be modulated at the tissue level, through changes in the availability of the free fraction and modifications of the glucocorticoid receptor activity. It has been proposed that tissue resistance to glucocorticoids may occur, at least in some patients, and relate to insufficient anti-inflammatory activity and development of shock, despite the high circulating levels of cortisol. Therefore, in the present project we assessed serum cortisol levels and the two isoforms of the intracellular signalling receptor for cortisol, the glucocorticoid receptor (GCR), in a cohort of critically ill patients at ICU admission.
Methods
A prospective observational study conducted on 42 critically ill adults not receiving steroids, in a university-affiliated, multidisciplinary intensive care unit (ICU). Blood samples were collected for measurement of glucocorticoid receptor expression and serum cortisol levels within 24-48 hours of admission to the ICU. Twenty-five age- and sex-matched healthy donors were used as controls.
Results
At ICU admission, critically ill patients expressed increased levels of both *GCR*s compared to healthy controls; *GCR*-αmRNA expression was 10-fold ($P<0.0001$), while *GCR*-βmRNA levels were 3-fold the expression of controls ($P<0.0001$). Patients with acute stress due to surgery or trauma had significantly higher *GCR*-αmRNA compared to medical patients. The increased levels of alpha and beta *GCR*mRNA at ICU admission, returned to control

values over ICU stay. *GCR-β*mRNA and cortisol levels were highly elevated in septic shock patients compared to patients without septic shock.
Conclusions
*GCR-α*mRNA expression rises acutely in response to stress, suggesting that resistance to glucocorticoids, if it occurs, is a later event. Septic shock may represent an exception where increased expression of the *GCR-β*may lead to glucocorticoid resistance despite elevated cortisol levels.

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P1027

Immune-related endocrine toxicities in non-small cell lung cancer: predictors of outcome to checkpoint inhibitors?

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Background
Immune checkpoint inhibitors (ICIs) are approved for the treatment of non-small cell lung cancer (NSCLC) and are associated with specific immune-related adverse events (iRAEs) including endocrine toxicities. However, data concerning the type, occurrence, and dynamics of iRAEs and their predictive value on treatment outcome are lacking. In this study, we evaluated the relation of iRAEs to anti-PD/L1 (programmed cell death protein/ligand-1) ICIs focusing particularly on endocrine iRAEs.
Materials and methods
A total of 147 patients, with locally advanced/metastatic (stage IIIb and IV) NSCLC, treated with anti-PD1 (N 140; 95%) or anti-PDL1 agents (N 7; 5%) as $\geq$ 2 line treatment were included in two independent, prospective cohorts at the Institut Curie (ALCINA-NCT02866149) and at Biella Hospital (Italy). Progression free-survival (PFS) and overall survival (OS) were estimated with Kaplan-Meier curves.
Results
Among 147 patients, [median(range) age, 66 (35–85) years; 100 men (68%), 47 women (32%)], irAEs were observed in 72 patients (49%) including endocrine-irAEs, mostly thyroid dysfunctions, in 47 patients (32%). Pre-existing thyroid disease was present in 6 patients (4%), while type 2 diabetes mellitus (T2DM) was documented in 18 patients (12%). After treatment initiation, 64 patients had $\leq$ 2 coexisting irAEs (43%), and 8 had $\geq$ 2 toxicities (5%). Most iRAEs were G1 (N 71; 48%) and G2 (N 23; 16%). Median PFS was 5.7 and 3.1 months in irAEs *vs* no-irAEs group (*P* 0.11, NS), respectively. Median OS was significantly longer (23.4 months) in irAEs group compared with no-iRAEs group (13.5 months) [HR 0.59 (95% CI 0.35–1.0), *P* 0.049]. Moreover, median OS in the endocrine-iRAEs group was 29.83 vs 14.60 months in the no-iRAEs group, showing a trend toward significance in the association between endocrine-iRAEs and clinical outcome [HR 0.55 (95% CI 0.31–0.99), *P* 0.06, NS] possibly due to a lack of power.
Conclusions
Endocrine-irAEs are frequent in patients treated for NSCLC. In this study, we confirm that development of irAEs is a predictor of survival outcome in patients with advanced NSCLC treated with ICIs.

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P1028

Impact of hormonal factors in the genesis of sarcopenia

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The European Working Group on Sarcopenia in Older People (EWGSOP2) defined in 2018 'sarcopenia as muscle disease (muscle failure), with low muscle strength overtaking the role of low muscle mass as a principal determinant'; sarcopenia increases risk of falls and fractures, impairs ability to perform activities of daily living, leads to mobility disorders and low quality of life and death. The diagnosis is confirmed by low muscle quantity or quality. The muscle quantity may depend on several hormonal factors that may decline with ageing. The association of sarcopenia with osteoporosis may increase the risk of osteoporotic fractures due to the increased risk of falls.
Aim
To evaluate the influence of some endocrine factors on the variability of skeletal muscle mass in elderly people.
Material and methods
In 469 women [mean age($\pm$s.d.)=72.8($\pm$5.5) years, mean postmenopausal years: 23.5] and in 249 men, mean age 72.7($\pm$5.7) years, total fat (TFM) and lean body (TLM) masses and BMD at several skeletal sites were measured by DXA. A skeletal muscle mass index (SMI) was also calculated. Fasting blood collection was performed for measurement of total and fere testosterone (men only), IGF-1 (ng/ml) and 25 (OH) D (ng/ml). Statistical analysis was performed using adequate tests and statistical significance was considered for $P<0.05$.
Results
The correlations between the SMI and hormone and IGF-1 blood levels are shown in Table 1.

Table 1

Measurements *vs.* **SMI**	**IGF-1** *ng/ml*	**25(OH)D** *ng/ml*
Women CC	0.1357	0.3564*
P	*0.0153*	*0.0000*
Men CC	0.4407*	0.1874
P	*0.0000*	*0.0412*

*adjusted for total body fat mass

Correlations between SMI and total testosterone (CC=0.2437, $P=0.0002$) and free testosterone (CC=0.3114, P=0.0002) were also detected.
Conclusions
These data show that in elderly people (both sexes) the skeletal muscle mass may be influenced and depends of endocrine factors such as somatotrophin, vitamin D and testosterone (in men). The progressive decrease of these hormones may increase the risks of sarcopenia development and of falls, adverse effects of the fragility syndrome, low quality of life due to loss of independence and death.

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P1029

It is a link between thyroid function and our empathy in relation to animals ?

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Introduction
Animals have long been considered the best friends of man, but as it turns out, the degree of empathy towards them is ontogenic variable. So far there have been studies showing the influence of mutations in the oxytocin gene on our level of empathy.
Method
It was decided to check if hormonal factors have the influence on our relations with animals. For this purpose, patients treated in our department of endocrinology were examined. The study included 162 people aged 18+, both women and men. 54 people were treated due to hypothyroidism, 33 due to hyperthyroidism, 14 due to non-toxic goiter, 33 patients were treated due to other diseases and the rest had several endocrine diseases diagnosed simultaneously. In order to increase the reliability of the study, the last two groups of patients were omitted in further analysis. The study took the form of a short questionnaire in which patients assessed their relationship with animals, the amount of time spent on them during the day, etc.
Results
The most frequent owners of pets were patients with hypothyroidism (70% of patients), slightly less frequently persons with hyperthyroidism (64% of patients), and the least frequently persons with non-toxic goiter (57% of patients). Patients

with hypothyroidism (64% very good, 29% good, 7% neutral, 0% bad, 0% very bad) rated their relations with animals the best. Indirect results were obtained from patients with non-toxic goitre, as 60% of patients rated their relationship with animals as very good, 28% as good, 6% as neutral, 6% as bad and 0% as very bad. Patients with hyperthyroidism turned out to be the least empathic, as only 57% of them rated their relations with animals as very good, 25% as good, 15% as neutral, 3% as bad and 0% as very bad. The survey results also showed that patients with hypothyroidism who have pets devote more time to them compared to patients with hyperthyroidism.

Conclusion

The hormonal factors, especially thyroid hormones, can play an certain role in our relationships with animals, the excess of which correlates with a worse attitude towards our pets.

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P1030

The role of adenosinergic system in patients with orthostatic intolerance

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Objectives

Adenosine is a purinergic mediator involved in the regulation of many physiological and pathological processes. It acts as neurotransmitter in the central and autonomic nervous system, where it counterbalanaces sympathetic activity. Adenosine is produced by majority of human cellsexerting autocrine, paracrine as well as systemic effects. Due toits vasodilatatory and negative inotropic effects it seems to play a role in ethiopathogenesis of orthostatic intolerance, particularly in vasovagal syncope.

Aim

Of this pilot study was to compare baseline (before head up tilt test - HUTT) and stimulated (after HUTT) serum levels of adenosine between patients with positive and negative HUTT and to compare serum levels of adenosinedeaminase (ADA) between positive and negative patients.

Subjects and methods

Group of 39 patients with history of at least one syncope or presyncope underwent HUTT. According to the response during the test, they were divided into HUTT positive ($n=29$, age $31.38+4.9$) and HUTT negative ($n=10$, age $39.85+2.7$). HUTT was performed according to Italian protocol, with continual ECG monitoring and BP measurement. Blood sampling was realized before and immediately after HUTT. Serum adenosine and ADA levels were evaluated by ELISA method.

Results

HUTT positive patients had significantly higher levels of baseline adenosine than those with HUTT negativity (3.17 vs 1.78 ng/ml; $P=0.03$). There was no significant difference in adenosine levels after HUTT, between HUTT positive and HUTT negative patients, but HUTT positive patients tended to have higher stimulated levels of adenosine (3.59 vs 1.87 ng/ml; $P=0.08$). Serum ADA activity was similar in both groups (10.9 vs 9.6 IU/l; $P=0.83$).

Conclusion

HUTT positive patients had significantly higher serum adenosine as compared to those HUTT negative. We conclude that adenosine may play a role in the etiopathogenesis of vasovagal syncope and states with orthostatic intolerance.

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P1031

Acid sphingomyelinase deficiency unusually associated with severe delay of growth

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Background

Acid Sphingomyelinase Deficiency (ASMD) is a rare lysosomal storage disease caused by mutations in the *SMPD1* gene. Typically, the p.Arg610del homozygotes had normal linear growth.

Case report

We reported the cases of 2 Tunisian brothers aged 23 and 13 years respectively, who have been admitted for splenomegaly and polyadenopathies. Physical examination showed pubertal and growth delay for both cases. Biological evaluation showed moderate anemia associated with dyslipidemia (decreased HDL and elevated TRG). Lysosphingomyelin and Lysophingomyelin-509 were both increased. Molecular testing of *SMPD1* gene revealed a p.Arg610del mutation confirming ASMD for both cases. GH deficiency was highly suspected and Growth Hormone stimulating tests were enrolled for both patients. GH response was acceptable for both.

Conclusion

We reported the first case of ASMD with p.Arg610del genotype that was associated with severe phenotype constitutional delay of growth. Nevertheless, GH deficiency should be investigated.

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P1032

Efficacy of growth hormone treatment in children with turner syndrome

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Objectives

To evaluate the efficacy of growth hormone (GH) treatment in children with Turner syndrome (TS) and to analyze the factors affecting the success of treatment.

Methods

Retrospective observational study was conducted for 62 patients with TS. 3 groups of patients were identified: group 1 with karyotype 45, X ($n=32$), group 2 with mosaic variant 45,X/46,XX ($n=8$), group 3 with structural anomalies of X chromosome ($n=22$). All patients were treated with GH at a dose of 0.33 mg/kg per day continuously for a year or more. A retrospective analysis of height (cm, SDS), growth velocity (cm/year), change in height SDS (ΔSDS), bone age before and during treatment was carried out. The results were processed using SPSS.22.

Results

TS was diagnosed in patients with characteristic phenotypic signs according to the results of karyotyping at the age of 6.7 ± 5.07 (0.1–17.3) years. The chronological age at the start of GH treatment was 9.1 ± 3.5 years (2.6–15.2). Most of the children had significant growth retardation (height SDS -2.87 ± 0.93) and a low growth velocity (4.7 ± 1.3 cm/year). Growth velocity increased with the use of GH in the first year of treatment. In group 1 the growth velocity was 7.2 [6.0; 9.5] cm/year versus 4.4 [3.48; 5.27] cm/year before treatment ($P<0.001$), in group 2 - 6.38 [6.1; 8.56] cm/year versus 3.95 [2.82; 5.42] cm/year ($P=0.004$) and in group 3–8.15 [7.02; 9.72] cm/year versus 5.05 [3.9; 6.1] cm/year ($P<0.001$). Height ΔSDS for 1 year of therapy was 0.49 ± 0.3. The maximum change in height SDS were observed in girls with TS due to structural anomalies of the X chromosome (ΔSDS = 0.55 [0.29; 0.72]), lower - in patients with monosomy X (ΔSDS = 0.43 [0.23; 0.71]). To assess the effect of the age at initiation of therapy on the efficacy of treatment, groups of patients have been identified: up to 5 years, from 5 to 13 years, after 13 years. There was a small increase in bone age after GH therapy for 12 months in children under 5 years of age (0.5 years [0.5; 0.94]) versus 1.25 years [0.96; 2.0] in children older than 5 years ($P=0.021$) and 1.0 years [0.56;1,74] in children over 13 years old. This may worsen the growth prognosis with long-term GH treatment, given the lower baseline growth rates in TS children over the 5 years old.

Conclusions

For TS patients, GH treatment significantly increases growth rate. The age at initiation of therapy is an important prognostic factor.

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P1033

Adipocytokines dynamics in patients operated for rectal neoplasm

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Adipose tissue performs an important endocrine role, mediated by hormones (adipocytokines) which are specifically secreted by the adipocytes. Epidemiological data consistently show an association between weight gain and the risk of colorectal cancer in adults.This observation led to the evaluation of a possible linking role of adipocytokines with cancer pathogenesis. There are several studies that associate adipocytokines with colorectal malignancy, but few data about patients suffering exclusively of rectal carcinoma. We evaluated leptin and adiponectin levels in patients with rectal cancer (RC) compared to healthy population and their dynamics after surgery. Serum leptin and adiponectin were measured in 59 patients (38 males and 21 females) before surgery and in age and weight matched healthy controls. Measurements were repeated at 24, 72 hours and 7 days after surgery. Adipokine levels were higher in women. Controls had higher leptin and lower adiponectin than RC patients. Surgery caused an increase of leptin and a decrease of adiponectin for all RC patients and returned to the initial range at 7 days. Adipokines were correlated with body weight. The significance of correlation persisted after surgery only in males, but disappeared in females. Adipokines were not modified by tumor position, surgical technique or presurgical chemoradiotherapy. Adipokine levels of patients with RC differ from the healthy population, possibly reflecting an adaptation to disease. Adipokine modifications after surgery may be related to acute surgical stress. Women have higher adipokine levels, more so after significant weight loss, but the strength of their correlation with BW decreases after surgery. These data suggest gender differences in the adipokine profile of RC patients which may find clinical applications.

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P1034

Harmonization status among ten European laboratories using liquid chromatography-tandem mass spectrometry (LC-MS/MS) for steroid measurements in serum: preliminary results from the HarmoSter consortium

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Background
LC-MS/MS is replacing immunoassays for serum steroid measurement in clinical labs worldwide. The intrinsic high specificity of LC-MS/MS is supposed to guarantee accurate quantitation, however, differences in pre-analytical and analytical procedures, and overall performance may influence the result. A few studies so far investigated the reproducibility among different LC-MS/MS assays for sex steroids. No data are available for adrenal steroids.
Aim
To compare the LC-MS/MS measurement of 13 serum steroids among 10 European Centers.
Methods
Blood from 13 women and 13 men aged 21–70 y was collected in fasting state, at 8:00–9:00 am, after 10 min saline infusion in three different vacuum tubes to obtain serum (gel separator, GS and beads-clot-activator) and plasma (Li-Heparin) (78 total samples). Aliquots were sent to each lab for LC-MS/MS measurement according to the lab's own procedure. Intra-lab duplicate measurement CV%, inter-lab CV% and Bland-Altman analyses were performed.
Results
Preliminary results from six labs were obtained on cortisol (F), cortisone (E), corticosterone (B), 11 deoxycortisol (11S), 17OH-progesterone (17OHP4), androstenedione (A4), testosterone (T) and DHEAS. Intra-lab CV% ranged 3.1–9.9 (F), 2.7–13.8 (E), 3.3–8.0 (B), 3.8–14.4 (11S), 5.8–18.1 (17OHP4 < 1 ng/ml) 2.0–9.9 (17OHP4 > 1 ng/ml), 4.2–8.8 (A4), 4.3–7.6 (T) and 4.1–11.4 (DHEAS). Median inter-lab CV% were 5.0, 5.1, 6.8. 7.3, 8.9, 14.0 and 15.5 for DHEAS, E, T, A4, B, 11S and F, respectively, and 13.2 and 5.9 for 17OHP4 < 1 ng/ml and > 1 ng/ml, respectively. Cases showing inter-lab CV > 15% were 0 for T; 1 (1.3%) for E and DHEAS; 3 (3.8%) for A4; 13 (16.7%) for B; 25 (32.1%) for 17OHP4; 36 (46.2%) for 11S and 42 (53.8%) for F. Among GS-sera, cases increased to 18 (69.2%) for both 11S and F. Results from each lab were compared to all-lab median values. Mean bias ranged −3.5 – 5.8%, -1.9 - 6.5%, −3.2 – 9.1%, -10.6 – 11.2%, −16.5 – 14.6% and −5.0 – 36.9% for DHEAS, E, A4, B, 11S, and F, respectively. Moreover, mean bias ranged −23.4 −7.5% and −6.7 − 4.7% for 17OHP4 < 1 ng/ml and > 1 ng/ml, respectively, and −2.9 – 6.4% and −8.5 – 8.7% for T < 1 ng/ml and > 1 ng/ml, respectively.
Conclusions
Variable intra-lab performances were observed. Inter-lab reproducibility was good for E, B, DHEAS, A4 and T, but poor for F and 11S. The specimen type may influence the results. 17OHP4 reproducibility was higher at high than low levels, while the opposite was unexpectedly found for T. Further analyses will help to define and correct major sources of variability.

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P1035

Ultrastructural changes of neuroendocrine and endocrine responding cells associated with reproductive timing in a hibernating mammal

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Reproductive timing strongly influences the fitness of the individual. While most vertebrates rely on photoperiodic changes to induce seasonal reproduction, the arctic ground squirrel (AGS) naturally undergoes reproductive maturation in a photoperiod-independent manner. In addition, males spontaneously activate their reproductive axis during hibernation, but the timing of reproduction is sensitive to external cues. We are using electron microscopy to examine, define, and measure ultrastructural remodeling in pars tuberalis (PT) thyrotroph cells, hypothalamic tanycytes, and pars distalis (PD) gonadotroph cells, as the AGS transitions from hibernation to the reproductive season. We are also quantifying how the morphology of these cells correspond with measures of reproductive axis outputs, including changes in steroidogenic gene expression in gonads, gonadal development and maturation, and plasma sex steroid concentrations. Finally, we are examining the mechanisms that underly plasticity in hibernation phenology and examining whether hypothalamic and PD activity can become dissociated from the PT signaling pathway by assessing cellular remodeling in males placed in a 30°C room during mid-hibernation, which induces early reproductive onset. We hypothesize that changes in PT morphology underlie the termination of torpor and initiation of reproduction in a photoperiod-independent manner. This basic system-level investigation of reproductive control mechanisms may inform researchers on how cellular ultrastructure influences connections between neuroendocrine circuits and the role this plays in directing activation of puberty onset, without photic cues.

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P1036

Epilepsy induced by severe hypoglycemia: about 3 cases

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Introduction
When hypoglycemia is deep and repeated, it can induce various neurological disorders, including epileptic seizures. The link between hypoglycemia and epileptic phenomena is complex and poorly explained. We report 3 cases of epilepsy induced by repeated episodes of deep hypoglycemia.
Cases report
Mr D.M, 48 years old, with a history of 3 episodes of hypoglycemic coma, admitted for status epilepticus with a blood glucose level of 0.4 g/l; cerebral CT was normal. The encephalogram showed a slowing of the background rhythm with paroxysmal fronto-central bilateral anomalies. Biological test shows endogenous hypersecretion of insulin; echoendoscopy revealed an hypoechogenicity of 2 cm/2.5 cm at the head of pancreas. The second case is a 38-year-old patient treated for epilepsy for 2 years, admitted for a major generalized tonic-clonic seizure with left hemiplegia. MRI brain was normal, glycemia was at 0.3 g/l, insulin levels and peptide C were too high, an Octreoscan is required; an endocrine tumor of the pancreas secreting insulin is strongly suspected in these two patients. The third case is a 22-year-old patient, diabetic type 1, receiving insulin for 6 years, he has a history of hypoglycemic coma and he is hospitalized for a new episode revealed by generalized tonic-clonic seizures. The encephalogram showed a slowing of the background rhythm with paroxysmal fronto-central bilateral anomalies. Cerebral MRI showed an hypersignal in T1 and T2 of the basal ganglia.
Discussion
The deep hypoglycemia can induce convulsive crises as far as it can predisposes to the development of epileptogenic foci. The induced seizures are mainly generalized and tonic-clonic and the described abnormalities predominate in the frontal and temporal lobes, which joins the cases of our three patients.

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P1037

A case report about endocrine disorders and post transfusion hemochromatosis: a fortuitous association?

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Introduction
Beta-thalassemia major is a genetic syndrome accompanied by a defect in hemoglobin synthesis leading to severe anemia. Conventional treatment of this hemoglobinopathy involves repeated blood transfusions exposing the patient to iron overload, which represents the main morbidity due to visceral and endocrine complications. We report the case of a patient treated for beta-thalassemia with endocrine complications associated with post transfusion hemochromatosis.
Observation
20-year-old female patient treated for beta-thalassemia major for 15 years, splenectomized at 10 years old, polytransfused 2 times per month, initially admitted for an inaugural ketosis of diabetes. The clinical examination found a patient with a delayed stature: weight at 28 kg (−2DS) for a height at 149 cm (−2DS) and a delayed puberty: patient in primary amenorrhea with a score TANNER P0S0. Paraclinically, ferritinemia was at 21763 µg/l, serum calcium at 82 mg/l. The hormonal assessment found a central hypothyroidism with a TSH at 2 µUi/l, a T4L at 0.6 ng/dl and a T3 at 1 µg/ml, a hypogonadism hypogonadotropic, a cortisolemia of 8 h at 19 µg/dl. The assay IGF1 levels and Anti GAD Antibodies were not performed due to lack of means. Hypothalamic-pituitary magnetic resonance imaging (MRI) showed no abnormality. Bone age was 13.5 years. The patient received insulin and estrogen/progestin treatment and levothyroxine supplementation.
Discussion
This observation illustrates the multiple endocrine complications that could be associated with post-transfusion hemochromatosis. Several endocrine organs including the pituitary, thyroid and parathyroid glands, as well as the gonads and the endocrine pancreas may be targets of post-transfusional iron overload, which may expose the patient to multiple endocrine complications. The most common one observed is diabetes mellitus. Functional insufficiency of gonadotropic, thyrotropic and somatotropic hormonal axes is also common, with repercussions on growth and sexual development. The frequency and diversity of endocrine abnormalities associated with hemochromatosis, make early diagnosis and appropriate management in endocrinology essential to improve the prognosis.

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P1038

Risk of type 2 diabetes (T2D) in patients with chronic hypoparathyroidism (HypoPT): A retrospective cohort study

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Background
Among chronic hypoparathyroidism (HypoPT) patients, the baseline prevalence of type 2 diabetes (T2D) appeared to be higher than the general population in previous studies. Since little is known about the potential assocation between HypoPT and T2D, this study evaluated whether HypoPT is associated with increased risk of T2D.
Methods
A retrospective cohort study, based on a US commercial claims database (Q1 2007 – Q2 2017), was conducted to investigate the risk of T2D associated with chronic HypoPT (both identified using diagnosis codes). The study cohort included chronic HypoPT patients (excluding those receiving parathyroid hormone) and randomly selected non-HypoPT patients during 5 years of follow-up. For HypoPT patients, the first date of follow-up (i.e., index date) was the earliest HypoPT diagnosis date $\geq$6 months after the initial HypoPT diagnosis (to establish chronic HypoPT); for non-HypoPT patients, it was the date of a randomly selected medical claim. Patient characteristics at baseline (the 6 months prior to index date) were compared between cohorts. The risk of development of incident T2D was compared between HypoPT and non-HypoPT cohorts among those free of T2D during the baseline period using Kaplan-Meier analysis and multivariable Cox proportional hazards models adjusting for baseline demographic characteristics (age, sex, race, region, and index year). A sensitivity analysis was conducted among the subset of patients with glucose monitoring (defined as having at least one procedure code for a glucose test) during the study period to address potential detection bias.
Results
The study included 8,097 chronic HypoPT patients and 40,485 non-HypoPT patients. At baseline, HypoPT patients were older than non-HypoPT patients (58.6 years vs 47.3 years) and higher proportions were female (76.2% vs 54.4%) and had T2D (20.6% vs 10.8%) (all $P<0.001$). HypoPT patients had an increased risk of developing incident T2D compared with non-HypoPT patients in both the main and the sensitivity analyses (both $P<0.001$ based on Kaplan-Meier analyses). The adjusted hazard ratios (95% confidence intervals) associated with HypoPT versus non-HypoPT were 1.80 (1.64, 1.96) in the overall analysis and 1.48 (1.35, 1.63) in the sensitivity analysis (both $P<0.001$).
Conclusions
Chronic HypoPT was associated with increased risk of developing type 2 diabetes. Further research is warranted to understand the potential mechanisms for the relationship of chronic HypoPT and/or its management with the observed risk of type 2 diabetes.

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P1039

The role of the growth hormone – insulin-like growth factor 1 axis in primary osteoarthritis

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Introduction
Increased insulin-like growth factor 1 (IGF-1) levels in patients with acromegaly are associated with clinical and radiological osteoarthritis (OA). We aimed to elucidate whether serum IGF-1 levels differ in patients with primary OA as

compared to healthy controls and whether genetic variants known to affect serum IGF-1 levels are also associated with primary OA.
Methods
Patients from the GARP study with familial generalized OA ($n=317$) were biochemically and clinically assessed, and 10 single nucleotide polymorphisms (SNPs) associated with serum IGF-1 levels were genotyped. Binary logistic regression was performed, stratified for gender, to calculate robust standard errors.
Results
IGF-1 levels correlated with age ($r=-0.142$, $P=0.001$) and BMI ($r=0.102$, $P=0.018$). Within the GARP study, solely males had higher IGF-1 levels compared to healthy controls (19.8 ± 6.18 nmol/l vs 16.9 ± 4.53 nmol/l, $P=0.001$). Within healthy controls, IGFBP-3 levels were significantly lower in males (4.29 ± 0.86 mg/l vs 4.50 ± 0.88 mg/l, $P=0.0094$). The association of the selected SNPs with IGF-1 levels and IGFBP-3 levels were confirmed. Male carriers of the minor allele of rs4946936 had significantly lower risk to develop hip OA specifically ($\beta=-0.860\pm0.417$, $P=0.039$), but not knee OA. In contrast, female carriers of the minor alleles of rs957755 and rs11769597, which are in high LD, had a significantly higher risk to develop knee OA ($\beta=0.695\pm0.235$, $P=0.003$). Furthermore, female carriers of the minor allele of rs700753 have significantly less risk to develop knee OA ($^{®}=-0.419\pm0.200$, $P=0.036$).
Conclusion
Since genetic variation could contribute to the occurrence of OA and GH and IGF-1 are involved in the healthy functioning of bone, variants that alter the function of the GH – IGF-1 axis influence the (susceptibility to the) development of primary OA. Male carriers of the minor allele of rs4946936 had less risk to develop hip OA, which is most likely due to lower IGF-1 levels. Moreover, female carriers of the minor alleles of rs957755 and rs11769597 had a significantly higher risk to develop knee OA and female carriers of the minor allele of rs700753 have significantly less risk to develop knee OA via the altering of IGFBP-3 levels. In future studies, the exact (patho)physiological mechanisms of (altering) the GH – IGF-1 axis in healthy, osteoarthritic and arthritic cartilage, bone and joints needs to be elucidated.

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P1040

Diabetes and Nivolumab: 2 clinical cases compared

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Monoclonal antibodies against the Programmed cell death-1 protein (PD-1) are a new treatment for advanced cancer. Endocrine and metabolic diseases are known to be frequently associated with this class of drugs. We describe two cases of Nivolumab-induced diabetes mellitus.
Case 1: A 73-year-old man with a mutated BRAF-V600K advanced stage melanoma was treated with Nivolumab (240 mg IV every 2 weeks). He had normal-weight (BMI: 21.6 Kg/mq), and no previous personal or family history for diabetes. After 15 months of therapy, fasting glucose levels started to raise from 105 mg/dl at the 32nd infusion to 139 mg/dl at the 33rd drug injection. At the following cycle of Nivolumab, the patient complained of lethargy, polyuria and polydipsia associated with rapid weight loss. Laboratory testing revealed diabetic ketoacidosis characterized by severe hyperglycaemia (726 mg/dl), hyperkalemia (5.5 mmol/l), increased of creatinine (1.9 mg/dl), glycosuria and ketonuria; glycated hemoglobin was 84 mmol/mol. At the time of the diagnosis and in the following months the anti-glutamate decarboxylase (anti-GAD), anti-insulin and pancreatic anti-insula antibodies titers resulted negative with extremely low C-peptide values (0.4 ng/ml), suggesting an immunomediate genesis of diabetes. The patient presented a genotype HLA-DRB1*10,*11 unrelated to the type 1 diabetes mellitus.
Case 2: A 52-year-old woman was treated with Nivolumab (150 mg IV every 2 weeks) for advanced lung cancer. She had a normal-weighted (BMI: 19.5 Kg/mq), and no previous personal and family history for diabetes. At the 3rd infusion of Nivolumab, the patient complained of rapid weight loss. Blood glucose was 346 mg/dl with a glycated hemoglobin equal to 66 mmol/M. The anti-GAD titers were positive (22.82 U/ml) and the anti-insulin and pancreatic anti-insula negative.
In both cases, diabetes had a sudden and overwhelming manifestation, but with a different time of onset. When glycemic alterations occurred, the oncological treatment was stopped and the basal-bolus insulin therapy was immediately established. As soon as the glycemic profiles stabilization was achieved, immunotherapy was resumed.
Conclusions
Diabetes mellitus is a rare side effect of immunotherapy and may appear in extremely variable time during treatment. Even if no specific antibody titers may be found, the clinical and biochemical presentation is suggestive for an immunomediate genesis of the diabetes. A correct management of diabetes and a rapid recovery of immunotherapy should be performed by close collaboration between Oncologists and Endocrinologists.

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P1041

Identification, management and outcome of endocrine toxicities related to immune checkpoint inhibitors

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Introduction
Immunotherapy has become standard treatment for an increasingly wide range of cancers. Checkpoint inhibitors (ICT; CTLA4, PD1 & PD-L-1) can cause endocrine toxicity, principally affecting the pituitary and thyroid glands. We have studied the clinical management and outcome of patients with endocrine adverse effects over 5 years at our cancer centre.
Methods
All patients treated with ICT agents between 1 Jan 2014 to 31 Jan 2019 were included for this retrospective analysis. Cases with pre-existing relevant endocrine conditions were excluded. Tests for endocrine surveillance were taken prior to each cycle as standard of care. We analysed these results and assessed time to onset of toxicity in relation to the ICT cycle, clinical recovery, nature of endocrine input and outcome.
Results
Out of the 356 patients treated with ICT, 87 patients (24.4%) developed an endocrine toxicity (24%). Mean age at onset of toxicity was 62 ± 14 years (mean $\pm$ S.D.), 41 males and 46 females. 8 patients were treated with CTLA4, 65 with PD1, 11 with combination of CTLA4 and PD1 and 3cases were treated PDL1. A total of 70 cases were found to have thyroid dysfunction, 15 with hypophysitis and 2 cases with type 1 DM. More than one endocrine toxicity occurred in 4 patients. Amongst the patients with hypophysitis 4 patients were treated with CTLA4, 8 with PD1 and 3 with combination therapy (CTLA4 and PD1). Thyroid dysfunction was the most common toxicity in PD1 treated cases with 64 patients presenting with transient painless thyroiditis, hypothyroidism or hyperthyroidism. Isolated ACTH deficiency was the most common pituitary abnormality (11/15) in patients with hypophysitis. Clinical recovery was only reported in 17/87 cases all of whom had thyroid dysfunction. 76/87 had mild toxicities (Common Terminology Criteria for Adverse Events CTCAE grade <3), 11/87 patients required hospitalisations (CTCAE ≥3). 31 patients were asymptomatic on diagnosis. In only 6/87 cases ICT was discontinued or delayed for endocrine causes.
Conclusion
ICT related endocrine toxicity occurred in approx. 25% patients with thyroid dysfunction, followed by hypophysitis the commonest conditions. 35% patients were asymptomatic and identified by blood testing. In the majority of cases the ICT could be safely continued. Surveillance protocols are required to allow safe use of ICT, and can help identify and manage adverse effects whilst facilitating uninterrupted use of immunotherapy.

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P1042

Use of Simple Referral system to provide quality care in the management of Endocrine Toxicities with Immune checkpoint therapy: Auditing the effectiveness of a new referral system

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Introduction
Immune checkpoint therapies are novel cancer agents, which have been associated with the development of endocrine toxicities. ESMO and SfE endorsed management guidelines have been helpful for the early recognition of these toxicities, but in clinical practice, having early access to specialist endocrine advice improves the decision making and effective use of these agents when toxicities occur. In response to need we developed an easily accessible interdisciplinary support team to provide prompt guidance for oncologists using immunotherapies. An electronic email based referral was set up in March 2018 to

provide high quality support to the oncology team, with the aim of having a dedicated specialist team with rapid response time.
Methods
We conducted a retrospective audit of the management of endocrine toxicities at our centre from 2014 to 2019. All patients treated with Immune checkpoint therapy (CTLA4, PD1, PDL1) were included for the audit, while patients with pre-existing endocrine diagnosis or incomplete clinical outcome data were excluded from the final analysis. Time to endocrine advice was noted before and after March 2018.
Results
Out of 356 patients included in the final audit 87 patients were identified to have endocrine toxicities (approx. 25%). Thyroid dysfunction was the most endocrinopathy, seen in 19.6% of total cases, followed by hypophysitis (4.2%). There were 2 cases of Graves' disease and 2 new type 1DM. Most patients with toxicities were found to have Common Terminology Criteria for Adverse Events (*CTCAE*) toxicity grade 1 or 2 (87.3%) while 11 (12.6%) cases had grade 3 toxicity or above. Between 2014 to Feb 2018, the mean time to endocrine advice/assessment was 9.7 days in cases with CTCAE toxicity grade 1 or 2, while this improved to 3.7 days after March 2018. Time to clinical input and urgent inperson review in CTCAE grade 3 or 4 was found have improved from 73 days to 20 days after the referral link was set up, with all patients receiving a virtual plan within 24 hours.
Conclusion
Simple governance steps of setting up 1. A Local Management Guideline, and 2. A virtually supported e-referral system, enabled improvement in the quality of care of endocrine toxicities. This did not need substantial additional resource and the majority of patients could continue uninterrupted immunotherapy.

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P1043

Differences in gut microbiota between patients with gestational diabetes treated with insulin in comparison to those treated with metformin: preliminary analysis

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Objective
To evaluate changes in gut microbiota induced by treatment in patients with gestational diabetes mellitus (GDM) treated with insulin in comparison to those treated with metformin.
Material and methods
Thirty-one patients with GDM not controlled by diet, included in MeDiGes study ('Efficacy of metformin in gestational diabetes not controlled by diet in comparison to insulin'), were aleatorized to receive insulin ($n=14$) or metformin ($n=17$). Stool samples were collected before the begining of the treatment and in prepartum visit. Clinical-analytical characteristics at baseline and changes in gut microbiota after treatment were compared between both treatment groups.
Results
Clinical-analytical characteristics at baseline are showed in Table 1. Non statistically significant differences were found between both treatment groups in any of parameters. Regarding gut microbiota diversity, after treatment, we found a significantly lower Shannon index in those patients treated with metformin in comparison to those treated with insulin ($P=0.04$). In metformin group, Firmicutes descended significantly while Proteobacteria increased significantly. No significant changes were found in Bacteroides, Verrucomicrobia, but Actinobacteria tended to reduction (despite non statistical significance). No significant changes were found in insulin group.

Table 1

	Insulin	Metformin	*P* value
Age (years)	33.7±5.6	36.6±2.7	0.081
Family history of DM (%)	73.3	64.7	0.599
Personal history of GDM (%)	20	17.6	0.865
Gestational age (weeks)	29 (16–32)	30 (23.5–32)	0.737
Pre-gestational BMI (kg/m2)	28.6±3.8	28.9±6.5	0.907
Baseline BMI (kg/m2)	32.2±4.5	32.1±7.2	0.978
Fasting glucose (mg/dl)	85.1±10.6	83.5±11.2	0.646
HbA1c (%)	5.2±0.3	5.2±0.5	0.834

Conclusions
- Metformin reduces gut microbiota diversity.
- Metformin cause specific changes in gut microbiota, reducing Firmicutes and increasing Proteobacteria.

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P1044

Current medical care in women with Turner syndrome-retrospective data from five different specialist endocrinology centers in Germany

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Introduction
Turner syndrome (TS) is characterized by the complete or partial loss of one X chromosome and associated with a wide range of clinical manifestations. The clinical appearance depends on the specific karyotype, which may include different mosaic forms. Main features of almost all the karyotypes are short stature and delayed or absent puberty. Adult women in particular are at high risk of developing cardiac complications, metabolic syndrome, increased liver enzyme values, thyroid abnormalities, sensorineural hearing loss and inflammatory bowel disease. In addition, these women also display a tendency to suffer from low bone mineral density (BMD). The aim of the present study was the investigation of the current endocrine medical care in TS patients.
Method
Data were collected from medical records of 258 women with TS treated between 2001 and 2017 in five different specialist endocrinology centers in Germany. The study was approved by the ethic committee of the University Medical Center.
Results
Data analyses across endocrine locations could successfully be performed. Data evaluation of laboratory values was difficult due to different analyzing laboratories. At last follow-up, mean age was 29.8±11.6 years, mean height 152±7.7 cm and mean body mass index (BMI) 26.6±6.3 kg/m^2. Most information was available on TSH (98%), liver values (93%) and the medication with hormone replacement therapy (90%). Less often parameters LDL (81%) and HbA1C (74%) were analyzed. Transition data on menarche (spontaneously or induced) and age at menarche were existent in 62% or 54%, respectively. The exact karyotype was documented in 50% of the medical records of the adult women. BMD was determined in 18% of the women, echocardiography in 42% and cardiac magnetic resonance imaging in 8.5%, the latter resulting in a diagnosis of cardiovascular disorder in 28% of those investigated.
Conclusion:
Before the publication of the TS guidelines, the endocrine care of TS women concentrated on thyroid and metabolic disease. From these retrospective data a structured work-up according to the TS guidelines is now implemented to improve the care of TS women in the participating centers.

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P1045

Clinical audit of immune related adverse events of the endocrine system with checkpoint inhibitor therapies – adopting a new algorithm for routine endocrine monitoring

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Background
Immune related adverse events (iRAEs) of the endocrine system are commonly recognised in Checkpoint Inhibitor Therapy treatment with current research suggesting clinically significant endocrinopathies occur in 10%. As the use of these drugs continues to rise, so too does the importance of routine endocrine monitoring in order to avoid potentially life-threatening adverse-events.

Aims
To establish the frequency, severity, management and outcomes of endocrine IRAEs in patients undergoing Checkpoint Inhibitor therapy in our institution and to review endocrine investigations initiated. We wished to develop an appropriate algorithm for routine monitoring of these patients.
Method
Using the hospital's database, a retrospective, anonymized audit of all patients receiving immunotherapy with Ipilimumab, Pembrolizumab, Nivolumab or a combination of these agents over the period from 2013 to 2018 were identified. The incidence, grade and outcome of thyroid dysfunction, hypophysitis, primary adrenal insufficiency and insulin-deficient diabetes in this group were recorded. The frequency of monitoring of TFTs, ACTH, cortisol, blood glucose level and HbA1c was also recorded.
Results
We reviewed the records of 37 patients. Patients receiving monotherapy included 21 receiving Nivolumab, 7 receiving Pembrolizumab and 4 receiving Ipilimumab. 5 patients received combination therapy. 8 patients (22%) in total reported an Endocrine IRAE. Thyroid dysfunction occurred in 7 patients (19%). 2 of which were Grade 1, 5 were Grade 2. TFTs were recorded regularly every 2 weeks on 35/37 patients (95%). 1 patient (2.7%) was diagnosed with Cortisol Deficiency, Grade 3 and occurred with combination therapy. Cortisol was recorded on just 10 patients (27%) although 27 patients (73%) reported fatigue during the course of their treatment. Glucose recordings were taken on 13 patients (35%) with 7 patients (19%) recording hyperglycaemia. There were no cases of Insulin-Deficient Diabetes diagnosed in our group.
Conclusion
We have noted a high incidence of endocrine related IRAEs and, with one exception, patients were able to continue or to recommence therapy. As knowledge of the iRAEs increased, monitoring was more common. While comprehensive monitoring for thyroid dysfunction was performed, routine evaluation of adrenal function for primary or secondary deficiency was not. For this reason, we have developed an algorithm for monitoring which will be presented.

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P1046

Recovery of the hypothalamic-pituitary-adrenal and gonadal axes following trans-sphenoidal adenomectomy, a single centre experience

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Hypopituitarism is a potential complication of trans-sphenoidal adenomectomy (TSA). Prediction of pituitary function (PF) recovery would inform hormonal replacement strategies. However, the frequency of re-testing of PF is variable across centres. The aim of this study was to determine rates, time and predictors of 6-weeks (6 w) recovery of hypothalamo-pituitary adrenal (HPA) and gonadal function after TSA.
Methods
We performed a single-centre, retrospective (2016–2018) analysis of patients undergoing TSA. Patients with apoplexy, corticotroph adenomas, malignancy or radiotherapy were excluded. HPA assessment: pre-op, post-op short synacthen test (SST) and day 8 post-op 9 am cortisol. Patients failing at 6w were re-tested at 3,6 and 9to12 months. Gonadal axes assessment: FSH, LH, estradiol (women)/testosterone (T, men) pre-op and 6 w post-op. Multiple regression models and ROC analysis were used to identify recovery predicting variables.
Results
Data on 135 patients (mean age 54 ± 17 years; 80 M) were analysed. 29% of patients had normal pre-op PF: they were younger (49 ± 16 *vs* 59 ± 15 years, $P=0.01$) and had smaller tumors (5.2 ± 4.6 *vs* 8.8 ± 10 mL, $P=0.02$) compared to those with at least one deficit. TV was able to predict the a pituitary deficit 6w post-op ($P=0.01$). 95% of patients (*odds ratio (OR)* 8.00, 95% CI 0.90–64.70) with a TV > 9 mL (ROC AUC = 0.66) had at least one deficit 6w post-op. *HPA axes*: 37% of patients failed the 6w assessment: 16%, 12%, 5% recovered at 3, 6 and 9–12 months respectively. Pre-op SST 30-minute cortisol, post-op day 8 cortisol and 6 w post-op SST baseline cortisol respectively above or below 430 nmol/L(AUC ROC = 0.83), 160 nmol/L (AUC ROC = 0.78) and 180 nmol/L (AUC ROC = 0.86) were identified as cut-offs for predicting 6 w HPA recovery respectively. None of the patients with all these three cut-offs below the threshold recovered within 12 months post-TSA. 89% of them with all the cut-offs above the threshold recovered HPA function within 6–w *(OR* 9.125, 95% CI 4.745–17.547). *Gonadal axes:* 39% of patients failed the 6 w assessment. In men, pre-op T level was associated with 6w gonadal axes deficit. 87% of patients having a pre-op T < 7 nmol/L (ROC AUC = 0.77) had gonadal deficit at 6 w *(OR* 11.5, 95% CI 2.27–58.33).
Conclusions
After TSA, PF recovered more frequently in patients with normal pre-op function and smaller tumor. There is the potential to use SST results and pre-op testosterone to predict HPA and gonadal axis recovery. This may aid clinicians to decide on treatment strategy and inform patients regarding likelihood of PF recovery. HPA axis recovery occurs even 12 months post-TSA, emphasizing the importance of periodic reassessment to avoid unnecessary treatment.

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P1047

Cerebrovascular events, secondary intracranial tumors and other neoplasia following radiotherapy for non-acromegaly pituitary tumors and craniopharyngiomas

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Background
Radiotherapy is part of the complex treatment of pituitary tumors; it is an effective treatment for residual postoperative tumors or recurrent tumors, but cerebrovascular events and secondary intracranial tumors may occur during long term follow-up.
Aim
To assess prevalence of cerebrovascular events, secondary intracranial tumors and other neoplasia in patients with non-acromegaly pituitary tumors and craniopharyngiomas submitted to radiotherapy.
Patients and methods
320 patients (156 M/164 F) with non-acromegaly pituitary tumors and craniopharyngiomas (246 prolactinomas, 70 nonfunctioning pituitary adenomas, 2 corticotropinomas, and 2 craniopharyngiomas), aged 46.8 ± 16.7 years at diagnosis, from a tertiary endocrine centre were retrospectively reviewed. Pituitary imaging was performed by computed tomography scan or MRI.
Results
The vast majority of patients had macroadenomas (313 patients, 97.8%). 79 patients were submitted to radiotherapy: 67 patients to 3D-conformal high voltage radiotherapy, median dose 50 Gy, 12 patients to gamma knife radiosurgery 14–17 Gy on 50% isodose. Radiotherapy was adjuvant therapy after surgery in cases with tumor regrowth or in patients with significant residual postoperative tumor in 76 patients (96.2%); in 3 patients who initially refused surgery, radiotherapy was the primary treatment. In non-irradiated patients ($n=241$), we found 3 cystic lesions (2 arachnoid cysts, one porencephalic cyst), 2 cavernomas, 5 meningiomas, carotid or basilar arteries ectasia ($n=5$), ischemic brain lesion or stroke ($n=7$), malignant tumors ($n=4$: one colorectal cancer, one renal cancer and two papillary thyroid carcinomas). In irradiated patients ($n=79$), we found a similar prevalence of cystic lesions ($n=2$: one arachnoid cyst, one pineal cyst), ischemic brain lesions ($n=2$), internal carotid arteria ectasia ($n=4$), and malignant tumors ($n=3$: one colorectal, one breast cancer, one malignant nonHodgkin lymphoma with B cells, stage III B), respectively. Neither glioma or sarcoma were diagnosed in patients following radiotherapy.
Conclusion
Similar prevalence of cerebral arteries ectasia, ischemic brain lesions and stroke, secondary intracranial tumors and other neoplasia was found in our series following radiotherapy for non-acromegaly pituitary tumors and craniopharyngiomas. However, long term follow-up is mandatory.

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P1048

Effectiveness of hight doses of cabergoline suppressive therapy in patients with prolactinoma

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Aim
The aim of the study was to investigate the clinical and hormonal effectiveness of different modes of suppressive cabergoline (CAB) therapy during 12 months in patients with prolactinoma.
Subjects and methods
It was examined and underwent a 12 month course of treatment by selective dopamine agonist CAB in 61 patients with prolactinoma (PROL) (9 male/ 52 female) aged 16–66 years. There were 40 women with microPROL, 12 with macro&giant PROL; among men it were 2 with microadenoma and 7 with macroadenoma. The total duration of the disease ranged from 1 to 60 months, average (12.3 ± 10.1) months. PROL was verified using MRI and PRL blood levels (ng/mL). Applied two modes of therapy: 1 – the mode of gradual increase of a CAB dose, since 0.5 mg a week with the subsequent control of the PRL blood level in each 4 weeks and titration CAB dose if necessary (increase in a week dose by 0.25 – 0.5 mg); group 2 – the mode of high starting doses from calculation: the quantity of tablets CAB (0.5 mg) corresponded to frequency rate of increase of the PRL blood level in relation to the upper limit of age norm, but no more than 4 mg (8 tablets) a week.
Results
Proposed an integrated system that allows estimating the effectiveness of clinical and hormonal parameters during CAB suppressive therapy in patients with PROL. It is enables in all stages to carry out the treatment, to assess the possible risks from using the large doses of medication and to optimize the selection of an adequate dose. The optimal mode of CAB therapy in patients aged 40 yrs and older with microPROL is the regime of gradually increasing the dose, the positive clinical and hormonal effect which is observed in 80% of patients 3 months after start of the treatment. Assigning mode high starting doses of CAB in young and middle-aged patients with macro- and giant PROL allows for a shorter time (1 month), to achieve reliable positive dynamics of neurological, somatic and hormonal status compared with the group of patients receiving therapy in the mode of gradually increasing CAB doses.
Keywords: prolactinoma, cabergoline, treatment
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P1049

Expression of programmed death ligand 1 (PD-L1) in human pituitary adenomas

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Introduction
Pituitary adenomas, second most common brain tumors, are mostly well controlled after surgery. However, some pituitary tumors present an aggressive evolution and are resistant to standard management. Immunotherapy with inhibitors of T-cell checkpoints have shown durable efficacy in a variety of malignancies. Moreover, immunotherapy has been associated with treatment-related hypophysitis, suggesting that pituitary could be a target of these treatments. Recently, it has been shown that adenomas frequently express programmed death ligand 1 (PD-L1) transcript and/or protein. However, association between expression and clinical characteristics has been poorly studied. The aim of this study was to assess the PD-L1 expression in each subtypes of pituitary adenomas.
Methods
The subjects enrolled in this study were patients who had been treated in the Academic Hospital of Angers (France) for a pituitary adenoma between 2012 and 2018. We performed immunohistochemical analysis on tissue of the surgical specimens using the validated PD-L1 antibody clone for therapeutic issue [Clone 22C3 pharmDx, Agilent-Dako]. Staining was performed using a Bond III from Leica. PDL-1 positivity was defined by the presence of partial or complete linear membrane staining on tumoral cell, with different cutoffs: 5%, 25%, and 50%. Mitotic count, Ki-67 and p53 expression were also assessed. The association between PD-L1 expression and clinicopathologic parameters and imaging features was analyzed.
Results
Among the 149 patients retrospectively included in this study, 134 pituitary tumors were analyzed, consisting in 83 (63%) nonfunctioning adenomas, 19 (14%) ACTH-secreting adenomas, 18 (13%) GH-secreting adenomas, 9 (7%) PRL-secreting adenomas and 4 (3%) PRL-GH secreting adenomas. Eleven of them were PD-L1 positive (8.3%), including 3 diffuse stainings ($>25\%$ of cells) and 8 weak stainings ($<5\%$ of cells). The positive PD-L1 immunostaining was more frequent in non-invasive tumors (80%) than in invasive pituitary adenomas (20% of PD-L1 positive) ($P=0.0014$). All tumors with Ki-67 $\geq$ 3% were PD-L1 negative and recurrent tumors didn't exhibit a PD-L1 expression. Moreover, PD-L1 expression was not different between functioning and non-functioning adenomas ($P=0.57$).
Conclusion
Our results showed that pituitary adenomas exhibited weak PD-L1 expression as compared to the literature, with another PD-L1 antibody. We found a significantly lower expression in proliferative and invasive adenomas. PD-L1 expression seems to be associated with non-aggressive behaviors in pituitary adenomas and may be a predictive marker for favorable outcomes. This study didn't raise the possibility of considering checkpoint blockade immunotherapy in cases of refractory adenomas.
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P1050

RNASeq of Pituitary Adenomas reveals dysfunctional metabolic, secretory and differentiation molecular pathways

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Pituitary adenomas consist of a group of highly heterogeneous intracranial tumours with variable presentation, clinical prognosis and management. High throughput sequencing was used in order to try and identify common de-regulated pathways and characterize tumours according to specific molecular behaviour. RNA sequencing (RNAseq) was chosen since it provides not only information regarding the expression profile but also the mutational load of each specific tumour analysed. 58 locally resected tumours (36 non-functional tumours; 17 growth hormone-secreting; 3 prolactin-secreting; 2 Cushing's) were stored in RNAlater (Qiagen, US) and RNA was extracted to purified. RNAseq was performed on all samples plus a control on the BGI-Seq500 platform (Beijing Genomics Ind., China). Bioinformatic analyses was also performed by BGI with additional analyses still being carried out. Preliminary data reveals a number of known and novel de-regulated pathways which characteristically differentiate between different tumour types such as hormone signalling and production pathways. However, novel metabolic pathways also appear to differ significantly, not only between controls and tumours but also between different tumour types with changes in lipid transport and glucose metabolism being observed. Additionally various hormone receptor signalling pathways were also found to be altered. Verification and additional bioinformatic analyses will be required to further delve into the vast data that is generated by this technique which has provided a wealth of information.
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P1051

A comparison of glucagon stimulation and insulin tolerance test in young adults followed craniospinal irradiation

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The glucagon stimulation test (GST) may be used as a good alternative to the insulin tolerance test (ITT) in the diagnosis of secondary adrenal insufficiency (SAI). The aim of the study was to compare the GST and

ITT for diagnostic SAI, to define cortisol cut-off points and factors affecting the appearance of false positive results in young adults followed CSI.
Subjects and Methods
A retrospective study of 28 patients (median age 19 [17; 23]) at least 2 years after CSI because of posterior fossa tumors and 10 healthy volunteers was conducted. ITT and GST were performed within 5–7 days in all patients and voluntaries. Age, sex ratio and BMI were comparable between the groups.
Results
9/10 healthy had maximum cortisol level (MCL) during ITT more than 540 nmol/l 1 healthy had 440 nmol/l only, therefore 540 nmol/l was chosen as cut-off for ITT. The best cut-off point for diagnosis of SAI by GST was 500 nmol/l (63% sensitivity, 100% specificity). AUC of GST was 93%. 19/28 patients had concordant results of ITT and GST (SAI was confirmed in 9/19 patients). MCL didn't differ in this groups. 3/28 patients failed ITT (MCL was 421; 471 and 472 nmol/l) but their MCL during ITT was 574, 551 and 660 nmol/l respectively. Therefore, we regarded this result as a false positive ITT. These patients were excluded from the comparison GST and ITT by ROC- analysis. They had statistically significant higher levels of leukocytes (7.44 [5.87; 9.25] vs 5.5 [4.9;6.9], $P=0.05$), monocytes (0.71 [0.59; 0.75] vs 0.43 [0.36; 0.52], $P=0{,}019$), neutrophils (5.11 [3.65; 6.04] vs 2.9 [2.6; 3.7], $P=0.019$) and lower lymphocytes (24.0% [17.85;25.8] vs 34.9% [28.5; 39.5], $P=0.014$) levels in comparison with concordant-result patients. 6/28 patients passed ITT and failed GST. They had statistically significant lower levels of leukocytes (5.01[4.04;5.61] vs 6.1 [5.4; 7.3], $P=0.012$), lymphocytes (1.4 [1.26;1.8] vs 2.3 [1.68; 2.5], $P=0.019$) and higher levels of cholesterol (5.54 [5.24;6.46] vs 4.9 [4.4; 5.4]), $P=0.042$) and triglycerides (1.31 [1.07; 1.82] vs 0.94 [0.74;1.5], $P=0.05$) in comparison with concordant-result patients.
Conclusions
The GST can use as alternative test for the diagnosis of SAI with optimal cut-off 500 nmol/l in young adults followed CSI. The leukocyte formula and lipid changes can lead to false positive ITT and GST results probably. Further prospective studies are required to confirm this data.

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P1052

Long-term treatment of chronic refractory SIADH with tolvaptan in the elderly: A report of three cases

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Background
Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a very common electrolyte disorder in older patients leading often to hospital admissions. Symptoms can vary between mild disabilities (e.g. nausea, dizziness, attention deficits, gait disturbance) to severe life-threatening conditions (e.g. seizures, coma). Treatment of SIADH is challenging in particular when fluid restriction is limited or even not effective in restoring normal sodium levels. Therefore, selective vasopressin receptor antagonists rising serum sodium levels by increasing the output of electrolyte-free water have become important treatment options. Tolvaptan, a selective vasopressin 2 receptor antagonist is approved for the treatment of patients with hyponatremia or autosomal dominant polycystic kidney disease. However, poor data is available especially concerning long-term treatment of elderly patients with tolvaptan and idiopathic SIADH.
Methods
Case report.
Results
We report three patients (mean age: 83 years) with refractory hypo-osmolar hyponatremia due to idiopathic SIADH. Two of them needed repeated treatment with hypertonic saline in the intensive-care unit because of severe symptomatic hyponatremia with confusion and seizures (serum sodium below 110 mmol/l in both cases). After initial stabilization of serum sodium levels subsequent treatment with tolvaptan (15 mg per day) was begun in all patients leading to a quick recovery and stabilization of serum sodium without any additional measures. Dosing interval then was extended stepwise and under close monitoring to an administration every second then every third day, thereby achieving persistent normal serum sodium values. Drug tolerance was excellent in all patients without any side effects (e.g. hepatotoxicity). After a mean follow-up of 28 months all patients treated with tolvaptan demonstrate persistent normal natremia and no need for re-hospitalization.
Conclusions
Tolvaptan should be recognized as a very effective, easy to handle, well-tolerated and probably cost-effective therapy in old patients with severe forms of chronic refractory SIADH. On a long term basis extended dosing regimens (e.g. every second/third day) under close monitoring are feasible.

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P1053

Prolactinoma and elderly subject: which caracteristics?

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Introduction
Prolactinoma is the most common secretory pituitary adenomas. It has clinical and biological characteristics that depend on age, gender and tumor size. Prolactinoma of the old subject is a rare clinical form that was not sufficiently treated in the literature.
Materiels and methods
It is a retrospective study including 77 cases of prolactinoma among which 3 cases aged over than 65 years. The collection of data was made between 2000 and 2017.
Results
The average age was 70 years [66–75 years]. They were all male. The diagnostic latency was on average 10.33 months (1-24 months). For two patients, the finding was with headache and bilateral visual acuity decrease. For the other case, the discovery was fortuitous by a brain scan in front of the suspicion of cerebral thrombophlebitis. Hyperprolactinemia syndrome (erectile dysfunction and a decrease in libido) and anterior pituitary insufficiency were noted in all 3 cases. A narrowing of the visual field was objectified in 2 patients. Initial prolactinemia averaged 827 ng/ml (470–1306 ng/ml). Radiologically, there were 2 cases of macroprolactinoma and 1 case of giant prolactinoma with an average size of 39.66 mm (30–51 mm). First-line surgical treatment was indicated for a patient in front of pituitary apoplexy. No postoperative complication was noted. The evolution in this patient was marked by the installation of a remission without recourse to medical treatment. For the other 2 patients, treatment with bromocriptine was indicated. But normalization of prolactinemia and tumor size decrease ($>50\%$) were noted in one of them after 24 months.
Conclusion
It seams that prolactinoma of the elderly was characterized by a fortuitous discovery or on the occasion of decreased visual acuity (66.6% of cases) which explained the initial diagnostic delay, because of non-specific clinical signs.

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P1054

Prolactinomas in women: clinical, neuroradiological and pathological predictive factors for efficacy of transphenoidal surgery

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Background
The treatment of choice in prolactinomas are dopamine agonists, with surgery reserved for cases refractory to or poorly tolerant of pharmacotherapy. Little is known on the associations between clinical, neuroradiological and pathological features influencing the efficacy of transphenoidal surgery.
The Aim
To evaluate clinical, neuroradiological and neuropathological aspects of surgically treated prolactinomas in women, with a particular emphasis on factors affecting treatment efficacy.
Methods
This cohort study included 44 female patients aged 29.11 ± 8.7 yr, qualified for surgery due to unsuccessful medical treatment. Clinical, pathological and imaging parameters were evaluated in light of surgical outcomes.
Results
The group included 25 microadenomas (56.8%) and 19 macroadenomas (43.2%). The mean maximum tumor diameter was 11.41 ± 5.2 mm (range: 3–31 mm). The median pre-operative PRL level was 220.5 mcg/dL (IQR: 151.8–365.5). There was a significant correlation between PRL levels and the maximum tumor diameter ($r_s=0.544$, $P<0.001$) and between PRL levels and patient's age (borderline significance: $r_s=0.273$, $P=0.073$). The median PRL level was 3.4 mcg/dL (IQR: 1.2–12.9) on postoperative day 1 and 9.4 mcg/dL (IQR: 4.1–17.4)

at month 3. PRL levels were within reference range in 81.8% on 1st day and at month 3, respectively. Mean follow-up was 81.7±34.4 months, with a 72.7% remission rate at the end of follow-up. The rates of secondary hypothyroidism was low at 2.3%, with no cases of hypoadrenalism or permanent diabetes insipidus. Remission rates were higher in microadenomas than macroadenomas (84.0% vs. 57.9%; $P=0.054$). Low tumor invasiveness (Knosp 0–1) was associated with a higher remission rate compared to grade 2–4 tumors (85.7% vs. 22.2%; $P<0.001$). None of the patients with Knosp grade 3–4 tumors ($n=5$) were cured. Plurihormonal adenomas (mostly alpha-subunit immunopositivity) were detected in 7 patients (15.9%). Plurihormonality was associated with lower remission rates at month 3 compared to pure lactotroph tumors (57.1% vs. 90.6%, respectively; $P=0.059$). Ki-67 expression was ≥3% in 25% of cases. There was no association between Ki-67 expression and tumor diameter or remission rate ($P=0.135$ and $P=0.884$, respectively). A logistic regression model showed that the remission rate at month 3 depended mainly on tumor invasiveness (Knosp 2-4) rather than tumor plurihormonality ($P=0.002$ and $P=0.292$, respectively).

Conclusion

Surgical treatment of prolactinomas in women is an effective and safe procedure, with success rate depending more on tumor invasiveness (Knosp grades 2-4) than on other parameters, such as tumor size, plurihormonality, or Ki-67 expression.

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P1055

Quality of life in patients with acromegaly assessed by AcroQoL-first application in South Poland

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Introduction

Acromegaly is a disease associated with increased secretion of growth hormone and subsequent growth of bones, soft tissues and internal organs. An important factor influencing therapeutic treatment in recent years is the patient's quality of life associated with the disease. In patients with acromegaly, it is significantly affected by the occurrence of depression and anxiety - agents undergoing treatment, which, however, still appear undiagnosed.

Aim of the study

The aim of the study was to assess the quality of life of patients with acromegaly based on the ACROQoL questionnaire with particular emphasis on depression (based on Beck's scale) and the assessment of patients' expectations regarding psychological care and its type.

Material and methods

The study included 59 patients with acromegaly: 38 women and 21 men, the mean age of 53.25 years ±12.46, (range 19–79 years) treated for acromegaly in the Department of Endocrinology in 2016–2017. Patients personally completed standardized questionnaires of the scale of Beck and ACROQoL extended with questions about preferences as to the form of psychological help. Data analysis was carried out in the Statistica 13.1 program. Statistically significant the value of $P<0.05$ was considered.

Results

Patients have shown a poorer quality of life in the physical and physiological spheres (psychological part), while the sphere of relationships had better scoring. The quality of life measured by the questionnaire did not correlate with age, nor depended on the presence of accompanying diseases or biochemical parameters. The AcroQoL result was inversely proportional to the Beck scale score ($r-0.6$, $P<0.001$). All patients with a higher AcroQoL score received a score of 0–13 points in the Beck scale. The Beck scale score is an independent predictor (destimulator) of AcroQoL. There were no differences between women and men in quality of life or other parameters. In patients below the age of 60, a lower quality of life was observed. This group more often searched for psychological help and was interested in various its forms, mainly consultation in the clinic (38.5%).

Conclusions

1. Improving the quality of life should be one of the goals of treatment of acromegaly. The routine AcroQoL questionnaire can help optimize the treatment of acromegalic patients.
2. The occurrence of depression worsens the quality of life in patients with acromegaly.
3. Patients interested in psychological help do not always actively looking for it themselves. Hence, the proper medical practice is to offer it to the attending physician.

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P1056

Pituitary stalk abnormalities: etiology aspects about 28 cases

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Introduction

The pituitary stalk is the target of various congenital or acquired pathologies. In this context we report a cohort of 28 patients with pathology of the pituitary stalk to analyze their clinical, hormonal and radiological characteristics.

Results

The average age of our patients was 28 years with extremes ranging from (15 to 64); Male dominance was noted in 60% of cases. The reason for consultation was either a staturo delay or a pubertal delay in the majority of cases. A personal history of fetal distress was found in 17.8% of cases as well the seat presentation the out of childbirth was 14.2% of cases. Hormonal exploration revealed a corticotrope deficit in 35.7% of cases; thyrotrophic deficiency in 32% of cases; somatoropic deficit in 35.7% of cases and a gonadtropic deficit in 28.5% of cases. Finally hyperprolactinemia was noted in 21.4% of patients. Hypothalamic-pituitary MRI showed thickening of the pituitary stalk in 13 cases, rupture in 15 cases including 7 cases associated with hypoplasia of the anterior pituitary. For the thickening of the pituitary stem the origin was: sarcoidosis in 2 cases; langerhansian histiocytosis in 2 cases; tuberculosis in 2 cases; lymphocytic hypophisitis in 2 cases; metastasis of cancers in 4 cases and two cases of unknown origin.

Conclusion

Given the multitude of pituitary stalk pathologies, a detailed etiologic inquiry must be performed in order to detect elements able to reclassify an initially idiopathic disorder.

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P1057

Differentially expressed miRNAs in spindle cell oncocytoma of the pituitary gland

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Introduction

Spindle cell oncocytomas (SCO) of the pituitary are rare tumors accounting for 0.1–0.4% of all sellar tumors. Due to its rarity, little information is available regarding its pathogonesis. The altered gene expression and the possible pathogenetic role of microRNAs (miRNAs) have been identified in many tumor types, however, until now ther is no data regarding their role in pituitary oncocytoma.

Materials and methods

Total RNA was extracted from 9 formalin-fixed paraffin embedded (FFPE) pituitary oncocytoma samples (4 primary, 3 recurrent oncocytomas and 2 normal tissues). miRNA library was performed for sequencing next-generation sequencing to identify miRNA profiling. For the comparative analysis microarray dataset of 6 samples were obtained from NBCI GEO database for gene expression reanalysis and tissue-specific target prediction. Bioinformatical analysis was applied to characterise function and biological processes of miRNAs and genes revealed to be significantly different between tumors and normal tissues.

Results

54 differentially expressed miRNAs and 485 genes in pituitary SCO vs. normal tissue and 8 miRNAs in recurrent vs. primary SCO were detected. Transcriptome analysis revealed cell cycle alterations while miRNAs influenced mainly metabolic processes (tricarboxylic acid cycle-TCA, carbohydrate, lipid metabolism). MiRNA-mRNA interaction network analysis revealed miR-744-5p, miR-127-3p and miR-7-5p as miRNAs with the most significant effect in SCO where the overexpressed Aconitase 2 (ACO2: fold change 2.78, $P<0.01$) was targeted by two downregulated miRNAs (miR-744-5p: fold change 0.20; $P=0.01$ and miR-127-3p, fold change: 0.05; $P<0.01$).

Conclusion
MiRNA profile distinguishes SCO, recurrent SCO and normal pituitary suggesting that miRNAs may have a role in SCO pathogenesis by influencing cell proliferation and metabolism. Based on our results and literature data the downregulated ACO2 targeting miRNAs miR-744-5p and miR-127-3p are tumor suppressors and they can be potential candidates for miRNA-based therapy. Earlier reports showed dysregulated TCA cycle in SCO and that ACO2 inhibition led to less efficient entry to cell cycle. These are extended by our results adding the role of miR-744-5p and miR-127-3p potentially targeting ACO2 and regulating cell proliferation.
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P1058

Pituitary apoplexy: diagnosis, management and outcome in 44 patients

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Introduction
Pituitary apoplexy (PA) is a rare incident defined by the occurrence of necrosis and/or haemorrhage of the pituitary gland. PA is a clinical syndrome characterized by the sudden onset of headache, vomiting, visual impairment and decreased consciousness in some cases. The objectives of our study are to describe its clinical, biological and imaging features as well as the management of PA in the region of Sfax.
Patients and methods
It is a retrospective study including a group of patients in the Endocrinology department of Hedi Chaker Hospital in Sfax over an 18-year period (2000–2017). The data collected was analysed by the SPSS version 20 software.
Results
This study included 44 patients (20 women versus 24 men) with a mean age of 50.04 ± 12.58 years. Fourteen patients (31.8%) had a pituitary adenoma known before the onset of apoplexy, secreting in 9 cases. Precipitating factors have been found in 14 cases (31.8%). Dopaminergic agonist treatment and head trauma were so far the commonest predisposing factors. In 2 cases, the PA was incidental. In the remaining 42 cases (95.5%), the PA was discovered during the investigation of a clinical symptomatology. Headache was present in 37 patients (84.1%). Visual disturbances were reported by 33 patients (75%), who were predominantly affected by visual acuity and visual field disturbance. We Partial pituitary insufficiency was confirmed after hormonal screening in 41 patients requiring hormonal replacement. Pituitary MRI was performed in 42 patients confirming the diagnosis of PA, and CT guided the diagnosis in the remaining 2 cases. Transsphenoidal surgery was performed in 24 patients and transient diabetes insipidus was noted postoperatively in two patients. Conservative management was adopted in the remaining 20 cases. The mean duration of follow-up was 43.7 ± 53.2 months. During follow-up, partial hypopituitarism persisted in 24 cases and he persistence of a tumor in 13 patients and tumor growth recurrence in a single patient after long term follow-up.
Conclusion
The low incidence of PA makes it difficult to establish guidelines for its management. However monitoring for tumour growth and assessing for pituitary gland function need to be continued post-operatively considering the possible risk of its recurrence.

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P1059

The expression of somatostatin receptor subtypes in immunohistochemistry and the response to somatostatin analogue therapy in non-functioning pituitary adenomas

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Introduction
Non-functioning pituitary adenomas (NFPA) are characterised by the expression of somatostatin receptors (SSTR), which is analysed using immunohistochemical investigations. The presence of SSTR forms the basis for the clinical use of somatostatin analogues (SSA) in the treatment of these tumours.
Aim
The study was undertaken to provide immunohistochemical analysis of SSTR and to correlate it with tumoral response to SSA therapy in NFPA.
Material and methods
Immunohistochemistry of SSTR in surgically removed tumour tissues was performed in 43 patients with NFPA. Expression of SSTR2 and STTR5 enabled to select a group of 17 patients after incomplete surgery who were treated with SSA (octreotide 20–30 mg intramuscular or lanreotide 120 mg subcutaneously every 28 days) for 2–10 years.
Results
Immunohistochemistry showed the presence of all SSTR with most common expression of SSTR5 (93%), SSTR2A (83.7%) and SSTR1 (83.7%). However, strong immunostaining was observed more frequently for SSTR1 and SSTR3 receptors. Considering patients treated with SSA, stabilisation of tumour size was noted in the majority of cases (88.24%). Adenoma shrinkage was confirmed with the use of magnetic resonance imaging in 2 patients.
Conclusions
Somatostatin analogues may be considered a therapeutic option for patients with NFPA after incomplete surgery. The expression of SSTR is a good predictive parameter for evaluation of SSA efficacy in NFPA. However, strong expression of SSTR1 and SSTR3 suggest that introduction of new, broad-spectrum somatostatin analogues may be more effective in the reduction of tumour size.

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P1060

Isolated ACTH deficiency secondary to combined immunotherapy-induced hypophysitis: predilection for corticotrophs

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Immunotherapy targeting the CTLA-4 and PD-1pathways has revolutionised the treatment of several cancer types, and is under investigation in many others. However, its use is associated with a variety of side effects, many of which associated with immune system activation. In metastatic melanoma, the combination of ipilimumab (an anti-CTLA-4 antibody) and nivolumab (an anti-PD-1 antibody) has been shown to have greater efficacy than either drug as monotherapy, though as expected the frequency of adverse effects is also higher with combination therapy.
Case
A 67 year old male was diagnosed with cutaneous melanoma, and following the discovery of metastatic disease was commenced on combined ipilimumab/nivolumab therapy. During the initial 4 cycles, he had developed colitis treated with glucocorticoids and infliximab. 7 months post initiation of treatment, he was admitted following a fall, with a history of preceding fatigue. There was no headache or visual disturbance. Initial evaluation revealed BP 111/69 mmHg, Na 130 (133–146 mmol/l) and K 3.6 (3.5–5.3 mmol/l). A cortisol done at 01.30 at presentation of 27 nmol/l was deemed inappropriately low given the stress of preceding events and admission. He was commenced on replacement hydrocortisone at stress physiological doses, a subsequent SST showed basal cortisol of 26 and 30 minute value of 119 nmol/l, with basal ACTH < 5 ng/l. The remaining pituitary hormones were normal. A subsequent MRI of the pituitary revealed a flattened pituitary – this was no different to a scan 2 years earlier. Whilst his fatigue improved with hydrocortisone, unfortunately he subsequently developed hepatitis.
Discussion
Hypophysitis is a well recognised immune related adverse effect of immunotherapy. Whilst case series of patients with ipilimumab-induced hypophysitis suggest typical multi-hormonal deficiencies (with suggestion of pituitary antibodies being involved), several cases have been reported of isolated ACTH deficiency with nivolumab suggesting an alternative mechanism. We thus hypothesise that this gentleman had nivolumab-induced hypophysitis. This phenomenon leads to the questions of potential nivolumab efficacy in patients with aggressive corticotroph pituitary tumours/carcinomas, though given the side effects, further research would have to be done to try and identify those patients that would be most likely to respond.

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P1061

Clinical features and endocrine evaluation of non-functioning pituitary adenomas at a secondary level hospital

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Introduction
Non-functioning pituitary adenomas are relatively common. A large number of these tumors are asintomathic pituitary microadenomas, that are increasingly detected because of sensitive imaging techniques improves. Those tumors that require treatment are generally macroadenomas and come to medical attention because of mass effect (visual field defects, headache, …) and/or hypopituitarism.
Objective
To assess non-functioning pituitary adenomas (NFPAs) clinical features and natural history at our hospital.
Patients and methods
All patients with pituitary incidentalomas on brain imaging between 2010 and 2018 were reviewed. The referral source, principal symptom, MRI scan findings, visual field defects, pituitary function and imaging evolution were analysed.
Results
Twenty three patients were analized (15 women (65.2%); age 46.1 ± 17 years). Most patients (85.7%) were diagnosed by magnetic resonance imaging (MRI.) 56.5% ($n=13$) were macroadenomas. Microadenomas were more common in women (43% vs 0%, $P<0.05$). About 36.4% of patients showed visual field defects (all of them macroadenomas); of these 6 (75%; $P=0.003$) were acompained by suprasellar extension. Invasion of the cavernous sinuses was present in 13.6% ($n=3$). Hypopituitarism was present in 4 (17.4%) patients. 7 patients (35%) underwent surgery (all of them macroadenomas). Our patients were evaluated after a median follow-up of 4.78 years by control MRI. In those whom surgical treatment was not performed, no significant changes were found in the maximum tumor diameter at the end of follow-up (9.53 ± 6.18 vs 7.11 ± 6.17 mm, NS). The majority of NFPAs evaluated did not show any changes in size.
Conclusions
The sample is too small to achieve significance but we can conclude that incidental NFPAs are diagnosed by MRI preferible from the 5th decade of life. Most of them are macroadenomas, more commonly diagnosed in men while microadenomas mostly appear in women. Suprasellar extension with chiasmatic compression are frequently related to visual field deffects. Hypopituitarism is not common at diagnosis. Most of the non-operated NFPAs remain with stable tumor size over time.
References
1. Iglesias P 2017 Clinical features and natural history of clinically non-functioning pituitary incidentalomas. Presented at Society for Endocrinology ECE 2017, Lisbon, Portugal. Endocrine Abstracts 49.
2. Gill G 2015 Pituitary incidentaloma: features and outcomes: recent experience at a tertiary centre. Presented at Society for Endocrinology BES 2015, Edinburgh, UK. Endocrine Abstracts 38.

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P1062

Osteitis fibrosa cystica of the skull in a patient with primary hyperparathyroidism

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Background
Overt parathyroid bone disease is a rare entity. We present a case of primary hyperparathyroidism (PHPT) and osteitis fibrosa cystica with involvement of multiple facial bones and neurocranium. Although the initial differential diagnosis was between acromegaly and bone malignancy, endocrine assessment demonstrated PHPT, with favorable outcome after parathyroidectomy.
Case report
A 59-year-old woman referred to our clinic with painful swelling of frontal and maxillary bones. A computed tomography (CT) of the skull performed before admission raised the suspicion of osteosarcoma which was invalidated by bone biopsy. The patient had no history of fractures and her family history was not significant. Although facial changes indicated acromegaly, biochemical evaluation showed normal IGF1 (169.3 ng/ml) with normal GH nadir (0.06 ng/ml) during OGTT and revealed high corrected serum calcium (12.06 mg/dl, $n=8.5$–10.2), low serum phosphorus (2.05 mg/dl, $n=2.5$–4.5) and high PTH level (384.2 pg/ml, $n=15$–65), demonstrating PHPT; the bone turnover markers were elevated: crosslaps = 0.89 ng/ml ($n=0.33$–0.78), osteocalcin = 53.77 ng/ml ($n=15$–46), P1NP = 89.16 ng/ml ($n=15$–74); alkaline phosphatase was 112 IU/L ($n=38$–105) and serum 25OHD was 9.61 ng/ml ($n=30$–100). 24 h urinary calcium was 760 mg/24h ($n=70$–300) and 24 h urinary phosphorus was 1080 mg/24 h ($n=300$–1000). Calcitonin, plasma metanephrines and normetanephrines, PRL and Chromogranin A were in normal range. Abdominal ultrasonography revealed unilateral nephrolithiasis and renal function was normal (GFR = 107.7 mL/min/1.73 m^2). We reevaluated the CT scan of the skull that showed expansive lytic and sclerotic mass lesions at the level of frontal sinuses, ethmoid cells and within the maxillary sinuses, together with 'salt and pepper' appearance of the skull. A neck CT-scan and 99 mTc sestamibi scintigraphy of the parathyroid glands showed a parathyroid adenoma. The patient underwent surgery and a right lower parathyroid adenoma was removed. The anatomopathological report described a chief cells parathyroid adenoma weighing 2.46 g. On a six months follow-up, under cholecalciferol treatment (2000 UI/day), DXA showed osteopenia with a T score of −1.6 DS for the lumbar spine and −1.1 DS for the distal radius and the patient had normal values of serum calcium (9.9 mg/dl), phosphorus (3.1 mg/dl) and PTH (57.46 pg/ml).
Conclusion
Even if osteitis fibrosa cystica is rare, when large lytic lesions are associated with hypercalcemia, PTH assay should be mandatory since PHPT must be always considered.

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P1063

Cumulative GH exposure as risk factor for mortality and morbidity in patients with acromegaly

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Background
In patients with acromegaly, mortality depends most on achievement of control of GH/IGF1 levels. However, some of the complications of acromegaly still develop, despite successful control of disease. The aim of the study is to correlate mortality and morbidity with cumulative GH exposure in these patients compared to last GH/IGF1 level.
Methods
We studied retrospectively 336 patients with acromegaly consecutively evaluated at least twice during January 2001–June 2017. Cumulative GH exposure was calculated as a weighted arithmetic mean of GH during time. IGF1 levels were expressed as IGF1/age and sex upper limit of normal (ULN) ratio. A multivariable Cox regression was used to calculate hazard ratios (HR) for all-cause mortality/morbidity risk factors.
Results
There were 226F/110M patients with acromegaly, mean age 48.14 ± 12.12 years. During follow up (9.43 ± 4.67 years), 53 patients died, mean age at death was 66.06 ± 10.88 years. Comorbidities were high blood pressure (HBP) (53.9%), cardiovascular diseases (14.4%), diabetes mellitus (27.4%), neoplasia (43.8%), colon polyps (6.8%), meningioma (1.5%). 49.1% of patients were cured after surgery/irradiation or controlled with medication. Patients who died were older at first visit (57.19 ± 9.93 vs 46.45 ± 11.75, $P<0.001$), had longer duration of GH hypersecretion exposure (15.43 ± 10.80 vs 9.13 ± 8.09 years, $P=0.01$), had at last evaluation higher blood pressure (131.86 ± 18.62 vs 125.02 ± 18.78 mmHg, $P=0.003$), higher levels of GH (11.20 ± 28.25 vs 4.36 ± 12.56 ng/ml, $P=0.02$), and nonsignificantly higher IGF1 levels (1.60 ± 1.74 vs 1.28 ± 0.93 xULN), and cumulative GH (13.63 ± 26.23 vs 9.64 ± 14.71 ng/ml) compared with patients who survived. Cumulative GH correlated with last GH levels ($r=0.4$, $P<0.001$). There was no correlation of last GH, IGF1 or cumulative GH with HBP, neoplasia, diabetes mellitus. Multivariate analysis revealed last GH level as an independent risk factor for mortality (HR = 1.010, 95% CI 1.003–1.018, $P=0.008$). When cumulative GH replaced last GH, HR = 1.021 (95%CI 1.010–1.032), $P<0.001$. Also, last IGF1 ratio proved as an independent factor correlated to mortality: HR = 1.352 (95%CI 1.108–1.672), $P=0.003$. A cutoff level of last GH > 1 ng/ml predicted mortality: AUC = 0.659, $P<0.001$, while for cumulative GH, a cutoff level of 5 ng/ml was found, AUC = 0.579, $P=0.06$.
Conclusion
This study confirms the importance of last GH levels and IGF1 ratio as mortality risk factors in patients with acromegaly. Last GH level is a stronger predictor for mortality than cumulative GH exposure. Continuous surveillance and treatment

of comorbidities should be done, apart for controlling GH levels, in order to enhance survival.

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P1064

Nighttime serum cortisol level for diagnosis of hypercortisolism in hospitalized patients

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Purpose
According to modern guidelines late night serum cortisol measurement is not considered to be among the first steps for screening of hypercortisolism. But in some cases it may be useful as it allows identifying the loss of normal circadian rhythm of cortisol secretion. This test is not rarely used in hospitalized patients when Cushing's syndrome is suspected. But the cutt-off point of nighttime serum cortisol level for the diagnosis of hypercortisolism is inconsistent yet for this category of patients.
Aim
To evaluate the nighttime serum cortisol level in hospitalized patients who were examined due to suspicion on Cushing's syndrome and to determine the cutt-off point of nighttime plasma cortisol level for the diagnosis of hypercortisolism.
Materials and methods
For the purpose of the study central laboratory and clinic database was analyzed. Results of 120 hospitalized patients (38 women and 82 men, mean age 51 + 1) were included. In the clinic of our center normally nighttime serum cortisol sampling is performed in awake patients at least 48 hours after submission between 2300 h and 2400 h Serum cortisol was measured with enzyme immunoassay (Roche Diagnostic). The results of patients with BMI > 35 kg/m^2; glycosylated hemoglobin >8%, uncontrolled hypertension, severe cardiovascular disease and other severe conditions were excluded from the analysis. The data on examination for the hypercortisolism confirmation were studied. Cushing's syndrome had been considered to be established if at least two recommended screening tests were positive. Receiver-operating-characteristic (ROC) curve analysis was used to determine an optimal threshold value of nighttime serum cortisol level for diagnosis of hypercortisolism.
Results
Cushing's syndrome was excluded in 97 patients. In 23 cases hypercortisolism was confirmed (in 15 patients – Cushing's disease, in 8 patients – ACTH independent Cushing's syndrome). According to the ROC curve analysis, the optimal threshold value of nighttime serum cortisol level for diagnosis of hypercortisolism was 169.45 nmol/l. The sensitivity and specificity of the method were 87% and 76.3%, respectively, the probability of incorrect prognosis (P = 0.0001).
Conclusion
According to our data the cutt-off point of nighttime serum cortisol level for the diagnosis of hypercortisolism in hospitalized patients was 169.45 nmol/l. It may be used in complex examination, but considering the data on sensitivity and specificity of the method other screening tests are necessary for the confirmation of hypercortisolism in hospitalized patients.

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P1065

Graves dermopathy associating toes lesion, pretibial myxedema and acropachy, rare, but aggressive extrathyroidal manifestation of Graves' disease

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Introduction
Graves' dermopathy (also known as pretibial myxedema, thyroid dermopathy, Jadassohn-Dösseker disease or myxedema tuberosum) is a rare extrathyroidal manifestation of Graves' disease, which is almost always associated with Graves' ophthalmopathy. Although pretibial myxedema is the most frequent localization of Graves' dermopathy, the involvement of toes with or without the involvement of pretibial area may occur.
Objectives
Presentation of a case with severe Graves' dermopathy involving toes and associating pretibial myxedema and acropachy, in a male patient with longstanding Basedow Graves' disease.
Case presentation
We present a case of a young adult male (37 years) with severe Graves' dermopathy associating pretibial myxedema and acropachy. The patient was diagnosed 9 years ago with hyperthyroidism due to Basedow Graves Disease, and performed total thyroidectomy 3 years later, being treated with levothyroxine since then. He also received methylprednisolone for ophthalmopathy, with a cumulative dose of 3 grams. At that time he presented a small erythematous lesion in pretibial area, and infiltrative lesions involving the toes, with symmetric and bilateral distribution. After being lost to follow-up for 4 years, he is admitted to our clinic accusing insomnia, and presenting extensive bilateral painless infiltrative lesions of the toes, with significant progression in the past years, despite local administration of glucocorticoids. The erythematous lesion in pretibial area did not show any signs of progression. He also presents asymmetric bilateral exophthalmia that was stable during the last 5 years, and acropachy. Blood samples revealed subclinical hypothyroidism suggesting suboptimal levothyroxine substitution with still very high levels of TRAb. The ophthalmologic exam suggested stationary ophthalmopathy. Due to the high recurrence of surgical treated Graves dermopathy, and the lack of response to local glucocorticoid treatment, systemic glucocorticoids and radiation therapy may be considered to be a part of therapeutic regimen and may improve the quality of life in this patient.
Conclusions
Although Graves dermopathy is almost always a benign condition, the extensiveness of the lessons may have an important influence in patient's quality of life, especially when glucocorthycoid therapy is uneffective, since surgical treatment is not an viable option due to high recurrence rate.

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P1066

Reduction in serum biomarkers of acromegaly post-surgery and post-pharmacotherapy: are insulin-like growth factor (IGF)-1 and soluble (s)Klotho levels decreased to a similar extent?

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Background, aims
Acromegaly is caused by excessive growth hormone (GH) secretion, usually by a pituitary adenoma. Surgical removal of the GH-producing adenoma is the most effective treatment. Drug treatment is second-line option. Earlier work suggested Soluble (s)Klotho levels to be a supplementary biomarker to IGF-1. We tested whether IGF-1 and sKlotho serum levels show a concomitant reduction under medical treatment. If yes, is the extent of reduction in serum IGF-1 and sKlotho comparable?
Methods
We determined IGF-1 and sKlotho levels (by ELISA) in serum samples of 29 patients with confirmed acromegaly treated in our hospital from 2013 onwards, before and after treatment (surgery alone or surgery and pharmacotherapy). All patients underwent transsphenoidal surgery. Patients with remnant adenomas were treated with drugs: two with cabergoline, three with lanreotide, one with octreotide LAR, and two with pegvisomant. One patient received pegvisomant before surgery to stabilise cardiomyopathy resulting from GH excess.
Results
Surgery (21 cases, 12 female) and drug treatment (eight cases, two female) decreased levels of both IGF-1 and sKlotho in the majority of cases (IGF-1, in 28, sKlotho in 29). As expected, surgery resulted in a significant decline in IGF-1 from median 841 ng/ml (interquartile range (IQR); 620–994) to median 266 ng/ml (IQR 185–383) with P-value <0.001. Likewise, sKlotho decreased significantly from median 4,502 pg/ml (IQR 1264–6677) to median 716 pg/ml (IQR 592–1177) with P-value <0.001. In eight patients with pharmacotherapy, IGF-1 declined significantly from median 632 ng/ml (IQR 455.3–1005) to median 381 ng/ml (IQR 305–438) with P-value <0.01. Similarly, sKlotho declined from median 2316 pg/ml (IQR 1755–4326) to median 927 pg/ml (IQR 803–1203) with P-value <0.01. After surgery, there was 68% decrease in IGF-1 and 84%

decrease in sKlotho. After medical treatment, IGF-1 decreased 40%and sKlotho decreased 60%. Overall, decrease in sKlotho appeared to be more pronounced than decrease in IGF-1.
Conclusion
sKlotho – supplementary to IGF-1 - is a serum biomarker reliably reflecting disease activity and treatment effect (both surgery and pharmacotherapy) in patients with acromegaly.

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P1067

A closer look at pituitary deficiency in Ipilimumab-induced hypophysitis

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Introduction
Ipilimumab is a monoclonal antibody directed against CTLA-4 used primarily in treatment of malignant melanoma. Immunological side effects are common, amongst others it may lead to hypophysitis. We studied clinical characteristics of IpiH and compared it to cases of primary hypophysitis (PH).
Methods
We conducted a retrospective single centre study in 75 hypophysitis patients (60 primary, 15 Ipilimumab-induced in patients with melanoma). Group differences were calculated using Mann-Whitney U test or chi-square test.
Results
Nominally, the number of affected pituitary axes did not significantly differ between groups (mean 2.5 ± 1.3 in IpiH vs. 1.9 ± 1.3; $P = 0.13$). Deficiency of anterior pituitary axes did not significantly differ between both groups. However, IpiH patients had less often diabetes insipidus (13% vs. 38%, $P = 0.044$) and none had hyperprolactinemia as sign of pituitary stalk damage (0% vs. 25%, $P = 0.045$). Male patients had significantly more gonadotropin deficiency than their female counterparts (IpiH: 88.9% vs. 16.7%, $P = 0.005$; PH: 75.0% vs. 30.2%, $P = 0.002$). Other axes showed no differences in sex distribution. Patients with IpiH didn't develop any further deficiency whereas 23.2% of PH-patients had further axes affected during follow-up. IpiH was diagnosed 2 months (median) after initiation of Ipilimumab treatment.
Discussion
Patients with IpiH have less diabetes insipidus and hyperprolactinemia than patients with PH. Possibly, IpiH seldomly involves the pituitary stalk. The course of IpiH seems more favorable as no further pituitary deficiency after diagnosis was observed in our cohort. Our findings show subtle differences between IpiH and PH, especially concerning neurohypophysis.

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P1068

Pituitary metastases of lung cancer in an elderly men mimiking pituitary apoplexy (3 cases)

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Introduction
Pituitary tumors are the most frequent intracranial neoplasm. However metastases in this location are rare and uncommon presentation of systemic malignancy. The clinical and radiologic features of most pituitary metastases can be characteristic and evocative but in no case pathognomic. The diabetes insipidus is the most common clinical manifestation of the disease. We report here four cases of pituitary metastases of lung cancer in an elderly patients mimiking pituitary apoplexy.
Observations
Case 1: A 69-year-old patient active smoker with history of type 2 diabetes mellitus presented with signs of acute adrenal insufficiency; vomiting, low blood pressure and hypoglycemia and polyuro polydipsic syndrom. Assessment of pituitary function revealed hypopituitarism and an insipidus diabetes; serum cortisol level of 12.6 ng/ml, Free T_4 level of 6.8 pg/ml, TSH level of 0.005 mUI/ml, total testosterone level of 0.025 ng/ml, FSH level of 0.5 IU/ml, luteinizing hormon level of 0.1 IU/l and low urine osmolarity. A hormone replacement therapy was indicated urgently. A magnetic resonance imaging (MRI) was demonstrated an inhomogeneous pituitary hypertrophy, appearance of central necrosis, with convexity of the sellar diaphragm, a nodular thickening of the pituitary stalk, and a loss of high intensity signal from the posterior pituitary. In front of the deterioration of the general condition, tobacco intoxication, the imagery founds and the very high level of carcinoembryonic antigen (CEA) at 197 µg/l, the computary tomography scan (CTS) of the Chest, Abdomen and Pelvis was performed and revealed a mass in the upper right lobe with mediastinal lymph nodes, liver and bilateral adrenal metastases.
Case 2 and 3: 72 and 68 year-old patient were admitted for pituitary apoplexy in MRI. Assessment of pituitary function revealed hypopituitarism and an partial insipidus diabetes. In front of weight loss, tobacco intoxication, the level of CEA (150 and 178 µg/l), chest-X-Ray abnormalities, hypothalamic and pituitary metastasis was suspected. The CTS scan revealed a mass in the lung with mediastinal lymph nodes, and bilateral adrenal masses. In all cases, a biopsy confirmed lung cancer. A specific treatment was planned.
Conclusion
Despite the fact that pituitary metastasis are rare, they must be evoked on the presence of pituitary apoplexy and sudden pituitary involvement associated to diabetes insipidus,, even in the absence of a neoplastic history. Pituitary tumor and / or metastasis should be taken in account in differential diagnosis.

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P1069

Apelin, copeptin, aldosterone and renin in patients with hyponatremia after transnasal surgery for pituitary tumors

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Introduction
Hyponatremia after transnasal neurosurgery for pituitary adenomas is a serious and not so rare complication. It often occurs in a delayed manner after patient's discharge and is a major cause of readmission. The pathogenesis of postneurosurgical hyponatremia is not clear yet.
Aims
To study the role of posterior pituitary hormones (antidiuretic hormone (ADH) and apelin) and reaction of renin-aldosterone system (RAS) at hyponatremia manifestation.
Materials and methods
The study included 13 patients with debut of hyponatremia after transnasal adenomectomy, three men and 10 women, with median age 58 years [46; 62], without decompensated pituitary deficiencies or desmopressin treatment. Median decrease in blood sodium level was 122 mmol/l [117; 126]. The control group consisted of healthy female volunteers of median age 24 years [23; 25]. Apelin-12 and copeptin (as surrogate for ADH) were measured by EIA (Phoenix Pharmaceuticals, Inc). Renin and aldosterone evaluated by Cobas 6000 (Roche Diagnostics).
Results
In patients with hyponatremia there were no significant differences compared to controls in levels of copeptin (0.382 ng/ml [0.274; 0.451] vs. 0.273 [0.200; 0.431], $P > 0.05$), increased levels of apelin-12 (0.111 ng/ml [0.098; 0.242] 0.072 [0.052; 0.109], $P = 0.02$), decreased concentrations of aldosterone (220 mmol/l [112; 345] vs. 594 [272; 979], $P = 0.03$) and no significant changers in renin activity (1.1 [0.6; 2.0] vs. 1.2 [0.6; 2.1], $P > 0.05$). Strong positive correlations were seen for apelin and blood sodium ($r = 0.64$, $P < 0.01$), plasma osmolality (0.67, $P = 0.009$), and urine osmolality (0.83, $P = 0.003$).
Conclusions
In case of hyponatremia after transnasal adenomectomy, there is not only an unsuppressed by hyponatremia blood levels of a surrogate marker of secretion of ADH, copeptin, but also an increase in its counterregulatory hormone apelin, which may correspond to increased secretion from damaged terminals of axons of magnocellular neurons along with ADH or increased secretion in response to hyponatremia and hypervolemia. RAS appears to be depressed.

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P1070

Childhood-onset growth hormone deficiency: evaluation after reaching final adult height

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Introduction
Growth hormone (GH) has multiple metabolic effects in adulthood, pointing to the need of identify those patients who would benefit of GH treatment after achievement of final height.
Objective
To assess GH secretion, bone mineral density (BMD) and metabolic profile in patients with childhood-onset GH deficiency (GHD) after completion of recombinant GH (rGH) therapy for linear growth.
Methodology
One hundred eleven patients (59 males) with childhood-onset GHD were investigated in 2007–2018 at least 3 months after discontinuation of rGH treatment. Permanent GHD was diagnosed when GH peak was less than 10 mU/l during GH stimulation test with insulin and less than 6 mU/l with glucagon. Fasting glycemia, insulin concentration and lipid profile were also assessed. Insulin resistance index (HOMA-IR) was calculated with formula: fasting glycemia (mmol/l) $\times$ fasting insulin concentration (mU/l) / 22.5. Bone mineral density (BMD) was determined by dual-energy x-ray absorptiometry (DXA) method (with Hologic Densitometer QDR4500A).
Results
Mean age of patients at the time of retesting was 16.2 ± 1.3, [median 16.33; min 11.4; max 19.6] years. 76 patients had isolated GHD and 35 - multiple pituitary hormone deficiency, – 13 of them PROP1 gene mutation was identified. Twenty four patients (21.6%) have been diagnosed with permanent GHD (4 (5.2%) in the isolated GHD and 20 (57%) in MPHD patients, ($P=0.001$) and 87 (78.4%) – with transient GHD. Patients with permanent GHD achieved a greater final height compared with transient GHD (-0.4 ± 1.4 vs. -1.4 ± 0.9, respectively, $P=0.003$). Hypercholesterolemia was significantly more frequent in patients with permanent GHD compared to the transient GHD group (38.9% vs. 6.8%, respectively, $P<0.01$), HOMA-IR was significantly higher in the group of transient GHD (42.9 vs. 6.7; $P=0.009$). BMI and BMD were comparable in patients with permanent and transient GHD groups.
Conclusions
21.6% of patients with childhood-onset GHD were found to have permanent GHD: 5.2% among patients with isolated and 57% in patients with MPHD. Patients with permanent GHD have reached a higher final height than patients with transient GHD. Patients with transient GHD were more insulin resistant, while those with permanent GHD had significantly higher cholesterol levels.

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P1071

A novel mutation in CHD 7 gene: hypogonadotropic hypogonadism without charge syndrome

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Congenital isolated *hypogonadotropic hypogonadism* (CHH), is a condition characterized by a defect in development, migration and action of GnRH neurons. Numerous genes are involved in CHH. It can present with anosmia, hyposmia or normosmia. Two cases presented to our department with late onset delayed puberty. First case was a 29 year old with absence of secondary sexual characters along with micropenis and anosmia. His younger brother, 22 year old had similar complaints and findings. Both cases were evaluated. They were detected to have isolated *hypogonadotropic hypogonadism*. All other pituitary hormone analysis done showed normal results. MR Imaging showed characteristic absence of olfactory bulb in one case and hypoplasia in the other. Genetic analysis (Clinical Exome sequencing) for 39 genes related to CHH was done. In genetic analysis we found similar heterozygous mutation at same location in both the brothers. The mutation found in CHD7 gene at exon 2 variant 1565G > T (p.Gly522Val) which was confirmed with Sangers sequencing. Kallmann syndrome with classic presentation usually has defects in KAL1 gene, but we found mutation in CHD7 gene with Kallmann phenotype without classic features of Charge syndrome which may be the mild phenotypic spectrum of Charge syndrome. For the first time we report a case of heterozygous mutation with pathogenic phenotypic spectrum. Further research is mandated to confirm this type of heterozygous mutation.

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P1072

Diabetes insipidus as first clinical manifestation of Xanthoma Disseminatum: a case report

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Introduction
Central diabetes insipidus (CDI) is a heterogeneous condition characterized by the presence of polyuria and polydipsia due to a deficiency of arginine vasopressin. Frequently, CDI is wrongly considered idiopathic if not associated with other signs and symptoms.
Case report
We report the case of a 50-year-old woman diagnosed with idiopathic central diabetes insipidus at the age of 34. The MRI scan of the hypothalamus and pituitary gland was performed and did not show any abnormality. No further diagnostic procedures were performed at that time. The patient presented 14 years later with back pain. The physical examination revealed a suspicious thyroid nodule. A thoracic, abdominal and pelvic computed tomography scan showed osteolytic lesions in the thoracic and dorsal spine. Total thyroidectomy was performed and pathology revealed papillary carcinoma with lymph node metastases. She received 3.7 GBq (100 mCi) of iodine-131. The results of Post-ablation 131I whole-body scintigraphy were reported as negative with a serum thyroglobulin $<$ 1 ng/mL. However the patient was still complaining of back pain.So we performed a second whole body bone scintigraphy which demonstrated increased uptake localised in the distal metaphysis of the femur and proximal of the shins, evoking in the first place a systemic origin. Dermatological examination revealed multiple papular lesions of 3 mm, non-itchy, discrete and confluent in some places. The lesions were coloured to yellow orange and red brown, affecting axillae and groins, appeared there 4 years ago. Anatomo - pathological examination of the cutaneous biopsy of these lesions concluded to a disseminated xanthoma.
Conclusion
Xanthoma disseminatum (XD) is an extremely rare and unique entity in the spectrum of non-Langerhans cell histiocytosis. XD may have central diabetes insipidus as their first manifestation. Involvement of the central nervous system occurs in approximately 40% of cases. The symptoms of diabetes insipidus may precede the dermatologic signs. This case highlighted the importance a long-term follow up of patients suffering from idiopathic CDI.

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P1073

Diagnostic challenges in Ectopic Cushing's Syndome: report of 2 cases

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Introduction
Ectopic Cushing's Syndrome (ECS) accounts for 5-10% of all cases of endogenous hypercortisolism. ACTH secreting intrathoracic masses is the most common cause of ECS. We present two patients with ectopic Cushing's syndrome, with particularities in diagnosis.
Case 1:
A 59-year-old female presented with arterial hypertension, and osteoporosis, along with weight gain and facial plethora, starting two years before. Screening tests were consistent with Cushing's syndrome, along with high plasma ACTH = 81.8 pg/ml (range 10–60 pg/ml). Pituitary MRI was negative for adenoma. CRH stimulation test and selective inferior petrosal sinus sampling were compatible with ectopic ACTH secretion. 99 mTc-Tektrotyde scintigraphy scan showed increased radiotracer uptake in the left lower pulmonary lobe, and the finding was attributed to inflammatory causes since repeated thoracic CT and bronchoscopy

were negative for any anatomic lesion. The patient was offered a trial with daily subcutaneous pasireotide, to which she responded. Subsequently, she remained in complete clinical and laboratory remission of hypercortisolism with a minimal dose of 300 mcg daily, and put under close surveillance for a two year period. Scintigraphy with Ga68 dotatoc demonstrated and confirmed the uptake in the lower left pulmonary field. The patient was subjected to thoracoscopic left lower lobectomy without complications. The histopathological examination revealed a typical bronchial carcinoid.

Case 2:

A 44-year-old man presented with arterial hypertension, facial plethora and mood changes introduced over a four-month period. He had no previous medical history, but reported daily alcohol consumption. Screening tests were diagnostic of Cushing's syndrome with plasma ACTH 95.1 pg/ml (range 10–60 pg/ml). However, upon hospital admission for verification of the diagnosis, all repeat tests returned normal. A third admission after 3 weeks confirmed the presence of cyclic ACTH dependent Cushing's syndrome, with ectopic origin according to CRH test. Pituitary MRI was negative for the presence of adenoma. Chest CT revealed a mediastinal mass of 2.0×1.5 cm. Scintigraphy with 99 mTc-Tectrotyd followed by SPECT-CT showed increased uptake. The patient underwent surgical excision of the mass and histopathological examination confirmed a typical thymic carcinoid. Postoperatively, the patient is in complete remission.

Conclusion

1. ECS can have a rather mild clinical presentation with ACTH levels similar to that of Cushing's disease and a very favorable response to medical treatment.
2. Ectopic ACTH secretion can appear, although less often, in a cyclic form.
3. Diagnostic approach of ECS can be a real challenge, where repeat testing and perseverance play a significant role.

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P1074

Local myofascitis: an unusual adverse reaction to lanreotide autogel injections

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Background

Somatostatin analogues are the mainstay medical treatment of acromegaly. Side effect of this treatment includes gastrointestinal disturbances, cholelithiasis, and local reactions at injection sites. Herein we report an unusual case of local myofascitis after one-year treatment with deep subcutaneous injections of lanreotide Autogel in a patient with acromegalo-gigantism.

Clinical case

A 25-year-old man was found to have an invasive macroadenoma responsible for acromegalo-gigantism during work up for shortness of breath and nocturnal dyspnea. He underwent transsphenoidal debulking pituitary surgery with residual tumor requiring post-operative medical treatment. He was treated by deep subcutaneous injections with lanreotide Autogel that was progressively increased to 120 mg every 28 days without adequate control. One year after initiation of medical therapy and three months after receiving a dose of 120 mg, he presented with a one-week history of sudden onset and painful induration of the right thigh at the site of injections impairing limb movement and occurring 3 days following the last lanreotide injection. There were no clinical or biological signs of bacterial infection. Contrast enhanced CT of the right thigh showed a fluid density collection of 6 mm thickness and 30 cm length on the lateral wall of the right thigh in contact with the vastus lateralis muscle and a poorly circumscribed heterogeneous hypodense multilobulated intramuscular lesion of 30×30×60 mm. MRI of the right thigh confirmed the presence of a collection and was consistent with myofascitis of the vastus lateralis muscle. Clinical evolution of the right thigh lesion was characterized by the onset of redness, warmth and non-purulent serous discharge. The patient then underwent surgical intervention with evacuation of a superficial collection reaching the vastus lateralis muscle. Analysis for bacterial infections was negative. Histology showed characteristics of foreign body giant cell reaction with homogeneous exogenous material surrounded by fibrosis and intramuscular granulomas.

Conclusion

To our knowledge, this is the first report of local myofascitis as an adverse event to deep subcutaneous injections of lanreotide Autogel. The patient developed an inflammatory foreign body reaction, previously described with lanreotide injections. However, in this case, the local reaction was not limited to the subcutaneous tissue but also involved the muscle tissue resulting in myofascitis and impaired motor function. The present case serves as a reminder that local injection site reactions can occur with lanreotide Autogel injections. Besides having very little adipose tissue on the site of injection, no other predisposing factors could be identified in our patient.

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P1075

Emotional disorders in the clinic of the thyrotropinoma

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Thyrotropinoma (TSH-secreting pituitary adenomas, TSH-AG) are rare tumor of the pituitary (0.5–2% of all pituitary adenomas). Localization of the tumor with the appropriate neuroendocrine disorders has features in the clinic. This is due to the direct damage to the nucleus and structures of the pituitary with hypersecretion of TSH, which leads to overstimulation of the thyroid gland and the emergence of the clinical picture of 'central' hyperthyroidism. Differentiated diagnosis of these disorders will help doctors to set the correct diagnosis of thyrotropinoma with an interdisciplinary approach.

Objective

To study the emotional disturbances in the structure of the clinic of thyrotropinoma.

Materials and methods

26 patients with pituitary adenoma, normal or elevated TSH levels in combination with elevated levels of St.T4, St.T3. They admitted to the Institute for treatment (2002–2017). 14 women (54%) and 12 men (46%), 15–67 years old (median 38.5 years). All tumors belonged to macroadenomas (by MRI), the diameter is 14–64 mm (median 26 mm). All patients underwent a study of the levels of TSH, St. T4, St. T3, prolactin, cortisol, LH, FSH, estradiol/testosterone, in 18 cases - the study of the levels of ICF-1. The reference values were: TSH (0.4–4.0) mU/l, St. T4 (11.5–22.7) mmol/l, St. T3 (3.5–6.5) mmol/l, antibodies to the TSH receptor (< 1.0 mU/l).

Results

The clinic was presented with symptoms of hyperthyroidism in 21 (80.7%) patients, anamnesis from 1 to 13 years (median 3 years). Emotional pathology was detected in 57.6% ($n=15$): anxiety-phobic disorders in 50%, panic attacks-46.1%, depression-11.5%. Patients complained of: increased fatigue and weakness - eight patients, heartbeat - 13, 'anxiety' - 9, mood lability - 14, sleep disorders - 5, sweating - 5, hand tremor - 3, subfebrile temperature - 2, weight loss - 2. And these symptoms combined with each other. The severity of psychopathological symptoms was often moderately severe (65%). eight patients received psychotropic therapy before a diagnosis, 5 of them were seen by a psychiatrist for a long time.

Conclusion

The clinical picture of TSH-AH consists of the symptoms of hyperthyroidism and the mass-effect of the tumor. Emotional disturbances are detected in 57.6%. The interdisciplinary approach will allow: 1) to carry out an early diagnosis of these tumors with the specification of the differential diagnosis of conditions with hyperthyroidism; 2) to conduct adequate medical treatment, including specialized neuropsychopharmacotherapy.

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P1076

Prolactinoma – is there a relationship between T2W signal intensity in MRI and response to treatment with dopamine agonists?

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Introduction

Prolactinomas are mostly benign tumours usually managed with pharmacological treatment. Some, however, seem to be resistant to dopamine agonists (DA) for unclear reasons. The relationship between T2W signal intensity (T2WSI) and response to treatment with somatostatin analogs is well described in acromegaly

patients. Some evidence suggests that prolactinoma's T2W hypointensity might be related to higher baseline prolactin levels and more resistance to DA.
Aim
Evaluate the relationship between MRI T2WSI and response to treatment with DA in adult patients with prolactinoma.
Methods
Retrospective study including data from patients with prolactinoma diagnosis followed at our outpatient clinic from 2005 to 2018. Signal intensity on MRI was observed by the same physician and compared to the normal pituitary gland. Response to DA was evaluated by mean dose necessary to normalize prolactin levels (bromocriptine and cabergoline considered separately) and time to normalization. When normal levels were not reached (resistant cases), the highest dose used was considered.
Results
70 patients were identified, 37 with feasible data, with a mean age at diagnosis of 45 years, 26 (70%) females. Most had macroprolactinoma ($n=26$; 70%). Mean initial prolactin levels were 1490 ng/mL; they normalized after a mean time of 9 months (mean prolactin 13.8 ng/mL). Four patients did not reach normal levels. Men had larger tumours and higher baseline prolactin levels, but only the last with statistical significance (P 0.04). There was no relationship between T2WSI and baseline prolactin levels (P 0.96). In 23 patients, the association between T2WSI and mean time for prolactin level normalization was evaluated: hyperintense lesions had a slightly longer mean time, but not statistically significant (P 0.89). In 10 patients treated with cabergoline and 22 treated with bromocriptine, there was no significant association between T2WSI and mean dose reached (P 0.55; P 0.63, respectively).
Conclusion
MRI signal intensity is related to tumour characteristics. Prolactinomas are usually not surgically removed, so it would be very useful if data from imaging studies could help predict clinical and biochemical behaviour, especially when it comes to response to treatment. We found that hyperintense lesions in T2W take slightly longer to normalize prolactin levels, but this was not statistically significant. Our results were not in accordance with other data in literature. This might be possibly related to differences in study design and small sample size in this study. Relationship between T2WSI and response to DA is still not clear. Larger, well designed studies will be needed to assess this.

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P1077

Long term observation of patients with pituitary stalk lesions – single center experience

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Background
Pituitary stalk lesions (PSL) are various changes located in the pituitary infundibulum. The underlying pathology and exact diagnosis are difficult to establish due to their difficult anatomical locus.
Aim
To present the etiological spectrum of pituitary stalk lesions and their clinical and hormonal characteristics on the basis of long term observation in the pediatric/adult endocrinology departments of our university.
Methods
A retrospective observational analysis of 28 patients (16M/12W) with pituitary lesions was performed. The mean age of diagnosis was 30.67 years (SD 23.93). The etiologies were divided into three groups (congenital, inflammatory, neoplastic) and classified as exact, probable or unknown.
Results
The most common causes of PSL were congenital malformations (14/28, 50.0%), an inflammatory etiology was found in 8/28 (28.6%), while neoplasms were diagnosed in 2/28 (7.1%) of patients. The exact etiology was established in 18/28 (64.3%) cases (14 congenital malformations, 2 histiocytosis, 1 Erdheim-Chester disease, 1 germinoma). The probable cause was suggested in 6/28 patients (21.4%) – five with the suspicion of lymphocytic hypophysitis and one with a metastatic tumor from a disseminated neuroendocrine cancer. The origin of 4/28 PSL (14.3%) remains unknown. During hormonal assessment the most common insufficiency concerned the thyroid axis found in 18/28 (64.3%) patients, followed by somatotropic (16/28, 57.1%), gonadal (14/28, 50.0%) and adrenal axis (13/28, 46.4% of cases) insufficiencies. 9/28 (32.1%) patients were diagnosed with diabetes insipidus. Some hormonal deficits were transient.
Conclusions
The diagnosis, management and treatment of the pituitary stalk lesions remains challenging. Difficulties in establishing the exact diagnosis might also be related to the non-specific, transient characteristics of the symptoms and hormonal insufficiencies. Long term observations might help better the understanding of the disease and result in improvement of management.

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P1078

Pituitary stalk interruption syndrome with late revelation: about 5 cases

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Introduction
Pituitary Stalk Interruption Syndrome (PSIS) is a distinct and rare clinical entity responsible for isolated or combined anterior pituitary insufficiency. The objective of this work is to describe the clinical, hormonal and radiological aspects of PSIS.
Patients and methods
Observational descriptive study of the files of 5 patients including 4 cases of congenital PSIS and one acquired, followed in the endocrinology and diabetology department of Ibn ROCHD University Hospital.
Results
These are male patients with a mean age of 19 years. The reasons for consultation were failure to thrive (3) and micropenis (2). The history of reported head trauma in a patient. The physical examination returned to a statural (-4SD), weight (-3SD) and pubertal (Tanner stages G1P1) delay (3 cases) with 1 case of psychomotor delay. Hormonal exploration revealed an isolated in 2 cases and a complete deficit in 3 cases. Pituitary MRI scan diagnosed ectopia of the post-pituitary gland (4) and pituitary stem hypoplasia without visualization of the anterior or post-pituitary parenchyma (1). Treatment consisted mainly of hormonal substitution.
Conclusion
PSIS is a rare abnormality revealed by a complete or partial hypopituitarism, the diagnosis is often late. Its management involves regular monitoring of the evolving nature of the disease.

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P1079

Familial hypogonadotropic hypogonadism: about a family

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Introduction
Congenital idiopathic hypogonadotropic hypogonadism is a rare genetic disorder caused by an isolated defect in GnRH secretion by the hypothalamus or, less frequently, by a defect in the action of GnRH on pituitary gonadotropes. The majority of cases are sporadic but there are also family forms. We report a case of one family.
Case report
These are 2 brothers with a family history of primary infertility in the maternal uncle. An 18-year-old girl who consults for primary amenorrhea and a 15-year-old boy admitted for micropenis. There was no anosmia, no tumoral syndrome, nor signs of pituitary insufficiency. The general examination did not show any growth retardation or dysmorphic syndrome, the genital examination in the boy revealed a 2 cm micropenis, non palpable testicles and a Tanner of G1P2. The Tanner in the girl was S1P2 without any abnormality. The hormonal assessment confirmed an isolated hypogonadotropic hypogonadism. Pituitary MRI was normal in both patients. The karyotype was normal in the brother. Abdominal-pelvic MRI showed ectopic testicles in the inguinal orifices. The girl was given estrogen/progesterone, her brother Testosterone Enanthate, he was referred in the same time to urology for orchydopexy.

Discussion
The diagnosis of congenital hypogonadotropic hypogonadism is usually easy. Etiological diagnosis is a field of research based essentially on genetic studies, especially in family forms. Early diagnosis requires vigilance of the parents, as well as prenatal consultations to anticipate treatment.

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P1080

Impairment of glucose tolerance in children and adolescentstreated for medulloblastoma

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Children and adolescents treated for solid brain tumors with chemotherapy and craniospinal irradiation are at increased risk of metabolic changes development. Current follow-up guidelines for cancer survivors recommend to monitor fasting glucose and HbA1 levels for diabetes/impaired glucose tolerance screening in these patients. The aim of our study was to evaluate metabolic changes in children treated for medulloblastoma with oral glucose tolerance test (OGTT). We examined 63 patients (40 males/23 females). Patients had a median age (range) of 11.3 (5.5–17.9) years. They were treated for medulloblastoma when aged 6.8 (1.2–16.2) years. The outcome measures were: BMI SDS, fasting glucose, HbA1c, OGTT (0, 30, 60, 90 and 120 min). We identified 4 patients with impaired glucose tolerance (120-min glucose $\geq$ 7.8 mmol/l). All patients with impaired glucose tolerance had normal values of fasting glucose (4.3 ÷ 5.04 mmol/l) and HbA1c (4.8 ÷ 5.8%). All these patients had normal BMI SDS (0.06 ÷ −1.7).
Conclusion
Children and adolescents treated for solid brain tumors by chemotherapy and craniospinal irradiation should be screened for glucose tolerance impairment by OGTT regardless of fasting glucose, HbA1c and BMI SDS values.

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P1081

ACTH-positive diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH)

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Introduction
DIPNECH is a preinvasive condition in which there is an idiopathic generalised proliferation of pulmonary neuroendocrine cells that can form tumourlets. There are very few cases described of ACTH secretion by these cells causing Cushing's syndrome, some of them cyclic.
Case report
A 41 year-old woman was sent to our Endocrinology outpatient clinic for menstrual disturbance, acne and excessive sweating. She had a recent diagnosis of DIPNECH after extensive investigation for long standing dry cough and dyspnea and was already on prednisone 35 mg/day and inhaled corticosteroids for a few months. Physical examination: moon face, slightly pletoric; excessive weight, prominent abdomen with purple striae; mild facial and dorsal acne; buffalo hump and cervical acanthosis nigricans. No other relevant findings. Blood tests revealed slightly elevated IGF-1 (242 ng/mL [58–219]) and hyperprolactinemia (85 pg/mL [4.8–23]). Cortisol metabolism was not tested at the time because of corticosteroid treatment. OGTT was performed, with no clear evidence of acromegaly. Immunohistochemistry of the tumourlet neuroendocrine cells was negative for GH, but strongly positive for ACTH. No lesions were present in the sellar MRI. The patient was then started on octreotide to optimize DIPNECH treatment because she still complained of dyspnea, with some improvement. Steroids were tapered down progressively with good tolerance but not much improvement of Cushingoid features. After full withdrawal for a few days, we tried to evaluate the patient for ectopic Cushing's syndrome. Cortisol rhythm was normal, CRH test had a raise in ACTH of 120% and 40% of cortisol. Overnight dexamethasone suppression test (2 mg) was negative (cortisol 0.2 mcg/dL [$<$1.8 mcg/dL]). Urinary free cortisol level is still pending. There is no evidence of hypersecretion so far, but the patient is going to be followed and repeat these tests after a longer period with full steroid withdrawal and just before the next octreotide administration, since it can also influence results.
Conclusion
This case represents a true diagnostic challenge, since we can be in the presence of inactive ACTH, real ectopic Cushing's syndrome that is biochemically responding to octreotide or cyclic ectopic Cushing's syndrome. Follow-up will be essential do unravel the true meaning of the immunohistochemistry findings.

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Nasopharyngeal carcinoma revealing acromegaly on pituitary adenoma

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Introduction
Acromegaly is a clinical syndrome caused by excessive production of growth hormone (GH). It is associated with an increase in the incidence of cancers. Through this observation, we illustrate the rare association of a somatotropic adenoma with a nasopharyngeal carcinoma.
Case report
57-year-old woman, having hypertension, followed for an undifferentiated nasopharyngeal carcinoma since 2011 under radio-chemotherapy, having recurred in January 2018. A Magnetic resonance imaging of the cavum with a pituitary cut was made as part of the extension assessment having revealed: a macro non-compressive intra and supra-pituitary adenoma and asymmetry of the walls of the nasopharynx enhanced by the contrast product, probably due to radiotherapy. The patient was referred to our department for investigations. During her hospitalization, we noticed a clinical acromegaloid syndrome made of an excessive sweating and body odor, a husky voice, snoring, and enlarged hands, feet, tongue and facial features. The diagnosis of acromegaly was confirmed by a high level of insulin growth factor1 (IGF-1): 329.4 ng/mL (48–241 ng/mL). Currently she is a candidate for pituitary surgery.
Discussion
Excess chronic secretion of growth hormone causes an increase in IGF-1, which has a promotive role on mitogenesis and malignant proliferation of soft tissues and bones. Although there is no cause and effect relationship between acromegaly and neoplastic pathology, it is well established that hypersomatotropism is associated with an increased risk of neoplasms in many organs, such as the gastrointestinal tract, lungs, breast, prostate, kidney and brain that are the most aggressive and frequent. Nasopharyngeal carcinoma with pituitary damage remains a rare association with acromegaly, and raises the problem of differential diagnosis with the sellar metastasis of nasopharyngeal cancer.
Conclusion
An additional case of nasopharyngeal neoplasia in a patient with acromegaly reinforces the evidence of increased risk of developing cancer in these patients.

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Diabetes mellitus and metabolic syndrome in acromegaly

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Acromegaly is a rare endocrine disorder, caused by hypersecretion of growth hormone. Cardiovascular and metabolic complications reduce life expectancy. Early carbohydrate metabolism disorders and diabetes mellitus are frequently associated with acromegaly.
Objective
The objective of this study was to evaluate the glycemic profile and cardiovascular complications in acromegaly.
Methods
We performed a retrospective study. We included 20 patients diagnosed with acromegaly and followed up in a tertiary endocrinology center. Patients who had not previously been diagnosed with diabetes underwent an oral glucose tolerance test (OGTT) - in the fasting state, and 30, 60, 90 and 120 min after oral administration of 75 g glucose, blood was collected for the simultaneous measurement of plasma levels of GH and glucose. Also the patients underwent an extensive evaluation which included the assessment of the cardiovascular risk.

Results
The average age was 48 years old, with a sex ratio (M/F) 0.5. 35% patients were diagnosed with diabetes mellitus and 30% had arterial hypertension. The duration of the disease was on average 12.4 years. % of the patients had active disease and were under medical therapy. 35% of the patients were diagnosed with acromegalic cardiomyopathy and 15% had major cardiovascular events. A gradual increase of diabetes prevalence was observed with age.
Conclusions
In this study we have observed a high prevalence of diabetes mellitus in patients with acromegaly. The patients had a long duration of the disease. A better glycemic control is achieved when the underlying endocrine disorder is treated.

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Case report: polynodular goiter and pituitary macroadenoma co-secreting growth hormone and thyroid stimulating hormone

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Purpose
The purpose is to draw attention to rare cases of Pituitary Macroadenoma co-secreting Growth Hormone and Thyroid Stimulating Hormone with Polynodular Goiter and their importance and approach in current practice.
Background
Pituitary adenomas with no hormonal clinical picture are known as 'silent' tumors. They are rarely reported and lacking pathogenic explanations.
Method
We describe a case of Pituitary Macroadenoma with both growth hormone (GH) and thyroid stimulating hormone (TSH) secretion, but with no clinical manifestations, such as features of acromegaly or hyperthyroidism.
Results
A 58-year-old male patient, diagnosed with essential arterial hypertension 3rd grade, persistent atrial fibrillation, carotid sinus syndrome, permanent cardiostimulation type VVI, overweight status, hepatic steatosis and hyperglycemic status was hospitalized to investigate a syncope episode two years ago. The CT scan revealed a pituitary adenoma, in the absence of any clinical signs. The diagnosis of Polynodular Goiter and Pituitary Macroadenoma co-secreting GH and TSH was confirmed by the following investigations:
1. CT: a nodular image with moderate contrast in diameter of 19/17.5/17 mm, moving normal pituitary tissue and the pituitary stem to the left, bombing the selar diaphragm on the right side without overtaking it and passing inferior to the sphenoidal sinus and extending laterally approximately 3 mm to the right cavernous sinus, without exceeding the plane of the internal carotid wall.
2. Pituitary Hormone profile: TSH: 3.03 lIU/ml (0.3–4.0); fT4: 2.23 pm/L (9–25)w; GH: 1.51 ng/ml (0.0–5.0); IGF-1: 404.00 ng/ml (70–197).
3. Thyroid ultrasound: Right thyroid lobe 3.2/4.22/1.86 cm, nodular formation (1) 0.69/0.86 cm, nodular formation (2) 1/1.13/1 cm, non-vascularized formations; left thyroid lobe 2.39/3.65/2.16 cm.
4. HGPO Test with GH values not exceeding 1 ng/ml.
Conclusion
Taking into account the associated cardiovascular pathology, treatment with Somatostatin analogues (Somatuline PR 30 mg/14 days), associated with Cabergolina and gamma knife radiotherapy has been established with clinical and biological re-evaluation every 6 months for the past two years, observing a slight dimensional reduction of the formation.

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Idiopathic Fanconi anemia and growth retardation: do not miss GH deficiency

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Introduction
Fanconi anemia (FA) is an autosomal recessive disease associated with chromosomal instability, it is marked by phenotypic heterogeneity. Patients with FS often exhibit growth retardation due to complex factors such as hypophosphatemia, metabolic acidosis, disturbed vitamin D metabolism. On the other hand, endocrinopathies are a common feature of FA specially such as Growth hormone deficiency (GHD). We report here two cases of Fanconi disease associated to GH deficiency.
Clinical observation
The first patient is 12 years old initially followed in haematology for Fanconi's disease discovered by bone marrow aplasia and confirmed by the presence of chromosomal breaks. For the 2nd patient, it is a 6-year-old child also followed in hematology for confirmed Fanconi disease and referred for suspicion of GH deficiency in front of a severe statural delay (height at 91 cm or between −3 and −4 DS). Explorations showed a bone age lower than chronological age for both patients (11 years and 4 years respectively), and celiac serology was negative in the two cases. GH stimulation test (insulin hypoglycemia test and catapressan test) demonstrated GHD. For the both patients the serum insulin-like growth factor I (IGF1) was low. Corticotropic deficiency confirmed by a lack of response to the insulin hypoglycemia test was associated with somatotropic deficiency in the first patient. The hypothalamic-pituitary MRI showed for an hypoplastic pituitary gland in the first case and a pituitary stem section syndrome in the 2nd patient. Both children received recombinant GH with a good response to treatment.
Conclusions
The differential diagnosis of GHD should be considered for FS patient with a short statue. The demonstration of abnormal endogenous GH secretion may demonstrate an underlying hypothalamic-pituitary dysfunction that results in poor growth. Proper management can improve the height prognosis.

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Predictive factors of surgical outcomes in acromegaly

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Introduction
Acromegaly is a chronic disorder usually caused by growth hormone (GH)-secreting pituitary adenomas. Transsphenoidal surgery remains a treatment of choice for restoring GH to normal levels. The aim of this study was to illustrate the relationship between some factors and transsphenoidal surgery outcomes.
Patients and methods
We retrospectively analysed the outcome of 31 patients with acromegaly after initial endoscopic transsphenoidal surgery in three university hospitals from 1988 until 2017. Laboratory values and tumor imaging data were collected pre and post-operatively. The criteria of biochemical remission were GH levels < 0.4 ng/ml after oral glucose tolerance test (OGTT) and normal IGF–I levels for age and sex within the first 3 months after surgery.
Results
Median age of the 31 patients was 37 [13; 77] at the time of surgery, with a female/male ratio of 1.35. Microadenomas were found only in one patient (3.2%) and macroadenomas in 30 patients (96.7%). Three months after surgery, a *radiological complete* response at MRI was achieved in 10 patients (32%) but biochemical remission was obtained in only 5 patients (16%). Age at diagnosis, gender, preoperative IGF-1, random GH levels and nadir GH/OGTT were not predictive of poor outcomes. MRI-results: a *radiological complete* response was obtained in significantly smaller tumors compared with those with an incomplete resection (median diameter 17 vs 31 mm; $P=0.02$). Tumor diameter greater than 15 mm ($P=0.03$) and intracavernous extension ($P=0.03$) were significantly associated with a higher probability of incomplete tumor resection.
Conclusion
Intracavernous invasion and tumor size seem to be the strongest predictive surgical outcome parameters. Earlier detection of acromegaly would be the key to improve overall outcomes.

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Surgical outcomes in cushing disease: Endoscopic transsphenoidal pituitary surgery

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Introduction
Endoscopic transsphenoidal pituitary surgery has become the first line method for removal pituitary tumours. A new way to see the surgical field and the cooperation of two neurosurgeons has supposed a revolution in the area.
Objetives
Analyse surgical outcomes and complications of a cohort of patients from a single center who underwent ETPS for Cushing disease.
Methods
Descriptive prospective-retrospective study including patients who underwent ETPS for Cushing disease in a single center from January/2013 to June/2018.
Results
27 patients underwent ETPS as first line treatment for Cushing disease, 22 (81.48%) were women; mean surgical age was 42.74 ± 19.77 years. 22 (81.48%) were microadenomas. Cavernous invasion according to Knosp score 3-4 was found in 3 (11.1%) patients. At december/2018, with a mean follow-up 2.42 ± 1.34 years, 22 (81.48%) were cured, this rate was similar for invasive tumours (100%), non invasive (79.16%), microadenomas (81.89%) and macroadenomas (80%). Before surgery only 1 patient has a campimetric commitment with a partial recovery after the intervention. Hormone dysfunction was found in 2 (7.4%) patients, 1 with hypothyroidism and hypogonadism and 1 with hypothyroidism. After the intervention, new thyroid dysfunction was observed in 2 (7.4%) patients, gonadal in 1 (3.7%) and permanent steroid deficiency in 11 (40.74%). 9 patients underwent ETPS after a microscopic transsphenoidal approach. 6 (66.67%) women; mean surgical age 42.62 ± 13.82 years. 6 (66.67%) macroadenomas, 3 (33.33%) 2 (22.22%) and 1 adenoma with cavernous sinus invasion. After this second surgery and at december/2018, with a mean follow-up 2.32 ± 1.37 years, 6 (66.67%) were cured, all (100%) macroadenomas and invasive tumors were cured, no invasive tumors cure rate was 62.5%, microadenomas cure rate was 50%. 2 patient has a campimetric commitment with a partial recovery after the intervention. After surgery, 3 (37.5%) new diabetes insipidous, 1 (11.1%) new steroid deficiency, 1 thyroid commitment were found.
Conclusions
ETPS is an effective and secure surgical approach as first line treatment in Cushing disease, with better outcomes than traditional approaches. Cure rates in reintervention after MTS put ETPS as an elective second line treatment in patients with relapse of disease after a first surgery. According to this results, the role of ETPS in algorithm treatment may be restated and reintervention could be propose before other second line treatment, at least in patient who underwent MPS as first line surgery.

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Acromegaly and papillary carcinoma of the thyroid: a case report

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Introduction
The pituitary adenoma is a benign hyperplasia of the pituitary gland; it often implies the presence of pathologies of the thyroid gland. The relation between the thyroid volume, the rate of IGF1 and the duration of the disease is not well specific, long time the secretion of GH and IGF1 have been associated with disorders of thyroid function.
Presentation of the case
We report the observation of a 37-year-old woman operated on in 2016 with a transphenoidal pituitary macro-adenoma with regression of the tumor and a left loboisthmectomy of a diving goiter classified papillary carcinoma. It should be noted that the level of IGF1 remained constant at twice normal despite surgery. The patient received a Levothyrox-based treatment. She represents for headaches with BAV, the pituitary MRI performed notes an upsurge of the pituitary adenoma and in parallel a recurrence at the level of loboisthmectomy stump and also a right thyroid nodule classified TIRADS 4. The assessment of neuroendocrine tumors is negative. The rate of thyroglobulin is increasing, four times more than 2 years ago. A second revision is planned in our patient with monitoring of thyroid function.
Conclusion
Although data on the coexistence of acromegaly and thyroid cancer remain controversial, it is important to diagnose early stage disease, eliminate thyroid cancer, and follow-up with careful evaluation of thyroid cancer. thyroid function to prevent recurrence. Also the upsurge of these two tumors can be explained by the high rate of IGF1.

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Modification of breast in hyperprolactenemic conditions

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Objective
Evaluate effect of hyperprolactinemia on breast's conditions.
Methods
Investigated 2 groups of patients with average age 34.9 ± 7.5. The first group is 30 women with hyperprolactinemia. Inclusion criterion was an increase in prolactin level above 1000 mU/l with a double determination, as well as duration of at least 6 month, lack of taking antidepressants and oral contraceptives for last 3 month before the start of study, absence of concomitant endocrine disruption: hypotiroidism, thyrotoxicosis, acromegaly. Clinical examination included anamnesis and determining prolactin, E2, TSH, LH, FSH, hormone levels, MRI-scan of brain with targeted pituitary research, ultrasound diagnosis of breasts, small pelvis, mammography, gynecologist and breast specialist consultation. The second control group includes 18 healthy women. Criteria for inclusion considered normal level of prolactin in double determination, lack of complaints during palpation, lack of lactorhea.The control group is similar to the first group was examined for hormonal and instrumental methods of research.
Results
In the first group level of prolactin ranged from 1005.1 to 8404.6 mU/l. On MRI-scan were identified: macroprolactinomas had 2 woman (6.66%), microprolactinomas had 10 (33.3%), hormonally inactive pituitary adenomas had 4 (13.3%), ETSS had 8 (26.6%), pituitary cystoadenoma had 1 (3.33%), unfundibulum had 1 (3.33%) and no pathology of the pituitary gland had 4 (13.3%). 26 women had colostrum, 4 woman had no discharge from the breast. Lactorhea severity assessed on a scale: 1 degree-single drops when pressed hard (+), 2 degree- abundant (++), 3 degree- spontaneous release of milk (+++). 4 patients had grade 1; 21 patients gad grade 2; 1 patient had grade 3. For results of mammological studies used Rozjkova's classification (1993). In the first group, 13 women had fibrocystic mastopathy (43.3%) 4 woman had- adenosis (13.3%), 5 woman had fibro fatty involution (16.6%) and in the 8 women (26.6%) the structure of breast did not differ from the norm. In women from the control group, fibrocystic mastopathy in 7 patients (38.8%),of which two had adenosis (11.1%), and 3 patients had fibro fatty involution (16.6%) and 6 patients had no deviations (33.3%).
Conclusion
Hyperprolactinemic condition is the result of damage to hypothalamic pituitary area & pituitary gland in 26 patients. Modification of the breast structure in hyperprolactinemic conditions is characterized by fibrocystic mastopathy (60%) ,fibrofatty involution (16.6%) and adenosis (13.3%). It's necessary to consider the higher level of prolactin, the higher the risk of fibro-fatty involution by 50%. With normalization of prolactin levels, the glandular tissue tends to increase.

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Growth retardation and brain imaging

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The diagnostic strategy in the face of stunted growth currently leaves an important place for brain imaging, which looks for growth hormone deficiency, a 'craniopharyngioma' tumor, or a malformation of the midline or pituitary region. The purpose of our work is to look for abnormalities of the pituitary area in case of stunted growth.

Patients and methods
A retrospective descriptive and analytical study involving 69 patients (30 girls/9 boys) with a mean age of 8.5 years ±8 years, the patient size was <−2 S.D. according to the Sempé and Sempé growth curve. Pedron with an average of 117.6 cm ±31.
Result
Of the 29 patients with growth hormone deficiency who had magnetic resonance imaging, 20 had normal MRI. 3 patients had an interruption of the pituitary stalk, moreover the imaging revealed pituitary atrophy in 04 cases and its thickening in 01 cases and a craniopharyngioma.
Conclusion
There is an extreme variety of pathology of the sellar region in children, but only a few are common. The diagnosis requires anatomical precision, the most precise tissue identification, and therefore a careful and complete imaging technique.

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Surgical outcomes in acromegaly disease: endoscopic transsphenoidal pituitary surgery

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Introduction
Endoscopic transsphenoidal pituitary surgery has become the first line method for removal pituitary tumours. A new way to see the surgical field and the cooperation of two neurosurgeons has supposed a revolution in the area.
Objetives
Analyse surgical outcomes and complications of a cohort of patients from a single center who underwent ETPS for GH secreting pituitary tumours.
Methods
Descriptive prospective-retrospective study among patients who underwent ETPS for GH pituitary tumours in a single center from January/2013 to June/2018.
Results
39 patients underwent ETPS as first line treatment, 24 (61.54%) were women, 15 (38.46%) men, mean surgical age was 48.57 years. 5 (12.82%) were microadenomas and 34 (87.18%) were macroadenomas, 8 (20.51%) were bigger than 25 mm. Cavernous sinus invasion according to Knosp score 3-4, was found in 20 (51.28%) patients, 5 (12.82%) patients had Knosp 4. At december/2018, after a follow-up of 3.1±1.14 years, 28 (71.79%) patients remained cured; cure rate was 100% for microadenomas, for no invasive tumours was 89.47%, for invasive tumours 55%. If we don't include Knosp 4 tumours (0% cure rate), cure rate for invasive tumours would be 68.75%. 5 patients underwent ETPS after an unsuccessful microscopic transsphenoidal approach. 100% were women; mean surgical age 47.94 years. 100% macroadenomas, 2 (40%) bigger than 25 mm and 3 (60%) with sphenoidal sinus invasion. At december/2018, after this second surgery and with a mean follow-up of 2.1±0.48 years, 3 (60%) patients remained cured. Non cured patients (2, 40%) were non invasive and bigger than 25 mm tumours. From all operated patients, 8 (18.18%) had campimetric commitment; after the intervention a full recovery was observed in 3 (37.5%) patients and partial recovery in 5 (62.5%). As hormonal complications, diabetes insipidous was observed in 2 patients, steroid deficiency in 3 patients, thyroid deficiency in 3 and gonadal dysfunction in 1 patient.
Conclusions
ETPS is an effective and secure surgical approach as first line treatment in GH secreting adenomas. ETPS is an effective approach even in highly invasive adenomas with Knosp 3 sinus invation.
Cure rates in reintervention from MTS put ETPS as an elective second line treatment in patients with relapse of disease after a first surgery.

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Factors predicting dopamine agonist treatment withdrawal in prolactinoma patients

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Aim
Dopamine agonist (DA) therapy is recommended as first-line treatment for prolactinomas, albeit with long treatment duration and high recurrence rate after treatment withdrawal. The aim of this retrospective study was to evaluate predictors for successful DA withdrawal.
Methods
The study included 59 prolactinoma patients (39 female, 20 male; age 34 (18–82) years) that were treated with DA (35.6% on cabergoline); the duration of treatment was 71 (12–216) months. Median tumor size at diagnosis was 10 (2–47) mm. Thirty two patients had macroprolactinomas. Thirty seven patients had disease recurrence or significant increase in PRL level during DA dose tapering, while 22 patients had normal PRL level on low DA dose (bromocriptine <2.5 mg/day or cabergoline ≤ 0.25 mg/week), hence treatment withdrawal was attempted. Patients were divided in remission and recurrence group, and factors that predict recurrence were evaluated.
Results
Patients in whom withdrawal was attempted had lower prolactin (PRL) level at diagnosis (104 (50–6780) ng/L vs 340 (58–8870) ng/L, $P=0.021$), smaller baseline tumor diameter (7 mm (2–43) vs 15 mm (2-47), $P=0.028$) and lower maximal bromocriptine dose during treatment (5 mg (1–23) vs. 10 mg (1–43), ($P=0.003$). Eleven of 22 patients (50%) had recurrence of disease after cessation of DA. Patients in remission, compared to those with recurrence, had lower baseline PRL level ($P=0.055$, OR 0.984, CI 0.969–1.000) and larger tumor size ($P=0.06$, OR 1.557, CI 0.982–2.467) but the differences were not significant.
Conclusion
Long term DA treatment resulted in remission in 18.6% of our patients. Pretreatment prolactin level and tumour size have no predictive value for disease remission.

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Medical treatment of cushing's disease during pregnancy with Ketoconazole and Cabergoline – Report of 3 cases

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Abstract
Cushing's syndrome (CS) during pregnancy is a rare condition with fewer an 200 cases reported in the literature, However, because CS results in increased fetal and maternal complications, its early diagnosis and treatment are critical. During pregnancy, 40-50% of cases are caused by adrenal adenomas, while Cushing's disease (CD) accounts for only one third of the cases. We describe here 3 patients with CD who needed to be treated during pregnancy.
CASE 1
A 25-year old woman had the diagnosis of CD confirmed in April 2010. Four months later, she was submitted to a transsphenoidal surgery (TSS) which failed. The patient was given ketoconazole and reached UFC normalization at a dose of 800 mg/day. Two years later, she became pregnant and ketoconazole was withdrawn. However, due to progressive increase in UFC, blood pressure and blood glucose levels, ketoconazole was re-started at 20 weeks of gestation, which resulted in hormonal and clinical control. The patient gave birth to a healthy male newborn at 38 weeks of gestation, APGAR 9/9.
CASE 2
A 30-year old woman had the diagnosis of CD confirmed in October 2012. Two months later, she was submitted to an unsuccessful TSS. The patient was treated with ketoconazole, reaching UFC normalization at a dose of 800 mg daily. Forteen months later, she became pregnant and ketoconazole was withdrawn. However, due to worsening of clinical status with increase of blood pressure and blood glucose, ketoconazole was re-started at 20 weeks of gestation (600 mg/day), which enabled transient hormonal, biochemical and clinical control. However, due to progressive increase of UFC, cabergoline was added at the 30th week, leading to hormonal normalization at the dose of 2 mg/week. The patient gave birth to a female newborn at 37 weeks of gestation, weighing 2850 g, 48 cm in length, Apgar 9/9, no congenital abnormalities, and normal female genitalia.
CASE 3
CD was confirmed at 30th week of gestation in a 27-year old woman who presented with excessive weight gain, easy bruising and hypertension. The CD diagnosis was based on the elevation of both UFC and midnight salivary cortisol (MNSV), plasma ACTH of 44.5 pg/ml and a 1.2 cm pituitary adenoma depicted on MRI scan. The patient was given CAB, reaching UFC normalization and

improvement of clinical status at the dose of 3 mg/week. The patient was submitted to a successful TSS 3 months after the delivery of a healthy male newborn.

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GH Deficiency in children: clinical, biological and radiological characteristics an experience of a tertiary care center

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Introduction
GH deficiency (GHD) represents less than 20% of short stature in children, the clinical, biological and radiological characteristics differ from one population to another.
Methods
Our retrospective study describe 59 children (37 boys and 22 girls) with confirmed GHD. The average age of discovery was 95 months. About 20.3% of these children were born from a consanguineous marriage. Family history of anterior pituitary insufficiency was present in 8.5% of cases and 22% of these children had a personal history of general disease of which 1.7% (3 patients) had Fanconi's disease associated with GH deficiency. The initial reason for consultation was mostly a growth delay (78%), other reasons such as pubertal delay, systematic hormonal exploration and the association of staturoponderal delay with pubertal delay were less frequent. A dysmorphic syndrome was present only in 2 patients and abnormalities of the urogenital system in boys were not frequent (a micropenis was found in 6.8% of cases, testicular ectopy in 3.4% of cases and cryptorchidism in 1.7% of cases). Celiac disease was eliminated in 69.5% of patients and was not done in the rest of patients. Karyotype was not performed in most patients (74.6%) and was normal in 8.5% of cases. The mean bone age was 68.38 months. Regarding the positive diagnosis of GH deficiency, the average IGF1 in our patients was 92 ng/ml. The stimulation tests used were the catapressan test which revealed a partial deficit in 20.3% of cases, a total deficit in 59.3% of cases, it was normal in 3.4% of cases and the insulin hypoglycemia test which showed a partial deficit in 13.6% of patients, a total deficit in 64.4% of patients. The avlocardyl/glucagon test was rarely performed. Regarding imaging, the first radiological exam requested was hypothalamic-pituitary MRI which revealed an hypoplastic pituitary gland in 15.3%, an isolated posthypophysis ectopic in 3.6% of cases, a stem section syndrome in 8.5% of cases and it was normal in 44.1% of patients. Somatotropic deficit was total and isolated in 45.3% of cases, partial and isolated in 10.9% of cases, combined and total in 39.1% of patients and partial and total in 3.1% of patients.
Conclusion
Our results are consistent with the results of the literature regarding the male predominance of GHD, the average age of discovery and the delay of the diagnosis and the heterogeneity of the etiologies.

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P1095

Poor response to pre-surgical treatment with Somatostatin Receptor Ligands is associated with diabetes in patients with acromegaly

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Purpose
To evaluate whether the degree of response to surgical pre-treatment with somatostatin receptor ligands (SRL) predicts alterations in blood glucose levels.
Patients and methods
We retrospectively studied 181 patients attending the Unit of Neurosurgery of our Hospital prior to transsphenoidal surgery. All patients had a diagnosis of acromegaly (nadir GH during OGTT >0.4 ng/ml; and IGF-I above age-standardized UNL); diagnosis of diabetes (DM) and impaired fasting glucose (IFG) was performed on fasting blood glucose (FBG) according to the American Diabetes Association guidelines; all parameters of the pituitary axes were determined. The response to SRL treatment was determined as percent change of GH levels. Data are presented as mean$\pm$s.d.; Continuous data normally distributed were analyzed using a two-tailed Student's t test to compare two groups, and one-way ANOVA to compare several groups, followed by the Bonferroni post-hoc procedure for pairwise comparison of groups after the null hypothesis was rejected ($P<0.05$); categorical data were analyzed by chi-squared test.
Results
97 (54%) patients with acromegaly underwent pre-surgical treatment with SRL; we found no difference in age (53 ± 11 vs 51 ± 12 years; $P=$NS) and sex (M/F: 51/46 vs 43/41; $P=$NS) between SRL treated and non-treated patients. We found no difference in FBG between SRL treated vs non-treated patients. In contrast, we found increased proportions of IFG and DM patients in SRL treated when compared to non-treated patients (euglycemic: 45%, IFG: 42%, DM: 13% vs euglycemic: 70%, IFG: 22%, DM: 8%, respectively; $P=0.006$). In addition, SRL treatment increased the odds ratio of IFG and DM (OR 4.7; 95%CI 2.1-10.3). When considering the degree of response to SRL pre-surgical treatment, we found that poor responders displayed at the time of surgery glycemias diagnostic of DM; whereas, good responders displayed glycemias in the range of IFG (percent change in GH levels 50 ± 35% vs 79 ± 22%, respectively; $P<0.05$).
Conclusions
Our findings show that the proportion of patients with acromegaly undergoing surgery with glycemic levels diagnostic of DM, is modest. Interestingly, pre-treatment with SRL represents an independent risk factor for high glucose levels. Moreover, among patients on SRL pre-treatment, the ones that respond poorly are the ones that at the time of surgery display glycemias diagnostic of DM. Our findings suggest that SRL pre-treatment may predispose to worsened glucose metabolism but selectively affecting those patients in whom biochemical control is not reached.

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P1096

Partial hypopituitarism and primary hypotiroidism associated with Diamond-Blackfan Anemia

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Introduction
Diamond-Blackfan anemia (DBA) is a severe congenital erythroid aplastic anemia with autosomal dominant inheritance. It is a rare disease (incidence 1/150000) and usually is discovered during the 2 first years after birth. Treatment includes steroids, blood transfusions and bone-marrow transplantation.
Case report
A 31 year-old woman with DBA had received multiple treatments including transfusion support since birth. Consequently, she had developed heart hemochromatosis disease which caused severe biventricular failure. Osteoporosis with vertebral compression fractures was noted in her clinical personal history. During hospitalisation due to heart failure, primary hypothyroidism (TSH 25.2 mcU/ml and free T4 0.56 ng/dl) with negative thyroid autoimmunity was discovered. Low dose of levothyroxine was started. Due to the patient's short stature and the presence of secondary amenorrhea for many years a pituitary hormonal study was performed showing FSH 0.8 mUI/ml; LH 0.2 mUI/ml; 17-beta-estradiol 16 pg/ml; PRL 26.4 ng/ml; GH 5.99 ng/ml; IGF-1 19 ng/ml [normal range (NR): 115–307]; ACTH 32.7 pg/ml (NR: 9-55); and Cortisol 19.5 mcg/dl compatible with central hypogonadism and GH deficiency. Albumin-corrected hypocalcemia (7.5 mg/dl) was also discovered. Pituitary MRI showed a marked hypointensity of the adenohypophysis in both T1 and T2 images suggestive of iron deposits. At the eleventh day at the hospital patient died due to cardiorespiratory arrest. Hemochromatosis secondary to multiple blood transfusions in DBA can lead to multiple endocrinonopathies, as was seen in our patient who presented primary non-autoimmune hypothyroidism due to probable iron thyroid infiltration and partial hypopituitarism due to iron pituitary infiltration. In our case we could not rule out the coexistence of an associated hypoparathyroidism by iron deposits in the parathyroid glands.
Conclusion
The diagnosis of DBA, particularly in those patients undergoing multiple blood transfusions, implies the need to screen multiple endocrinopathies secondary to iron deposit disease in different endocrine glands.

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P1097

Predictive factor of hypopituitarism in prolactinoma

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Intoduction
Pitiutary tumor is considered as the first etiology responsable of secondary hypopituitarism. Hypogonadotropic hypogonadism is the most commonly reported lesion.
Meterials and methods
It is a retrospective study including 77 cases of prolactinoma. The data collection was done over 17 years, between 2000 and 2017.
Results
Gonadotropic deficiency was confirmed in 48 patients (63.6%). A significant negative correlation was found between prolactinoma size and LH level ($r=-0.348$ $P=0.006$). This correlation was present but not significant with the level of FSH. In men, a negative correlation was found between testosterone levels and prolactinoma size. In women, we did not show a correlation between estradiolemia and tumor size. Thyrotropic deficiency was confirmed in 18 patients (25.3%). The hormonal assessment confirmed the corticotropic deficit in 4 patients (4.2%). A total of 58 (75.3%) patients had dissociated hypopituitarism among which, 30 (51.7%) had isolated hormone deficiency, and 28 (48.2%) had 2 or 3 pituitary deficits.Gonadotropic deficiency was 3-fold greater than thyrotropic deficiency and 15-fold higher than corticotropic deficiency. A significant positive correlation was found between the tumor size and the number of deficits observed ($P=0.000$ and Pearson $r=0.594$).
Conclusion
It seams that prolactinoma size was the most important predictive factor influencing the appearance of hypopituitarisme. For that we must fight against the increase of the tumor size to avoid this complication.

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P1098

The long time observation, treatment modalities and outcomes in patients with childhood/adult onset of craniopharyngioma

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Background
Craniopharyngiomas are rare, relatively benign, slowly growing intracranial tumors originating in pituitary gland embryonic tissue. They may present at any age, with two peaks of occurrence in children and in older adults. Clinical symptoms are the result of mass effects. Treatment options include surgery, radio- and chemotherapy and unfortunately are connected with a high ratio of postoperative pituitary insufficiency.
Aim
To present the long time observation, treatment modalities and outcomes in patients with childhood/adult onset of craniopharyngioma.
Methods
A retrospective analysis of 17 patients (11M/6W)was performed. The average follow-up time was 11.9 years (s.d. 8.3) with the longest observation lasting 31 years (6/17 patients with childhood onset).
Results
All patients were operated at a mean age (MA) of 28.4 years (s.d. 18.3), with 11/17 (64.7%) operated once and 6/17 (35.3%) requiring at least one re-operation. 8/17 (47.1%) patients underwent subsequent radiotherapy. In most patients the first symptoms were related to the tumor mass. All of the patients (17/17 – 100.0%) developed secondary hypothyroidism. Gonadal axis insufficiency was diagnosed in 16/17 patients (94.1%), while 82.4% (14/17) of the patients presented with secondary hypocortisolism. One patient (1/17, 5.9%) required transient substitution of glucocorticoids. Diabetes insipidus was found in 12/17 (70.6%) of cases. 16/17 (94.1%) of the patients had multiple hormonal deficiencies; one patient (1/17, 5.9%) was diagnosed with isolated thyroid axis insufficiency.
Conclusions
The diagnosis, management and treatment of craniopharyngiomas remains challenging. The diagnosis is usually delayed. The treatment leads to multiple hormonal deficiencies and a decreased QoL. Long term observations might help better the understanding of the disease and lead to the improvement of its management.

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P1099

Pituitary apoplexy (PA) – a relatively rare condition requiring early recognition, individualized treatment and longterm follow-up

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Background
PA is a clinical syndrome secondary to hemorrhage or infarction of pituitary tumour, presenting with sudden onset headache and oculomotor palsy. PA may be managed conservatively in patients without visual disturbances.
Aim
To describe PA patients illustrating typical aspects and peculiarities.
Results
Case 1, a 49 years old (yo) male, presented for loss of consciousness in the ER. MRI showed a giant pituitary tumour, which was operated transcranially. Pathology revealed a pituitary adenoma, with extreme hyperprolactinemia, uncontrolled by high-dose cabergoline (5 mg/week). Full remission was achieved following external irradiation and longterm cabergoline. At last follow-up, prolactinemia was normal off cabergoline. Panhypopituitarism was controlled on levothyroxin, prednisone and testosterone. Case 2, a 2.10 m tall male, presented with acromegalic features at age 59 and negative history for PA symptoms. MRI showed a pituitary cystic mass. IGF-I was normal (0.81 $\times$ ULN) and GH suppressed during OGTT, suggesting spontaneous cure, presumably due to asymptomatic PA. Case 3, a 62 yo male, presented with thunderclap headache and oculomotor nerve palsy. MRI showed a sellar mass compressing the chiasm, and he underwent transcranial surgery, resulting in empty sella. Pathology and hormonal evaluation demonstrated a non-functioning pituitary adenoma. He associated macular degeneration and developed severe loss of visual acuity and panhypopituitarism. At last follow up, the tumour showed recurrent intrasellar growth. Case 4, a 70 yo female on oral anticoagulants for atrial fibrillation, presented in an Emergency Department for severe headache, nausea and emesis. CT imaging showed a suprasellar mass abutting the chiasm, with subtle temporal superior right quadranopsia. Hormonal evaluation revealed a non-functional tumour with no pituitary insufficiency and symptoms resolved with conservative management. Case 5, a 78 yo male presented for severe headache and diplopia. He displayed typical acromegalic features, included progressive acral enlargement since his 30's. IGF-I was 8 $\times$ ULN and pituitary CT demonstrated a large macroadenoma. Delayed (1 month) transsphenoidal surgery led to complete biochemical remission.
Conclusions
Our cases illustrate key aspects of PA: diagnosis can be missed even with classical presentation, more so in asymptomatic patients. PA can lead to apparent cure of both non-functional and functional adenomas, yet longterm follow-up is required for the risk of recurrence. Optimal management (conservative vs. surgical) is still debated and should be individualized.
Keywords: pituitary apoplexy, severe headache sellar mass
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P1100

Outcome of prolactinoma during pregnancy

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Introduction
Infertility is a classic consequence of prolactinoma in women. The treatment of hyperprolactinemia allows the restoration of ovulatory cycles and therefore of fertility in 80–90% of cases.

Methods and materials
The study is a retrospective cohort study done over 17 years from 2000 to 2017. It includes 77 cases of prolactinomas among which 12 women had one or more pregnancies after the diagnosis of prolactinoma.
Results
Among our 12 patients, 10 of them were presented for primary infertility. The average age of patients at the time of pregnancy was 39.9 years (19–44 years). In these patients, 4 had one or more abortions during the first trimester of pregnancy. It was a microprolactinoma in 10 cases with an average size of 5.4 mm (range 0 to 14 mm). All women were medically treated before pregnancy. During pregnancy, no clinical worsening was reported in these patients. Two women had pituitary MRI. Imaging showed stable microprolactinoma for one patient and macroprolactinoma increasing in size for the other. Treatment with agonist dopaminergic was discontinued on the discovery of pregnancy in nine patients and continued in three patients. The continuation of the treatment was indicated in a woman in front of the increase of the size of the adenoma in the MRI. For the other two women, they did not consult during their pregnancies. All women had vaginal birth. Two deliveries were premature. No cases of neonatal malformation were noted. The resumption of medical treatment was done 8 months after delivery (range 3–12 months) for all patients. The majority of women were breastfeeding (9 cases). There were 7 cases of microprolactinoma and 2 cases of macroprolactinoma. The duration of breastfeeding was on average 11.6 months with extremes ranging from 1 month to 24 months. None of these women showed worsening clinical signs or increased prolactin levels during lactation.
Conclusion
The reduction of size tumor or disappearance of prolactinoma on MRI before pregnancy are considered as predictive factors of remission. For this, the evolution of the tumor size during pregnancy is different according to whether it is a micro- or a macroprolactinoma.

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P1101

Pegvisomant: daily versus non daily administration a single centre real life study

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Background
Pegvisomant (PEG) is a second line medical treatment for active acromegalic patients. PEG efficacy is between 61.5 and 92% and even if it is administered daily its long half-life suggests a possible use with a non-daily regime.
Aim
We aim to compare acromegalic patients on daily PEG administration (DP) with patients on non-daily PEG administration (NDP).
Methods
We studied 43 acromegalic patients under PEG treatment between 2005 and 2017. Patients were divided into two groups: DP and NDP. DP were evaluated three times: at PEG start (T0), at PEG maximum dose after up-titration period (T1) and at the last follow-up visit (T3); after T1 we started the non-daily administration and only the NDP patients had an additional evaluation after 6 months (T2). At every time (T0, T1, T2, T3) we collected PAQ15 questionaries, anthropometric, clinical and endocrinological data.
Results
14/43 patients were switched to a non-daily therapy and, before T3 only 1 patient returned to daily therapy because of increased lipohypertrophy. Both DP and NDP patients had a significantly decreased IGF-1 levels (DP: IGF-1 ULN: T0 2.30 ± 1.06, T1 1.08 ± 0.37, T3 1.20 ± 0.46; $P<0.000001$ with mean follow-up 65 ± 47 months vs NDP: IGF-1 ULN: T0 1.95 ± 0.81, T1 0.74 ± 0.25, T2 0.91 ± 0.29, T3 0.87 ± 0.26 $P<0.000001$ with mean follow-up period 81 ± 39 months). DP patients mean PEG dose was 27 ± 8 mg/die with 20% of the patients on combination therapy (CT) at T1 and 24 ± 8 mg/die with 35% of the patients on CT at T3; NDP patients mean PEG dose was lower at T2 than at T1 (T2 vs T1: 12 ± 7 -7% of patients on CT- vs 16 ± 9 mg/die -14% of patients on CT-, $P<0.01$) with no difference on IGF-1 ULN levels (IGF-1 ULN: T2 0.91 ± 0.29, T3 0.89 ± 0.26). At T1, NDP patients presented lower IGF-1 levels, lower PEG dose, shorter mean drug titration period when compared with DP; at T3, NDP patients had lower IGF-1 levels and lower mean PEG dose when compared with DP. PAQ15 was not different in DP patients when compared to NDP patients.
Conclusions
In selected patients, non-daily PEG treatment is a good therapeutic option to control disease activity, reducing PEG dose and ameliorating compliance and patients' quality of life.

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P1102

The significance of low TSH value – case report

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Introduction
Suppression of TSH usually indicates hyperthyroidism. But the etiology of low TSH is very wide, including pituitary pathology. In this report we describe a case diagnosed and treated for hyperthyroidism. Later on, the persistence of suppressed TSH after therapy of hyperthyroidism was due to a GH-secreting pituitary adenoma.
Case presentation
A 47-year old woman was referred to our clinic for investigations, due to thyroid pathology. The patient was diagnosed in 2016 with hyperthyroidism, due to Toxic adenoma. Therapy was antithyroid drug Methymazole was given for few months and radioiodine treatment was done thereafter. After therapy with radioiodine the patient developed hypothyroidism, TSH increased and Levothyroxine therapy was started. After 1 year, laboratory determinations revealed low TSH and low/normal FT_4. The patient developed exophthalmos. Levothyroxine therapy was stopped, antithyroid therapy was restarted but TSH had continuing to be suppressed. Thyroid ultrasound presented a right nodular goiter, with a solid nodule with increased Doppler vascularization. Thyroid immunological determinations revealed high titers for TSH-Receptors antibodies and anti-Thyroglobulin antibodies, indicating an autoimmune thyroid disease. Laboratory determinations at admittance in our Clinic detected high values for Phosphorus (5.8 mg/dl, NR 2–4.5) and Alkaline Phosphatase (127 U/l). Renal failure and other frequent causes of hyperphosphatemia were excluded. At clinical examination, no signs of hyperthyroidism were detected, but a mild form of mandible prognathism and enlarged hands were notified. IGH-1 determinations revealed high values (891 ng/ml) and increased GH level didn't suppress after OGTT (GH after OGTT 14.6 ng/dl). Acromegaly was diagnosed and pituitary MRI was performed, that indicated a 13mm pituitary adenoma. The suppression of TSH after treatment with radioactive iodine was due to a pituitary insufficiency.
Conclusion
This case, with an associated thyroid and pituitary pathology, highlights the multiple etiologies for TSH suppression. The presentation illustrates the importance of clinical examination of the patient and the values of all pathological laboratory determinations.

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P1103

Mild weakness as an only symptom for panhypopituitarism with empty sella syndrome: case report

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Introduction
Weakness is one of the most common complaints among the patients. Clinical manifestations of a hypopituitarism depend on the extent of hormone deficiency and may be non-specific and thus the diagnosis is often missed. The progressive loss of pituitary hormone secretion is usually a slow process, which can occur over a period of months or years.
Clinical case
A 62 years old women who complained of mild weakness mostly in the evenings in the past 3 months was referred to an endocrinologist in Vilnius University hospital Santaros clinics. Her accompanying documentation reported a background of hypothyroidism, biochemical blood test showed low level of thyroid stimulating hormone (TSH) 0.05 mU/l (normal 0.4–4.1 mU/l), FT4 – 11.90 pmol/l (normal 9.0–19.0 pmol/l). Patient was treated with 75 μg of levothyroxine at least 15 years. Patients medical history revealed primary hypertension, menopauses from age of 30 years old, short period of breastfeeding due to insufficient lactation. Her list of regular medications comprised of valsartan and hydrochlorothiazide. Patient denied any headaches or visual disturbance. She also denied dizziness on standing, but her blood pressures revealed a significant postural drop (110/70 mm Hg lying, 88/64 mm Hg standing).
Management and Outcome
Further pituitary function testing also revealed a low level of prolactin – 31.9 mU/l (108.7–557.1 mU/l), low insulin- like growth factor-1 – 18.8 μg/l (normal 43–220 μg/l), low luteinizing hormone – 0.09 U/l (normal 5.16–61.99 U/l) and

low follicle- stimulating hormone – 0.3 U/l (normal 26.72–13.41 U/l). A synacthen stimulation test was arranged which demonstrated an inadequate cortisol response (basal: 139 nmol/l, 30 minutes: 338 nmol/l, 60 minutes: 416 nmol/l) and a baseline ACTH level within the normal range. These results were suggestive of pan- anterior hypopituitarism, and a subsequent MRI pituitary confirmed an almost empty sella with a small area of residual pituitary tissue visible. Finally, we prescribed her hydrocortisone 20 mg and levothyroxine 0.1 mg daily. In subsequent follow-up the patient's symptoms resolved and her life status had improved.

Conclusion

High index of suspicion is required to seek hypopituitarism in patients with non-specific symptoms such as mild weakness. In our case, the diagnosis and treatment of his hypothyroidism and adrenal insufficiency were delayed, potentially early diagnosis would have a significant effect on her quality of life.

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P1104

Prevalence and study of neuroendocrine deficits in a series of 75 patients following traumatic brain injury

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Introduction

Clinical research studies over the last 15 years have reported a significant burden of hypopituitarism in survivors of traumatic brain injury (TBI). However, these endocrine anomalies remain underdiagnosed.

Patients and methods

We are studying data from a series of 75 TBI patients. They had a basal hormonal test, and dynamic confirmation tests if necessary. Somatotropic deficiency was defined by growth hormone (GH) remaining under 3 µg/l on two dynamic tests, with glucagon or insulin. Gonadotropic deficiency was defined in men by a total testosterone lower than 10 nmol/l without peripheral cause. Gonadotropic deficiency was defined in non-menopausal women with amenorrhea, and low estradiol in absence of elevated FSH. Gonadotropic deficiency was defined in postmenopausal women by inappropriately low FSH and LH. Corticotropic deficit was defined by a basal cortisol less than 180 µg/l, without stimulation by a glucagon, insulin or synachten test. Thyrotrophic deficit was defined as low free T4 without compensatory elevated TSH. Hyperprolactinemia was defined as prolactin greater than 15 µg/l, TSH less than 2 mUI/l, and absence of interfering medication. Prolactin deficiency was defined by prolactin under 4 µg/l. Diabetes insipidus was defined by the need to use vasopressin to correct a hydro-electrolytic disorder.

Results

The prevalence of neuroendocrine disorders in this series is 37% (28/75). Hypopituitary patients had a mean age of 41 ± 15 years (19M/9F). TBI patients with endocrine deficiencies had significantly higher BMI (29 ± 4.4 vs 25 ± 4.4 kg/m^2, $P < 0.001$) and lower IGF1 (134 ± 54 vs 161 ± 57 ng/ml, $P = 0.04$) than TBI patients without hormonal deficiencies. A first glucagon test was abnormal in 22/43 patients, a second insulin or glucagon test was abnormal in 6/12 patients. The biological explorations found: somatotropic deficits (17/28), gonadotropic deficits (13/28), corticotropic deficits (16/28), thyrotrophic deficits (4/28), hypoprolactinemia (3/28), hyperprolactinemia (2/28), and diabetes insipidus (1/28). Pituitary MRI objective: interruption of stem (1 case), aspect of empty sella (2 cases), hypothalamic hemorrhage (1 case). Hormonal substitution improved quality of life: data is still under analysis.

Conclusion

Searching for a neuroendocrine deficit is necessary during the assessment of a patient with TBI. We suggest an approach to the diagnosis of post-traumatic hypopituitarism in routine clinical practice. More importantly, this search should also be integrated into medical insurance expertise. Therefore, it is of great importance to evaluate the pituitary function and take appropriate hormone replacement in TBI patients with apparent clinical symptoms and hormonal disturbances.

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P1105

Aggressive corticotroph adenoma

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Aggressive pituitary tumors (APT) causing Cushing's Disease are very rare, difficult to treat. The majority of Crooke's corticotropinomas are macroadenomas, exhibiting rapid growth, resistance to conventional treatments, a high recurrence rate. To date, there is no fully effective method of treatment for these tumors. Pituitary carcinomas (PC) are defined by distant metastasis. PC is exceedingly rare, comprising only 0.1–0.2% of all pituitary neoplasms but APT may account for up to 15% of all pituitary neoplasms. We report the case of a young female patient with Cushing's disease (macroadenoma, right cavernous sinus invading, nerve VI palsy) who underwent three transsphenoidal surgeries and two γ-knife radiosurgery (GKR). Pathological findings: 'hyalin Crooke' cell type; ACTH positive immunohistochemistry and a very high Ki67 labeling index. She achieved hypocortisolism and healed the palsy after the 1st surgery but early tumor recurrence occurred thereafter. One year and a half after first GKR she returned with rapidly progressive recurrence: headache, right orbital pain, palpebral ptosis and diplopia; hypercortisolism and tumoral rest progression (MRI showed tumoral rest progression 41/31/36 mm). Ophtalmologic exam: nerve III palsy. She underwent urgent endonasal endoscopic surgery for cavernous sinus decompression and short time after, double approach: transsphenoidal and pterional craniotomy was done. The resection was limited by fibrous tumor that invade the cavernous sinus and cause internal carotid artery compression. Histopathological analysis did not show substantial change compared with the first examination. Hypercortisolism persisted and Pasireotide treatment and CBG was started and also she underwent the second GKR. For 6 months she had hormonal response under Pasireotide treatment but fasting blood glucose and Hba1c increased during therapy. And, a new lession with extension in left nasopharynx rapidly increased (40/20 mm). Aggressive corticotroph tumors is a 'high risk pituitary adenomas' and should be followed carefully for early recurrence and clinical aggressive behavior and expand treatment intensity; these patients often require medical therapy to reduce hypercortisolism.

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P1106

Analysis of gender-related differences in clinically non-functioning pituitary adenomas

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Introduction

Clinically non-functioning pituitary adenomas (NFPA) are heterogeneous group. Some previous research has found that this type of pituitary adenomas may be smaller and have better prognostic in men. The aim of this study is to analyze if there are gender-related differences in NFPA.

Material and methods

Retrospective study of patients with NFPA followed up in regional hospitals (Community of Madrid, Spain). All NFPA had molecular analysis. The collected variables were: age, sex (women were divided according to premenopausal and menopausal status), diagnostic (NFPA were divided according to type of expression, classified as unihormonal, plurihormonal or null cell), initial tumor size, need of reintervention and radiotherapy. Concerning the molecular study we also included prolactin, GH, POMC, betaLH, betaFSH, betaTSH, alpha subunit, somatostatin receptors (SSTR 1–5), dopamine D1, D2 long, D4 and D5 receptor. Statistical analysis was made with SPSS version 22.0.0.0.

Results

44 patients were included (age at diagnosis 61 ± 14 years). 54.5% were women (17 menopausal women and 7 premenopausal). All of them were macroadenomas. 3 were silent corticotroph adenomas, 21 gonadotropinomas, 10 plurihormonal adenomas, 1 silent TSH adenomas, 2 silent prolactinomas and 10 were null cell. We found that dopamine receptor D1 expression was higher in silent prolactinomas and null cell adenomas, and was very low in gonadotropinomas ($P = 0.001$). There were statistically significant differences in the type of adenoma according to gender and to menopausal and premenopausal status. Adenomas with hormonal expression were more frequent in premenopausal woman. The most frequent adenomas in men were gonadotropinomas and in menopausal women gonadotropinomas, plurihormonal and null cell adenomas. We observed

that dopamine receptor D4 expression was higher in women than in men. There was a trend, although it was not statistically significant, in the need for reintervention (7/13 in men vs 3/21 in women; $P = 0.076$). Gonadotropinomas had higher expression of prolactina and dopamine receptor D4 in women. No difference between tumor size and need of radiotherapy was found.
Conclusion
In our cohort, we found difference in the type of NFPA and dopamine receptor D4 expression between men and women. Also, the dopamine receptor D1 expression was higher in silent prolactinomas and null cell adenomas, and very low in gonadotropinomas.

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P1107

European observational study of ketoconazole for endogenous cushing's syndrome in collaboration with European registry on cushing's syndrome ERCUSYN: PASS ketoconazole study design and rationale

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Introduction and rationale
Cushing's syndrome (CS) is a rare disease with hypercortisolism caused either by ACTH excess from a pituitary or non-pituitary tumor or by an ACTH-independent primary adrenal overproduction of cortisol. It is associated with significant comorbidities potentially lethal: hypertension, diabetes, coagulopathy, cardiovascular disease, infections, and osteoporotic fractures. It is usually managed by surgery and/or medical treatment with steroidogenesis inhibitors or pituitary targeted therapies. As a condition of marketing authorization granting by European Commission for the use of ketoconazole for the treatment of CS in adults and adolescents above 12 years, the company (HRA Pharma) has to perform a mandatory pharmacovigilance activity with respect to some safety concerns in the format of a non-interventional PASS (Post-Authorization Safety Study).
Objectives
The primary objective of this non-interventional study is to document liver (hepatotoxicity) and cardiac (QT prolongation) tolerability profile of ketoconazole. The secondary objectives are overall safety of ketoconazole, effectiveness evaluations, drug utilization patterns of ketoconazole and the impact of the treatment on quality of life (QoL).
Patients and Methods
Patients (>12 years of age) with endogenous CS starting treatment (prospective dataset) with HRA ketoconazole® in routine clinical practice and included in ERCUSYN (European Registry on C.S) may be enrolled in the study. Two hundred prospective patients are to be enrolled. Safety assessments include adverse events, hepatic enzymes and ECG. Effectiveness assessments include cortisol levels, number and type of comorbidities (hypertension, diabetes, dyslipidemia, osteoporosis, psychiatric disorders, cardiovascular diseases) and related treatments and clinical symptoms of CS (weight, Body Mass Index, waist, blood pressure) over time. QoL assessment includes self-reported questionnaires CushingQoL & EuroQoL 5D. The primary endpoint is the incidence of hepatotoxicity and QT prolongation, time to onset since ketoconazole initiation, and time to recovery. This study is performed in collaboration with ESE as the owner of the ERCUSYN database comprising three major sections (baseline characteristics, therapies of CS and long term biochemical and clinical outcome). Twenty three sites in 9 European countries (Croatia, France, Germany, Italy, Portugal, The Netherlands, UK, Spain and Sweden) involved in ERCUSYN will participate. After obtaining patient's informed consent, and having completed the core ERCUSYN data entry, the investigator will enter data in additional HRA modules created specifically for this study to collect safety data. Data entered in ERCUSYN and in HRA modules will be analyzed. Interim analyses will be performed yearly.
Conclusion
PASS ketoconazole will provide European real-world data to confirm the long-term safety and effectiveness of ketoconazole used in the treatment of CS.

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P1108

Variability of momentarily measured fatigue in patients with pituitary insufficiency receiving hydrocortisone replacement therapy

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Background
Secondary adrenal insufficiency is usually treated with hydrocortisone replacement therapy twice or thrice daily in varying doses to mimic the physiological rhythm of cortisol release. However, despite efforts to optimize treatment regimens patients report impaired quality of life (QoL), including important aspects such as fatigue. A possible explanation is a suboptimal imitation of cortisol release resulting in an inadequate substitution at certain times during the day. Such subtle variations are difficult to capture by standard, retrospective QoL questionnaires. The objective of this study was to investigate short-term variability of fatigue in patients with secondary adrenal insufficiency using ecological momentary assessments.
Methods
Thirty-one patients with pituitary insufficiency in steady twice- or thrice-daily hydrocortisone replacement therapy and replacement of other pituitary insufficiencies were included. The majority were males (27/31) with a median age of 63 years (range: 38–76 years). For 20 days participants answered questions about their current fatigue levels four times daily at semi-randomized time points. Questions were administered by a smartphone application and consisted of a momentary version of the Multidimensional Fatigue Inventory (MFI-20). The questionnaire comprised 20 items organized in five scales, each containing four items. Each scale score ranges from 4 to 20, with higher scores indicating more fatigue. Analysis of variance and analysis of temporal patterns were performed using mixed models for repeated measurements.
Results
The response rate of ecological momentary assessments was 80 percent. General Fatigue and Reduced Motivation varied considerably for each participant (within-person variances of 8.9 and 8.8, respectively (Intraclass correlation coefficients (ICC): 0.53 and 0.50, respectively)). Mental and Physical Fatigue showed the most stable within-person patterns (within-person variances of 3.7 and 5.8, respectively (ICC: 0.73 and 0.70, respectively)). A significant diurnal variation of momentary fatigue was shown ($P < 0.001$) with lowest levels in the morning and increasing levels across the day.
Conclusion
Findings indicate that fatigue in patients with secondary adrenal insufficiency varies considerably over short time periods, especially when measuring General Fatigue and Reduced Motivation. Ecological momentary assessment is thus a promising tool for individual profiling to customize timing and dosing of hydrocortisone replacement therapy.

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P1109

HPA axis function in patients with clinically non-functioning pituitary adenomas: effects of surgery and risk factors for HPA failure

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Introduction
Patients planned for first time surgery for clinically non-functioning pituitary adenoma (NFPA) were included in this prospective study.
Aims
– To study the prevalence of hypothalamic-pituitary-adrenal (HPA) axis failure preoperatively and 3 months after surgery for clinically NFPA.
– To investigate factors predicting risk of HPA axis failure postoperatively.
Hypotheses
– Endoscopic transsphenoidal surgery rescues the HPA axis in patients with NFPA.
– Postoperative pituitary failure mainly occurs after surgery for pituitary apoplexy.
Method
The study included 116 patients, (51 women, 65 men), mean age 58.6 years (range 18-93) with macroadenomas, mean largest diameter 26.9 mm, range 13-61 mm. The pathologists confirmed the diagnosis of pituitary adenoma. Fourteen patients were excluded after histopathological diagnosis other than NFPA. The surgeries were performed in a single tertiary referral centre, Oslo University Hospital, from December 2014 to October 2018. The subjects gave signed informed consent. Regional Ethics Committee approved the study. Two surgeons performed the majority of operations (102). Transsphenoidal endoscopic technique was used in 113 patients, while three were operated with open transcranial resection. The surgical indications in our series were visual disturbance (92), tumour growth and elevated/compressed optic chiasm (16), acute apoplexy (6) and headache (2).
Results
All patients were alive three months after surgery. HPA-axis failure was diagnosed with low morning cortisol in 15 patients pre-operatively. Eight of these had normal HPA axis 3 months postop confirmed by SynACTHen test. Patients with a rescued HPA function were younger; mean age 57.5 years vs. 71.0, ($P=0.06$). In addition, failure of HPA function three months post-operatively was found in five out of six patients undergoing acute surgery for a pituitary apoplexy, two of three patients operated trans-cranially and in two patients operated transsphenoidally for large macroadenomas (34 and 40 mm). In patients with HPA failure, the mean number of pituitary axes with failure was 2.7, compared to 0.7 axes ($P<0.01$) in patients with normal HPA function. Visual symptoms improved in 70 of 93 of patients with visual disturbance preoperatively. Vision was unchanged in 12 and examination of vision was missing in ten patients. Postoperatively MRI revealed a residual tumour in 62 patients.
Conclusion
Endoscopic transsphenoidal surgery rescues the HPA-axis and the visual function in most patients with clinically NFPA in our centre. Acute pituitary apoplexy, older age, open transcranial surgery and larger tumours are all risk factors for HPA-axis failure post-operatively.

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P1110

Isolated central hypothyroidism as a clue for empty sella syndrome

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Introduction
Isolated central hypothyroidism is a rare disease. Acquired causes for central hypothyroidism include iatrogenic, traumatic, immunologic, infiltrative, infectious, vascular or space-occupying lesions. Empty sella may present with endocrine dysfunction, mainly hyperprolactinemia and growth hormone or gonadotropin deficiency. Few cases of empty sella associated with isolated TSH deficiency were published.
Case report
A 66-years-old female with a diagnosis of hypothyroidism established five years before was referred to Department of Endocrinology due to challenges on levothyroxine dose management. She had a previous history of acute coronary syndrome, heart failure, bronchitis, obesity, hypertension, type 2 diabetes and depression. She had three uneventful pregnancies and entered menopause at 55. She denied previous cranial surgery, trauma or irradiation. At first Endocrinology's appointment, her pharmacologic habits included 137 µg levothyroxine, pantoprazole, clopidogrel, telmisartan, lercanidipine, ivabradine, sitagliptin/metformin, tiotropium, fluoxetine, bupropion, sertraline, quetiapine, alprazolam and vinpocetine. Cervical ultrasound showed a normal sized homogeneous thyroid. Her blood results were the following: TSH-2.73 µUI/mL[0.40–4.40], FT4-0.73ng/dL[0.80–1.80], TT4-3.60 µg/dL[4.50–10.90], FT3-2.43pg/mL[2.0–4.2], TT3-0.99ng/dL[0.60–1.81], TPOAb-42.7U/mL[0–60], TGAb-15.5U/mL[0–60]. She also presented analysis performed 8 years earlier (without levothyroxine replacement) with a TSH of 2.21 µUI/mL[0.40–4.40] and a FT4 of 0.67ng/dL[0.89–1.76]. Levothyroxine dose was increased to 150 µg and the patient was advised to take it 30 minutes before pantoprazole and breakfast. Considering the low FT4/TT4 levels and normal TSH, a pituitary MRI and hormonal evaluation were requested. MRI showed an empty sella without evidence of adenoma on the flattened pituitary tissue. No further pituitary hormone deficiencies were detected: FSH-43.69UI/L[23.0–116.3], LH-21.19UI/L [15.9–54.0], estradiol-13.35pg/mL[0–32.2], progesterone <0.21ng/mL [<0.73], prolactin-4.25ng/mL [1.8–20.3], TSH-0.18 µUI/mL[0.40–4.40], FT4-0.83ng/dL [0.80–1.80], IGF1-95ng/mL[81–225], ACTH-10pg/mL[9–52]; cortisol post-tetracosactide at 0/30/60 minutes-5.21/23.35/27.32 µg/dL[4.3–22.40] and urine specific gravity 1.017. Anti-pituitary antibodies were negative.
Discussion
It needs to be emphasized that low FT4 levels with inappropriate low/normal TSH (without a background of non-thyroidal illness syndrome or pharmacologic interference) should trigger investigation for central hypothyroidism. It is crucial to determine the underlying cause and exclude multiple pituitary hormone deficiencies, which may alter the therapeutic approach. Central hypothyroidism is sometimes overlooked. In the current case, the type of hypothyroidism was misdiagnosed for a long period of time, which could have had a deleterious impact in case of an underlying sellar/suprasellar tumour or concomitant adrenal insufficiency. The only identified cause for central hypothyroidism in this patient was empty sella. This disorder remains as an uncommon cause for isolated TSH deficiency.

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P1111

Hypoglycemic coma revealing sheehan syndrome: a case reported

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Introduction
Sheehan's syndrome is a rare postpartum complication. Recurrent hypoglycaemia,though described is a rare complication of Sheehan syndrome. Here we report a case of Sheehan syndrome which presented with hypoglycemic coma.
Case Presentation
We report the case of a 47-year-old woman who presented to the medical emergency unit with coma. There was no history of chest pain, fever, headache, vomiting, trauma, or seizures. She had no history of chronic illness or addictions. She delivered her last baby at home 18 years old back when she was gravida 5, parity 3 during which severe PPH occurred, for which she was hospitalized, and 2 units of packed cells were transfused. She did not breast feed the baby. On examination, she was inconscious, cool, and clammy. The systolic blood pressure was 50 mmHg, pulse rate was 60 beats/min regular, temperature was 37 by axilla, and blood sugar was 25 mg/dL. She regained consciousness after bolus intravenous infusion of dextrose solution. There was dryness of skin, conjunctival pallor, facial puffiness, delayed ankle jerk, and slowness of speech. Pubic and axillary hairs were scanty. Hematology revealed pancytopenia, with the diagnosis of iron deficiency anemia. Hypothalamic-pituitary MRI showed arachnoidocele and hormonal evaluation revealed adenohypophyseal insufficiency as evident from decreased levels of cortisol, thyroid-stimulating hormone, triiodothyronine, free thyroxine, follicle-stimulating hormone, luteinising hormone and prolactin. Based on clinical, radiological and laboratory parameters her final diagnosis was Sheehan syndrome with hypoglycaemia.
Discussion
Presentation of Sheehan syndrome can be acute or chronic; acute presentation being even rarer. The diagnosis of Sheehan syndrome is often delayed by many years, may be up to 15–20 years, because other signs of adenohypophyseal insufficiency are often delayed and subtle. Hypoglycaemia is a rare presentation of this syndrome in acute and delayed cases. In our case, diagnosis was made 18 years after the last obstetric event The delay in making diagnosis was 16.3 ± 4.7 years in a series of 20 cases of Sheehan syndrome 2.

Conclusion
Hypopituitarism should be kept in differential diagnosis while working up a case of severe or recurrent hypoglycaemia 2.
Bibliography
1. HK Aggarwal and al,Recurrent Hypoglycaemia: an Uncommon Presentation in Sheehan Syndrome. Eur J Gen Med 2016;13(2):155–157.
2. Naresh kumar and al:Recurrent hypoglycaemia: a delayed presentation of Sheehan syndrome. BMJ Case Rep. 2014.
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P1112

Metabolic phenotype in acromegaly
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Introduction
Previous studies reported increased unfavorable metabolic phenotype in patients with active acromegaly.
Aim of the study
We studied the metabolic phenotype in unselected cohort of 133 patients with active acromegaly (83 female, 62.4%), diagnosed at Clinic of Endocrinology, University Clinical Center, Belgrade, Serbia in the period 2007–2018. Mean age at diagnosis of acromegaly was 50.5 ± 1.2 years and mean BMI was 28.4 ± 0.4 kg/m^2. Pituitary macroadenoma was diagnosed in 72% of patients ($n=96$).
Methods
We collected demographic and anthropometric data (weight, height, BMI) at diagnosis of acromegaly, before the operative or medical therapy. We measured concentration of IGF-1, growth hormone (GH), lipids (cholesterol, HDL, LDL, triglycerides) and HbA1c. We measured glycemia and insulin levels during oral glucose tolerance test (OGTT) and calculated area under the curve (AUC) for glycemia and insulin during OGTT, HOMA and Matsuda index of insulin sensitivity (ISI).
Results
In this cross-sectional study, 37.6% of patients were overweight ($n=50$) and 36.8% of patients were obese ($n=49$). Prevalence of diabetes mellitus (DM) was 25.6% ($n=34$) and prevalence of impaired fasting glucose (IFG) plus impaired glucose tolerance (IGT) was 18.0% ($n=24$). DM, IFG and IGT were more prevalent in females than males (45.7% vs 40.0%). Prevalence of arterial hypertension in the cohort was 62.4% ($n=83$), hypercholesterolemia 61.7% ($n=82$), low HDL 18.8% ($n=25$), high LDL 50.4% ($n=67$) and hypertriglyceridemia 47.4% (n=63). Arterial hypertension, hypercholesterolemia and hypertriglyceridemia were more common in females compared with males (arterial hypertension: 70.4% vs 47.9%; hypercholesterolemia: 66.7% in females vs 53.3% in males; hypertriglyceridemia: 50.0% in females vs 44.4% in males), while low HDL was more prevalent in males (28.6% vs 12.1%). Statistically significant associations were found between IGF1 or GH levels with baseline glycemia ($P=0.004$) and insulin ($P=0.002$), AUCinsulin ($P=0.05$), HOMA ($P=0.001$) and ISI ($P=0.008$).
Conclusions
Unfavorable metabolic phenotype characterized by insulin resistance with high prevalence of hypertension, dyslipidemia and obesity is common in active acromegaly, especially in females.
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P1113

The impact of clomiphene citrate as add-on therapy in male acromegalic patients non-responsive to combined medical therapy
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Introduction
Clomiphene citrate (CC), a selective estrogen receptor modulator that increases LH and FSH secretion, improves hypogonadism and fertility outcomes. Moreover, there is limited evidence that it may also be helpful as add-on therapy to normalize IGF-1 levels in male acromegalic patients.
Objective
To assess the effect impact of CC on serum IGF-1 and testosterone levels in male acromegalic patients not controlled by the combination of lanreotide autogel (a first generation somatostatin analogue) and cabergoline (a dopamine agonist).
Study Design
In this prospective, open-label, single-center trial, CC (50 mg/day) was added to previous medical treatment (combination of lanreotide autogel and cabergoline) for 3 months. Hormonal assessment (GH, IGF-1 and testosterone levels) was performed before and 3 months after CC introduction.
Patients
Eight male patients (mean age, 40.75 ± 9.32 years; median age, 42 years; range, 26–54 years) met the following criteria: IGF-1 above the upper limit of normal (ULN) range for at least 1 year despite the use of combined medical therapy.
Results
Three months after CC introduction, serum IGF-1 levels decreased in all patients and reached normal values in 2 patients (25%). Noteworthy, IGF-1 normalization occurred in two of the three patients (66.7%) with baseline IGF-1 levels of up to 2 times the ULN. There was no significant change in GH levels. Conversely, total serum testosterone levels increased in all patients, reaching normal levels in 50% (three of six) of those considered to be hypogonadal (total testosterone < 300 ng/dL). Overall, CC was well tolerated and no patient needed to interrupt the treatment.
Conclusion
Addition of the low cost CC may be hepful to normalize IGF-1 levels in male acromegalic patients not controlled by the combination of SAs and cabergoline, particularly those with mild IGF-1 elevation (up to two times the ULN). Moreover, improvement of testosterone levels can be obtained in patients with concurrent central hypogonadism.
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P1114

Evolution of patients with discordance between growth hormone and insulin-like growth factor-1 after pituitary surgery for acromegaly
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Introduction
Persistent or intermittent postoperative discordance between growth hormone (GH) after OGTT and insulin-like growth factor-1 adjusted for age and gender (IGF-1) is up to 39% according to different studies. The aim of this study was to evaluate the impact of this discrepancy (normal GH and elevated IGF1 or vice versa) over the risk of biochemical and tumour recurrence after initial successful surgery for acromegaly.
Methods
In this retrospective study, we examined 180 patients who have been treated or were under follow-up for acromegaly in our department between 2014–2018. We excluded patients who have undergone gamma-knife or had a tumour remnant at 3 months after initial surgery or with any medical treatment for acromegaly before/at the time of objectified discrepancy. Patients with factors that could possibly influence IGF1/GH levels, such as poorly controlled diabetes, hypothyroidism, renal or hepatic failure, glucocorticoid, estrogens or testosterone therapy, were also excluded. We included 16 patients with persistent or intermittent GH-IFG1 discordance.
Results
Study group included 5M/11F, with mean age at diagnosis of 42.6 ± 11.2 years, and a mean tumor size 13.7 ± 8.3 mm (CT scan) or 20 ± 12.8 mm (MRI scan). The mean duration of follow-up was 4.2 ± 1.9 years. Preoperative, the mean IGF1 level was 878 ± 266 ng/ml and mean nadir GH during OGTT 11.5 ± 13.7 ng/ml. At 3 months after surgery, the mean IGF1 level was 297.5 ng/ml and mean GH after OGTT 0.76 ng/ml. During follow-up of 16 patients, 9 normalized IGF1 and GH without any further treatment, with a mean period until normalization of 23 month; 5/16 had persistence of discordant values and no tumor recurrence on imagistic scans during follow-up and 2 patients presented biochemical and tumor recurrence at 15 months; 2 patients had GH and PRL co-secretion before surgery, both with discordant IGF1 and GH at 3 months after surgery and normal imagery. In one PRL secretion persisted, but responded at dopamine analogues and the other one normalized during follow-up.
Conclusions
Out of 10 patients with discordant IGF1-GH levels and no imagistic tumour evidence at 3 months, the majority had IGF 1 and GH normalization at 12 months postoperative without recurrence disease during follow-up. Therapeutic approach

should be individualized between additional medical treatment and close follow-up in biochemically discordant patient. Further studies are needed to clarify the influence of discordant values on mortality and morbidity of the disease.

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P1115

Pituitary apoplexy occurs more frequently in the morning

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Pituitary apoplexy (PA) is a rare clinical syndrome due to sudden haemorrhage and/or infarction of the pituitary gland, usually within a pre-existent pituitary tumour. Even though some sporadic cases of PA associated with rare sellar lesions (such as Rathke cleft cysts) have been reported, in the vast majority of cases the syndrome occurs within a pituitary adenoma. At presentation, patients with PA usually complain of sudden and severe headache, often associated with visual loss or ocular palsy. Arterial hypertension, major surgery, anticoagulant therapy, angiography, dynamic tests, dopamine-agonists, GnRH agonists have been advocated as possible precipitating factors. However, they may be identified in a minority of cases altogether (10–40%). The pathophysiology of PA has not been completely clarified. Interestingly, imaging studies, surgical exploration and histopatological analysis may identify both haemorrhage and ischemic necrosis, but all these procedures cannot always clarify the first step that has triggered the dangerous cascade of events. There is evidence that some unpredictable cardiovascular events, such as acute myocardial infarction and stroke, often occur early in the morning. In order to verify whether a circadian pattern in the occurrence of PA may exist, we conducted a retrospective analysis in a cohort of patients who presented with signs and symptoms of acute PA. Twenty-five patients with PA were excluded because of the lack of information about the time of occurrence of the syndrome. A total of 60 patients with PA who referred to our centre during the last two decades were included in the study. Of these, 24 (40%) showed the first signs and symptoms of PA in the morning (6 a.m. to 12 a.m.), 12 (20%) in the afternoon (12 a.m. to 18 p.m.), 13 (20.6%) in the evening (18 p.m. to 24 p.m.), and 11 (18.3%) during the night (0 p.m. to 6 a.m.). The tumour associated with PA was a non-functioning pituitary adenoma in 41 cases (68.3%), a PRL-secreting adenoma in 12 cases (20%), an ACTH-secreting adenoma in 4 cases (6.6%), and a GH-secreting adenoma in 3 cases (5%). In conclusion, our data suggest that PA occurs more frequently during the morning hours. To the best of our knowledge, our study represents the first demonstration of circadian variation in the the occurrence of PA.

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P1116

Giant cerebral aneurysm a rare cause of hypopituitarism: a case report

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Introduction
Hypophysary aneurysms are rare, they account for 1% to 2% of all intracranial aneurysms (1) and can be mistaken for pituitary adenomas, since they can have similar symptoms and even radiological signs especially if it's an aneurysm completely thrombosed as angiography will show only avascular mass (2).
Clinical case
A 84 year old female with past medical history of hypertension, dyslipidemia and depressive disorder, presents to emergency room with vomits and somnolence, a brain CT Scan was performed that showed a hypophysary mass of 2×3,3 cm reported as pituitary macroadenoma vs Meningioma, and was discharged with a diagnosis of gastrointestinal infection. The patient missed the follow-up appointment to continue the study of the sellar mass. Tree years later she came back with anorexia, drowsiness, inespecific abdominal pain and hyponatremia. Physical exam was normal. Laboratory Test: Cr 0.73 mg/dl (0.60–1.00); Na 117 mmol/l (135–150); K 3.72 mmol/l (3.50–5.50); 241 mOsm/kg (285–295), TSH 0.137 microUI/ml (0.270–4.200), FT3 L 1.55 pg/ml (2.3–4.4), FT4 0.94 ng/dl (0.93–1.70) FSH 2.28 microUI/ml (3.35–21.63), LH 0.22 microUI/ml (2.80–21.70), Prolactin 65.93 ng/ml (1.20–30.00), IGF-I 40.33 ng/ml (17.00–200.00), Basal Cortisol 3.41 μg/dl (6.24–18.00) Synacthen Test (60 min) 18.45 μg/dl. Hypophysary MRI (contrast)**:** Sellar lesion markedly hypointense in T2 sequence, with peripheral enhancement**,** heterogeneous signal in its interior, in continuity with left ICA, suggestive of aneurysmal malformation, with no remaining pituitary glandular. Cerebral Angiography**:** Giant saccular aneurysm dependent on the intracavernous left ICA, without mural thrombosis, of approximately 22.4×26.7×23 mm. Because of the high-risk surgery, a conservative management was approached**.** Replacement therapy was started with Hydrocortisone and Levothyroxine with improvement of the symptoms.
Conclusion
Hypopituitarism as result of an aneurysm extending into the sellar region is rare accounting for a prevalence of 0.17% (1) but it is important to kept in mind as differential diagnosis. Careful evaluation of the MRI and an angiogram should be considered for prevent unfortunate consequences in case surgery is an option
Reference
1) Heshmati HM, *et al*. Hypopituitarism caused by intrasellar aneurysms. *Mayo Clin Proc*., 2001;76 (8):789–93.
2) Nguyen, Ha Son *et al*. A completely thrombosed, nongiant middle cerebral artery aneurysm mimicking an intra-axial neoplasm. *Surgical neurology International*, vol. 6 146. 7 Sep. 2015, doi:10.4103/2152-7806.164696.

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P1117

Epidemiology of acromegaly in Russian Federation: evaluation of National registry-based data

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According to state statistics service, Russia's population in 2018 is more than 146.8 mil people. The total prevalence of acromegaly may range between 2.8 and 13.7 cases per 100,000 people and the annual incidence rates vary between 0.2 and 1.1 cases per 100,000 people (Lavrentaki A, *et al*. 2016). The epidemiological data for acromegaly in Russian population is lacking. The Russian hypothalamic and pituitary tumors registry was founded in 2004 and for 2018 it contains the medical data of 8543 patients, among them – 4076 patients with acromegaly. Our aim was to compare the epidemiological data from Russian hypothalamic and pituitary tumors registry with the calculated prevalence and incidence rates. According to the database, highest prevalence of acromegaly is registered in Kirov federal subject – 8.7 per 100 000 people, Penza federal subject – 7.5 per 100,000 people and in Krasnoyarsk federal subject −7.2 per 100,000 people. The prevalence in these regions is within the predicted range. However, other federal subjects show significantly less prevalence of the disease. Moreover, not all of the regions participate in the registry. According to the previously mentioned data, the calculated amount of patients with acromegaly could vary from 4110 to 20112 cases and the annual incidence rate from 293,6 to 1614,8 cases. For the 2017 and 2018, there were 107 and 37 new registered cases of acromegaly added to the registry, respectively. The number of patients in the registry is lower than the population-based calculated values. This could be attributed to the fact that not all of the regions participate in the registry and even in participating regions there is a probability of missing the data due to human factor or lack of communication between health care centres. These data suggest that more effort should be put in order to establish health care continuity to ensure the high quality of epidemiological registry-based data.

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P1118

Diagnostic evaluation of a large cohort of Brazilian patients with endogenous Cushing's syndrome

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Introduction
Cushing's syndrome (CS) is certainly one of the most challenging disorders to physicians due to the difficulties that often appear during its investigation. The diagnosis of CS involves two steps: confirmation of hypercortisolism and determination of its etiology. Biochemical confirmation of the hypercortisolemic

state must be established before any attempt for differential diagnosis. Failure to do so will result in misdiagnosis, inappropriate treatment, and poor management.
Objective
To assess the accurarcy of the various tests used in the diagnostic evaluation of endogenous CS.
Study design
A retrospective analysis of medical records was of patients with endogenous CS routinely followed in the Division of Endocrinology of Hospital das Clínicas, Federal University of Pernambuco, and in Pernambuco Endocrine Research Center, in Recife, northeast of Brazil, from January 2005 to December 2017.
Results
A total of 158 patients were enrolled: 99 (62.7%) with Cushing's disease, 48 (30.4% with adrenal disorders), and 11 (6.9%) with ectopic ACTH secretion (EAS). Concerning diagnostic tests, serum cortisol (SC) levels $\geq$1.8 µg/dl after the 1mg overnight dexametahosne suppression test (1 mg-DST) were found in all but 10 patients (6.3%) who had cyclical hypercortisolism, whereas elevation of urinary free cortisol (UFC) and late-night salivary cortisol (LNSC) had sensitivites of 85% and 94%, respectively. Regarding tests used in the differential diagnosis of CS, ACTH levels were shown to be suppressed ($<$10 pg/ml) in all patients with adrenal adenomas or carcinomas, normal (40%) ou elevated (60%) in CD, and invariably high in cases of EAS. SC suppression $>$50% after the 8 mg overnight dexamethose suppression test (8 mg-HDDST) was encountered in 80% of patients of CD and in 27% of those with EAS. By contrast, SC suppression $>$ 80% were only seen in cases of CD (54% sensitivity). ACTH increase $>$ 50% after desmopressin or CRH had 90% sensitivity and 90% specificity for CD. A positive response to both 8 mg-HDDST and desmopressin (or CRH) was only seen in subjects with CD. Magnetic resonance imaging (MRI) depicted adenomas in 65% of CD patients (19% with macroadenomas). Finally, bilateral inferior petrosal sinus sampling had a 94% accuracy in the diagnosis of CD.
Conclusion
In our cohort, 1 mg-DST and LNSC were the most accurate options to confirm hypercortisolism. Non-invasive dynamic tests have greater performance when performed in combination. However, SC suppression $>$80% after 8 mg-HDDST had 100% specificity for CD.

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P1119

The role of omentin in inflammation and metabolic syndrome risk assessment in women with PCO-S

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Introduction
Omentin is a visceral fat tissue adipokine which regulates metabolism (insulin sensitivity) and presents an anti-inflammatory activities, by lowering C-reactive protein concentration, in obesity and diabetes mellitus type 2. Polycystic ovary syndrome is the most common endocrinopathy in women of childbearing age. One of the major disorders in the PCOS metabolic phenotype is obesity and hyperinsulinaemia. The anthropometric indicators are useful tools for carbohydrate and lipid profiles disorders.
Aim
The aim of the study was to estimate the omentin serum concentration and its relationship with the new anthropometric indicators (BAI, VAI, ABSI, BRI and LAP) and inflammation parameters (insulin, C-reactive protein) in PCO-S.
Material and methods
The study included 29 women diagnosed with PCO-S according to Rotterdam criteria and hospitalized in Endocrinology City Hospital in Piekary in 2015–2018. Anthropometric and biochemical parameters were used to calculate: BAI, VAI, ABSI, BRI and LAP. Blood pressure was regularly measured. PCO-S patients blood was centrifuged and the omentin serum concentration was determined in duplicates by ELISA method. Intra-assay variation was 4.1% and inter-assay – 4.8%. Statistically significant value $P<0.05$ was assumed.
Results
In the examined group of women the average age was 27 years ($\pm$6,3), body mass 78kg ($\pm$22.9), height 165 cm ($\pm$5.7), waist circumference 91 cm ($\pm$19.5) and hip circumference 108 cm ($\pm$13.5). The average omentin serum concentration was 261ng/ml ($\pm$6,3). Omentin serum concentration was statistically higher in PCO-S patients with lower insulin concentration ($P<0.05$, $r=-0.5$). There was no significant correlation between omentin serum concentration and C-reactive protein concentration. Omentin serum concentration correlated negatively with BAI ($P<0.05$, $r=-0.6$), BRI ($P<0.05$, $r=-0.6$) and LAP ($P<0.05$, $r=-0.4$) values. There was observed significant correlation between omentin serum concentration and ABSI value in the examined women ($P<0.05$, $r=+0.4$). Significant correlation between omentin serum concentration and VAI value was not foud. The interesting observation was the strong negative correlation between omentin serum concentration and diastolic pressure value in PCO-S women ($P<0.05$, $r=-0.6$). The observed results requires further studies to explain the possible meaning.
Conclusion
Omentin concentration could be a functional tool to estimate metabolic disorders and inflammation risk in women with PCO-S. Further studies, involving a larger group of PCO-S women, to confirm these conclusions are needed.

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P1120

Immunomodulatory effects of dihydrotestosterone (DHT) in rat vaginal smooth muscle cells

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Pathologies of the female reproductive system, characterized by chronic pain, are frequent and it has been hypothesized that inflammation may play an essential role in their pathogenesis. It is known that androgens, including dihydrotestosterone (DHT), have shown immunomodulatory effects in experimental models of chronic inflammation. The aim of this study was to evaluate the immunomodulatory effects of DHT in smooth muscle cells (rSMCs) isolated from vagina of intact Sprague-Dawley rats and investigate the tissue expression of steroidogenesis enzymes, in order to evaluate the hormone on-site role. rSMC isolated from rat distal vagina were characterized with α-smooth muscle actin (α-SMA) and myosin heavy chain 11 (MHCII). Then rSMC were left untreated (NT, taken as control) or pre-treated for 24 h with DHT (30 nM) with or without the antiandrogen bicalutamide (BICA; 1 µM) and then stimulated with LPS (100 ng/ml). Using Real-Time RT PCR we evaluated the mRNA expression of membrane Toll-Like Receptors (TLRs), mediators of inflammatory response, and the expression of the main pro-inflammatory markers (IL-6, IL-1β, chemokine C-X-C motif ligand 1 (CXCL1), COX-2 and MCP). In addition, the expression of the main genes involved in the steroidogenesis was evaluated in distal vaginal tissue. Finally, immunofluorescence studies were performed to analyse the nuclear translocation of NF-kB, an important transcriptional mediator of the inflammatory response. Our results showed that rSMCs expressed constitutively all TLR receptors, identifying rSMCs as potential non-professional Antigen Presenting Cells (APC). LPS stimulation increased mRNA expression of CXCL1, IL-1β, MCP1, IL-6 and COX2, whereas DHT counteracted this effect. In addition, DHT significantly decreased LPS-induced nuclear translocation of NF-kB, and all these effects were blunted by BICA co-treatment. Finally, distal vagina tissues expressed enzymes related to the production of androgenic precursors (CYP11A1) and DHEA (CYP17A1), albeit to a lower level when compared to the ovary, whereas genes related to the synthesis of testosterone (HSD17β3) and DHT (SRD5A2) were significantly more expressed. In conclusion, our data show that in rSMCs DHT plays an anti-inflammatory role, inhibiting the mRNA expression of pro-inflammatory genes as well as the NF-kB nuclear translocation induced by LPS. These effects are blunted by BICA, thus suggesting a direct involvement of the androgenic receptor in this pathway. Moreover, the high expression of genes involved in androgen synthesis in the distal vagina suggests the possible therapeutic use of androgen precursors (e.g. DHEA) for the treatment of genitourinary trait disorders in women.

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P1121

Clinical and diagnostic criteria for patients with thyroid diseases in disturbances of the menstrual cycle

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The project study thyroid diseases which are common endocrine pathology in Uzbekistan appearing in women of reproductive age. We study thyroid hormones, since its close relation with the female reproductive hormones (estrogen and progesterone), ensure the normal functioning of the ovaries and the maturation of the eggs or its disorder. The study evaluated thyroid dysfunction – such as thyrotoxicosis or hypothyroidism – that might lead to an imbalance of reproductive hormones and might result in problems with fertility such as: impaired ovulation, irregular menstruation, the inability to conceive a child or premature birth.

Materials and methods

The subject of the research was the study of the effects of hypothyroidism and hyperthyroidism on menstrual dysfunction in women. The study involved 35 women aged between 19 to 40 years with a pathology of thyroid function, of which 20 patients with hyperthyroidism (Group A) and 15 patients with hypothyroidism (Group B). The diagnoses were determined on the basis of hormonal results, ultrasound examination of the thyroid gland and the ultrasound examination of uterus and appendages.

Results

Group A – examination of patients with hyperthyroidism, menstrual dysfunction was noted such as polymenorrhea in 7 patiens, algomenorrhea in 8 patients and oligomenorrhea in 5 of them. And among patients with hypothyroidism, amenorrhea in y4, oligomenorrhea in 6 and hypermenorrhea in 5 were detected. Group B – in the examination of patients with hypothyroidism, 7 of out 15 had complaints about galactorrhea, amenorrhea, hirsutism and anovulation. In these patients, we examined an increase in blood free fractions of testosterone, estradiol and prolactin. We also conducted an ultrasound study of the thyroid gland. In the Group A (hyperthyroidism), an increase in grade 2 thyroid gland was found in 9 patients, an increase in grade 3 thyroid gland in 8 patients, and a nodular goiter in 3 patients. In the Group B (hypothyroidism), an increase in grade 2 thyroid gland was observed in 4 patients, an increase in grade 3 thyroid gland in 5 patients and a nodular goiter in 6 patients.

Conclusion

Diseases of the thyroid gland, might adversely affect the functioning of the whole organism of women as a whole, and especially the reproductive system. Observed hyperthyroidism and hypothyroidism may cause reproductive disorders and menstrual disorders, we might conclude that, these studies show us that dysfunction of the thyroid gland may lead in patients to menstrual disorders and farther to such deviations such as polymenorrhea, algomenorrhea, oligomenorrhea, amenorrhea and hypermenorrhea.

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P1122

Severely elevated testosterone in a woman with ovarian hyperthecosis

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A 73-year-old lady presented to our department with a 6-month history of facial hirsutism and frontal hair loss. Her past medical history comprised of type 2 diabetes and hypertension. Initial blood tests showed testosterone 15.9 nmol/l (normal range 0–1.7), SHBG 123.6 nmol/l, LH 23.1 iu/l (normal range 16–64), FSH 33.5 iu/l (normal range 16–64), oestradiol 281 pmol/l (normal <43), mild erythrocytosis, mild hyperbilirubinaemia and HbA1c 56 mmol/mol (normal <42). Her DHEAS, androstenedione, short synacten test with 17-hydroxy progesterone, TSH and overnight dexamethasone suppression test were normal. Repeat testosterone levels, even with different asseys, remained elevated (highest 20.3 nmol/l). A CT scan showed normal adrenal glands, but severe liver cirrhosis and abdominal varices. Pelvic US and MRI showed normal ovaries. Ovarian hyperthecosis was suspected. Subsequently, she was referred to the Gastro-enterology and Gynaecology teams and she underwent variceal banding and total abdominal hysterectomy with bilateral oophorectomy. Histopathology revealed ovarian hyperthecosis. Her post-op testosterone level was 1.1 nmol/l and oestradiol 43 pmol/l. Also, her hair started regrowing in the scalp and her hirsutism improved significantly. Ovarian hyperthecosis is a non-neoplastic disorder mainly diagnosed in postmenopausal women mimicking the clinical manifestations and metabolic sequel of PCOS. Aetiology is thought to be related to elevated postmenopausal gonadotropin levels. Patients typically present with a long history of slowly progressive hyperandrogenism often resulting in virilization. Testosterone is usually <7 nmol/l. Imaging shows bilaterally enlarged ovaries. The diagnosis is confirmed histologically. However, this was a case of histo-pathologically confirmed ovarian hyperthecosis with severe hyperandrogenaemia and normal ovarian imaging.

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P1123

Study of the anti-inflammatory effects of dihydrotestosterone in human vaginal smooth muscle cells

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Inflammation is hypothesized to play an important role in several diseases associated to the female genital tract and dihydrotestosterone (DHT) has shown immunomodulatory protective effects in experimental models of chronic inflammation. In the present study we aimed to evaluate the potential anti-inflammatory effects of DHT in a model of smooth muscle cells (hSMCs) isolated from human vagina biopsies and their potential role as APCs (Antigen Presenting Cells), crucial for the immune response. In addition we investigated the tissue expression of enzymes involved in steroidogenic machinery, to evaluate the potential role of the hormone on-site production. hSMCs were isolated by tissue samples obtained from laparoscopic patients and were characterized with the main smooth muscle markers α-smooth muscle actin (α-SMA) and myosin heavy chain 11 (MHC11). The cells were stimulated *in vitro* with the Toll-Like Receptors (TLRs) agonist lipopolysaccharide (LPS), with or without DHT (30 nM), for 24 h in order to analyze, by real time RT PCR, the expression of the main pro-inflammatory genes, such as IL-4, IL-6, IL-12, MCP1 and cyclooxygenase-2 (COX-2). In addition, immunofluorescence studies were performed to analyze the LPS-induced NF-kB translocation, with or without DHT (30 nM) co-treatment. In the flow cytometry studies, hSMC were stimulated with INFγ 1000 UI/ml, in absence or in presence of DHT (30 nM) for 48h. Finally, the mRNA expression of enzymes involved in the steroidogenesis pathway in human vagina tissues was evaluated by RT-PCR, taking the ovary as a control. Our data showed that LPS significantly increased the expression of several pro-inflammatory genes (IL-4, IL-6, MCP1 and COX2) and induced a consistent NF-kB nuclear translocation, while DHT treatment counteracted these effects. Moreover, DHT reverted the HLA-DR expression up-regulated by INFγ stimulation. Finally, the genes linked to the synthesis of androgenic precursors were expressed in vagina tissues. In particular, genes related to DHT synthesis (5α-reductase 1, 2 and 3; SRD5A1, SRD5A2, SRD5A3) were significantly higher expressed compared to ovary. In conclusion, the results of this study showed that in our experimental model, DHT has anti-inflammatory properties inhibiting the mRNA expression of several pro-inflammatory genes as well as LPS-induced NF-kB nuclear translocation. In addition, the counteracting effects of DHT on the INFγ-induced HLA-DR expression suggested an immunomodulatory profile similar to APC. Finally, the high expression of androgen synthesis-related genes in vagina tissues suggests an on-site production. Taken together, our data support the possible therapeutic role of androgens in genital trait disorders in women.

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P1124

Evaluation of insulin resistance and endocrine hormone parameters on etiopathogenesis of acne vulgaris, analyzing whether there is a change in insulin resistance and hormonal parameters after oral isotretinoin treatment

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Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit and it can be seen on postadolescence period. Several studies show that adrenal and

pituitary hormones have an important role in the pathogenesis. The studies which show the isotretinoin treatment takes effect on hormones are phenomenal in the literature. The aim of our study is to identify a hormonal alteration in the etiopathogenesis of acne vulgaris and to observe whether there is an alteration with insulin resistance and hormones with a systematic treatment.
Patients and methods
30 patients with acne vulgaris applied to the department of endocrinology and metabolic diseases and the department of dermatology in Ankara University Faculty of medicine between February 2015 and June 2015 were enrolled into the study. The patient group was composed of women diagnosed with acne vulgaris clinically and given the isotretinoin treatment. As for that, 30 healthy volunteer individuals who had similar sociodemographic characteristics to the patient group participated in the control group. Patient and control groups were compared to each other in terms of demographic, basal insulin resistance and endocrine hormones. Insulin resistance and endocrine hormonal parameters were evaluated on the third month of isotretinoin treatment.
Results
In our study, Age, menarche age, waist circumference, and BMI were similar between patient and control groups. There was no difference in the homeostatic model assessment of insulin resistance (HOMA-IR) values between groups. Values of ALT,AST,LDL,TSH, free T4, ACTH, cortisol, prolactin, progesterone, 17-OH progesterone, total testosterone was seen increased on patient group compared to control group ($P<0.05$). In our study, basal IGF1 was associated with DHEAS and total testosterone. When basal values with values of the third month after isotretinoin treatment were compared, values of DHEAS, free T4, ALT, AST, LDL, triglyceride showed an increase while values of HOMA-IR did not change ($P<0.05$). It is identified that rate of change in the triglyceride was correlated with IGF-1, DHEAS, total testosterone, progesterone, LDL, estradiol ($P<0.05$).
Conclusion
In etiopathogenesis, both interactions with hormones and their interactions play important roles. İsotretinoin, is used in acne vulgaris, do not affect significantly pituitary, adrenal hormones, and insulin resistance. Hypertriglyceridemia is an important adverse effect in patient used isotretinoin. Particularly, triglyceride increase should be expected to the patient whom hormone levels are high. Further studies are necessary to evaluate both etiopathogenesis and the effect of isotretinoin.

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P1125

Both comorbidity burden and low testosterone can explain symptoms and signs of testosterone deficiency in men consulting for sexual dysfunction

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Background
Low testosterone (T) is frequent in men with chronical illnesses. The clinical features of T deficiency (TD) overlap with those of chronic diseases. The aim of this study is to evaluate the relative contribution of chronic disease score (CDS) and low T to the presence of TD symptoms.
Methods
A consecutive series of 3862 men (aged 52.1 ± 13.1 years) consulting for sexual dysfunction was studied. Several clinical and biochemical parameters were collected, including the structured interview ANDROTEST, for the assessment of TD symptoms. Penile colour Doppler ultrasound (PCDU) was also performed. Based on the medications taken, the CDS was calculated. For a subset of 1687 men, information on mortality was collected (follow-up of 4.3 ± 2.6 years).
Results
Higher CDS was associated with lower free and total T (TT) as well as with higher ANDROTEST score. When introducing CDS and TT in multivariable models adjusted for age, severe erectile dysfunction and impaired morning erections were associated with both CDS (odds ratio (OR) = 1.25(1.13;1.37) and 1.38(1.29;1.48), respectively) and low TT (OR = 1.11(1.00;1.23) and 1.13(1.06;1.21), respectively). Similar results were obtained for PCDU parameters. Hypoactive sexual desire was associated with low TT (OR = 1.21(1.13; 1.30)), whereas it was inversely related to CDS (OR = 0.91(0.84; 0.97)). When considering mortality for major cardiovascular events, TT < 8 nmol/l, but not CDS, was a significant predictor (hazard ratio = 5.57(1.51;20.63)).
Conclusions
Chronical illnesses are associated with an overt TD. Both chronic diseases and low T can be involved in determining symptoms present in subjects complaining about sexual dysfunction. This should be considered in the diagnostic workup for TD.

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P1126

Hormonal predictors of pathologic findings at magnetic resonance imaging in secondary hypogonadal men

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Introduction
Secondary hypogonadism (sHG) is the most common form of hypogonadism. sHG can arise from any dysregulation of hypothalamic-pituitary (HP) axis due to functional or organic disorders. HP organic disorders are often diagnosed using pituitary magnetic resonance imaging (MRI). However, MRI is an expensive and not widespread exam and it cannot be routinely offered to all sHG patient. The Endocrine Society guidelines suggest MRI scan in sHG men with total testosterone (TT) below 5.2 nmol/l. However, this suggestion is not supported by robust experimental evidence.To evaluate whether hormonal parameters can predict a pathologic finding at MRI in sHG men.
Methods
A consecutive series of 126 men (exploratory sample) attending the Outpatient Clinic of the University of Florence for sexual dysfunction and diagnosed as sHG according to the European Male Ageing Study criteria [LH < 9.4 U/l and TT < 10.5 nmol/l] performed a pituitary MRI. A cohort of 50 men attending the Outpatient Clinic of the Endocrinology section of the Maggiore Hospital of Bologna for sexual dysfunction and diagnosed as sHG was used as a validation sample.
Results
Among men of the exploratory sample, 46 reported pathologic findings at pituitary MRI (15 microadenomas, six macroadenomas, two pituitary hypoplasia, two Rathke's cleft cysts, four pituitary stalk diseases, one radiology signs of iron overload and 16 empty sella). These men did not differ from those with normal MRI, except for LH, FSH and TT. In the exploratory sample, the ROC curve analysis for the accuracy of TT in predicting a pathologic MRI was 0.62[0.52;0.73], $P=0.021$) and the best threshold was identified by the Youden index at 6.0 nmol/l (sensitivity = 48.9% and specificity 83.1%). The threshold of 5.2 nmol/l proposed by the Endocrine Society had a sensitivity of 36.2% and a specificity of 94.4%. Concerning LH and FSH, their accuracy was 0.65[0.55;0.75], $P=0.007$ and 0.68[0.58;0.77], $P=0.002$, respectively) showing the best threshold value at 1.9 U/l for LH (sensitivity = 61.4% and specificity 62.0%) and 4.2 U/l for FSH (sensitivity = 90.2% and specificity 43.8%). When applying these thresholds in the validation sample, TT < 6.0 nmol/l and LH < 1.9 U/l adequately recognized pathologic MRI, whereas TT < 5.2 nmol/l and FSH < 4.2 U/l did not.
Conclusions
In sHG subjects consulting for sexual dysfunction, hormonal parameters can help in recognizing men who deserve performing pituitary MRI. In particular, TT < 6.0 nmol/l and LH < 1.9 U/l adequately recognize patients with hypothalamic-pituitary organic disorders.

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P1127

If insulin resistance lowering therapy is effective in polycystic ovary syndrome patients with androgen excess, why to start with various symptom-oriented treatment forms?

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Insulin resistance (IR) is a dominant feature in polycystic ovary syndrome (PCOS). The author could treat more patients of comparable effect on

hyperandrogenic symptoms with metformin than with the contraceptive pill because of less contraindication and side effects. Since 2004, combining metformin with lifestyle modification, he has observed also reduction in BMI and waist-to-hip circumference ratio (WH). Guidelines recommend different treatment options according to the phenotype and main complaint of the patient. The author questions the validity of this concept. 25 hyperandrogenic PCOS patients diagnosed using the Rotterdam criteria (age 19–48; mean, 26 years) were treated uniformly with metformin 500 mg tablet three times daily, low glycaemic index diet (hypocaloric in the overweight), and increased physical activity for 12 months. Global Acne (A) and Ferriman-Gallwey hirsutism (H) scores, BMI, WH, and menstrual regularity were recorded every three month. In another group of 26 women who wanted to conceive (age 23–36, mean, 29 years), pregnancies and outcome were followed during treatment. By 12 months, significant mean decrease of A was 55%, H 32%, BMI 6% and WH 3%. Menstrual irregularity of 13/25 normalized in 9 (69%). Among 26 women desiring pregnancy, 24 conceived (89%) between 1st and 27th months of treatment; mean 9 months, modus 6.5. In 21 singleton pregnancies followed up till the end, 4 early pregnancy losses (19%) and 17 live births (81%) occurred; including 13 women with previous unsuccessful infertility treatment: eight singleton pregnancies, five live births (38%). Based on these observations, the author argues against the guidelines. The Rotterdam criteria increased the prevalence of PCOS by adding a group without hyperandrogenism, having lower IR. This distorts the efficacy of metformin if used in PCOS patients without hyperandrogenism. Treating select symptoms is not pathogenesis-oriented, and does not improve the other existing symptoms of the patient. Phenotype and main complaint change by time. There are no recommendations on the length of treatment; infertility studies restricted to six cycles are unable to reveal the real efficacy of metformin on infertility. If the combined treatment fails to improve a symptom with satisfaction, additional treatment can be added. In contrast to any other first choice drug recommended in the guidelines, metformin is cheaper, has a far better safety record and less contraindication, without time limit. The author recommends the early start and calm, long-lasting treatment with healthy lifestyle and metformin for all hyperandrogenic PCOS women.

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P1128

Turner's syndrome: adult life's implications

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Introduction
Turner syndrome (TS) is one of the most common chromosomal abnormalities, characterized by systemic involvement and susceptibility to some disorders that begin or progress in adult life. These lead to an increase in morbidity and mortality and a decrease in quality of life. The aim of this study was to analyse the profile of women with TS, who are currently followed in endocrinology, regarding: karyotype, age, final height and weight, puberty and fertility, and most prevalent comorbidities.
Methods
Retrospective cohort study of 74 women with TS followed in outpatient. Statistical analysis in SPSS,v.23 with correlation between karyotype and most frequent comorbidities.
Results
74 women with TS were followed, with a mean age of 35.5 ± 10.7 years. The age at diagnosis was 12.8 ± 6.15years. The karyotypes are: 45X at 39.2% ($n=29$), with deletion at 27% ($n=20$) and mosaicisms at 33.8% ($n=25$). Regarding the anthropometric data, the final height was 145.3 ± 7.2 cm and currently 32.4% ($n=24$) are overweight and 24.3% ($n=18$) obese. Gonadal dysgenesis is common, with 86.5% ($n=64$) under long-term hormone replacement therapy. Spontaneous puberty occurred in 12.2% ($n=9$) and one woman had a successful pregnancy. Amongst the most prevalent comorbidities, the metabolic disorders are: diabetes in 13.6% ($n=10$), only one patient with DM1, and dyslipidaemia in 63.5% ($n=47$). Thyroid disease: Hypothyroidism in 45.9% ($n=34$) by autoimmune thyroiditis. Osteometabolic disease: osteoporosis in 29.7% ($n=22$) and osteopenia in 31.1% ($n=23$). Cardiovascular: bicuspid aortic valve with aortic insufficiency in 10.8% ($n=8$) and coarctation of the aorta in 12.2% ($n=9$). Genito-urinary: horseshoe kidney in 4.1% ($n=3$) and 27% ($n=20$) with recurrent pyelonephritis. Dermatologic: nevi in 89.2% ($n=66$). Ophthalmologic: refractive error in 41.9% ($n=31$). Otorhinolaryngological: repetitive otitis in 54.1% ($n=40$) and 50% ($n=37$) with decreased auditory acuity. Neoplasms: 2 melanomas, 2 ovary dysgerminoma, 1 Willms tumour, 1 endometrial neoplasia, 1 gonadoblastoma, 1 appendix carcinoid. Psychosocial and cognitive: 35.2% ($n=26$) with basic education and 23% ($n=17$) higher education. 60.8% ($n=45$) with cognitive deficit and 14.9% ($n=11$) with depression. 79.7% ($n=59$) are single and 16.2% ($n=12$) are married. The monosomy 45X, compared to deletions or mosaic karyotypes, is more often associated with: atrioventricular block ($P=0.048$) and coarctation of the aorta ($P=0.048$)and less frequently with spontaneous puberty ($P=0.006$).
Conclusions
The most frequent comorbidities were: dyslipidaemia, hypothyroidism, nevi, refractive errors, repetitive otitis, and cognitive deficit. The follow-up in outpatient endocrinology clinics and the multidisciplinary approach to women with Turner's syndrome becomes essential for early diagnosis and early treatment of life-long comorbidities, as well as preventive counselling.

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P1129

Features of the clinical course of prolactinomas in women

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Aim
To study the course of clinical symptoms in women with prolactinomas.
Material and research methods
The study included the results of clinical examination and treatment of 73 patients with prolactin-secreting pituitary adenomas. In the main group, 84.9% (62 women) and 15.1% (11 men) aged from 17 to 74 years old, the average age was (38.5 ± 12.6 years). All patients were divided into 2 groups depending on the size of the education. Group I consisted of 47 patients with microprolactinomas (tumor size up to 10 mm). Group II of 15 patients with macroprolactinomas (tumor size more than 10 mm).
Results
Analysis of the age gradation of the studied patients by sex showed that men have a peak in the incidence of 41–50 years, and women 21–30 years old, that is, the vast majority of both men (63.6%) and women (74.2%) refers to the active working age – 21–50 years.The average age of women is 37.6 ± 13.0 years. If we consider the occurrence of adenomas by sex, then in men (72.1%) and women (64.5%) macroadenomas are significantly more common. The clinical manifestations of hyperprolactinemia in our cases were characterized as follows: neurological disorders were often observed in 28 (45.2%) patients with headache, dizziness, sleep disturbances, memory loss,, visual impairment in 10 (16.1%), metabolic disorders in 4 (6.45%) patients obesity, dyslipidemia, psycho-emotional disorders in 11 (17.7%) depression, asthenia, irritability and endocrine disorders caused by loss of other functions pituitary hypothyroidism in 19 (30.6%), diabetes insipidus in 2 (3.2%). In gynecological practice, pathologies accompanied by hyperprolactinemia are: dyshormonal diseases of the mammary gland (DGMG) in 17 (25.8%), hypogonadotropic amenorrhea in 25 (40.3%), premenstrual syndrome in 16 (25.8%), luteal phase insufficiency in 22 (35.5%), uterine myoma in 3 (4.8%), diencephalic puberty syndrome in 9 (14.5%), osteopenic syndrome in 6 (9.7%) patients.
Conclusion
Thus, with prolactinomas in women, neurological symptoms are more common, along with endocrine disorders.

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P1130

The metabolic effects of metformin, cyproterone-acetate and their combination in women with polycystic ovary syndrome

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Introduction
Metformin and oral contraceptive pills (OCP) are the most commonly prescribed medications among women with polycystic ovary syndrome (PCOS). The aim of this study was to compare effects of pill containing cyproterone-acetate (CPA) and metformin (METF) in women with PCOS during six months of follow-up.
Methods
Group of 60 women with PCOS diagnosed by ESHRE/ASRM criteria were divided into 3 subgroups (20 women each), which were treated with different therapeutic modalities over 6 months: 1)METF (age: 23.5±5.9 years, BMI: 24.8±4.2 kg/m^2); 2)CPA (Diane35®) (age:23.7±3.2 years; BMI: 22.6±4.6 kg/m^2); 3)METF+CPA (age: 22.3±4.0 years BMI: 25.8±4.8 kg/m^2). There were no between-group differences in age and BMI. The fasting glucose (FG), lipids and hormones (FSH, LH, testosterone, SHBG, insulin) were analyzed; menstrual cycles (MC) and hirsutism were monitored. Insulin resistance (IR) was determined by HOMA-IR.
Results
After six months of treatment, there were no significant change in BMI or FG in any group. The CPA group had significantly lower HOMA-IR compared to the METF and METF+CPA groups initially ($P=0.040$ and $P=0.039$, respectively). After treatment, HOMA-IR increased only in CPA group (2.7±2.3 vs. 4.3±2.2, $P=0.038$), and the between-group differences were lost. Initially there were no between-group differences in the lipids. After the therapy, in CPA and METF+CPA groups, total cholesterol rose ($P=0.005$ and $P<0.001$, respectively), as well as HDL ($P=0.003$ and $P=0.039$, respectively), and triglycerides ($P=0.001$ and $P=0.024$, respectively), while LDL did not change. Only in CPA group testosterone significantly decreased (2.6±1.3 vs. 2.0±0.6 nmol/l), while SHBG increased in both CPA (30.9±18.9 vs. 152.9±65.1 nmol/l, $P=0.036$) and in METF+CPA group (31.9±14.4 vs. 153.2±1.4, $P<0.001$). In all groups MC frequency significantly increased and hirsutism significantly reduced.
Conclusion
Different therapeutic modalities in women with PCOS may have a similar, clinically favorable response to the hirsutism and frequency of MC. However, it is of clinical importance to know the impact of long-term use of these modalities for the development of potential cardiometabolic comorbidities of this complex syndrome.

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P1131

Influence of kidney function on sex hormone profile in postmenopausal women

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Introduction
Disturbances in menstruation and fertility are often reported in women with chronic kidney disease (CKD), particularly in women undergoing dialysis treatment (CKD stage 5). Prolactin (Prl) seems to play a major role in this pathomechanism. However, there are only very few data on the gonadal axis and the androgen status in postmenopausal women with mild to moderate renal failure and in dialysis patients. Therefore, we prospectively studied the sex hormone profile in such a patient cohort.
Methods
197 female postmenopausal patients (median age:74 years, median. BMI: 28.6 kg/m^2) in the CKD stages 1–5 and 38 patients on chronic hemodialysis (CHD=stage CKD 5D) were prospectively evaluated. Besides renal function and routine parameters (estimated Glomerular Filtration Rate (eGFR)), CRP, albumin, the following hormones were measured: DHEAS, Testosterone (T), SHBG, Estradiol (E2), LH, FSH and Prl. Free Androgen (FAI) and free Estrogen Index (FEI) were calculated.
Results
The mean eGFR was 33.7 ml/min (range 10–140). The decrease in renal function from stage1 to 5 was associated (rho=−0.5; $P<0.001$) with an increase in Prl from median 6.9 to 16.3 ng/ml ($P<0.001$). Prl was significantly higher in the CHD group (median: 20.5 ng/ml vs. 9.5 ng/ml; $P<0.001$) in CKD patients. 9.3% had Prl values > 23.7 ng/ml in the CKD vs. 41% in the CHD patient group. LH and FSH were not affected by Prl. The androgens DHEAS and Testosterone as well as SHBG, FAI and FEI were unaffected by renal function. We found a negative correlation of BMI with SHBG (rho=−0.44; $P<0.001$), and a positive correlation for BMI with Testosterone (rho=0.18; $P<0.012$), FAI (rho=0.353; $P<0.001$) and with E2 (rho=0.2; $P<0.006$). E2, however, was significantly higher in the CHD group (median 21.7 vs. 11.7 pg/ml; $P<0.001$) and positively correlated with CRP (rho=0.502; $P<0.002$).
Summary
The decline in renal function from CKD stage 1 to 5 in postmenopausal women is mainly associated with an increase in Prl. Testosterone and FAI are independent from renal function but positively associated with BMI and negatively correlated with SHBG values. The significant higher E2 concentrations in patients undergoing hemodialysis are correlated with a higher inflammation status and most likely due to enhanced aromatization from Testosterone.

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P1132

Optimization of hyperproliferative syndrome treatment in woman on the background of obesity

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Nowadays fat tissue is considered as endocrine organ responsible for metabolism of sex hormones. Obesity is accompanied by a decrease in biosynthesis of 17β-estradiol (2-hydroxyestrone) inactive metabolites and increased production of aggressive metabolites (16-hydroxyestrone). This factor leads to hyperproliferative syndrome, which includes hormonal-dependent lesions of target organs: uterine leiomyomas, adenomyosis, hyperplasia of endometrium, tumor-like lesions of the ovaries, fibrocystic disease of the mammary glands, dysplasia of the cervical epithelium. Materials and methods. We observed 50 women of reproductive age (mean age 34.6±2.5 years) with adenomyosis, diffuse form of fibrocystic disease of the mammary gland and obesity. We studied complaints, anamnesis of diseases, made physical examination (BMI, waist/hip ratio), gynecological examination, ultrasound of small pelvis organs and mammary glands, laboratory tests (carbohydrate and lipid metabolism, HOMA-IR indexes). The main group consisted of 25 patients receiving dienogest (2.0 mg daily on continuous mode) and a combined drug (indole-3-carbinol - 200 mg and epigallocatechin-3-gallate - 45 mg) (two capsules twice a day). Comparative group took monotherapy with dienogest (2.0 mg per day in continuous mode). Duration of treatment was 6 months. All the examined patients complained of increased volume, sensitivity and soreness of the breasts in the second phase of the menstrual cycle. Aching pain of in the lower abdomen, which prevailed before menstruation disturbed 74.0% of investigated. Menstrual dysfunction was noted in 96.0% of women: dysmenorrhea in 64.0%, irregular menstrual cycle in 22.0%, and hyperpolymenorrhea in 78.2% patients, 64.0% of surveyed had a bloody discharge before/after menstruation. Waist circumference, as marker of excess visceral fat associated with the presence of insulin resistance, in all examined patients exceeded 85 cm. The presence of visceral obesity was associated with signs of dyslipidemia (hypercholesterolemia, increased levels of low density lipoprotein), and a carbohydrate metabolism disorder, which manifested in increased fasting glucose and the HOMA-IR levels. After the end of treatment sensitivity and pain in the mammary glands in the second phase of menstrual cycle were decreased in all patients. Normalization of menstrual function was noted by 82.0% of women. Also in main group, levels of total cholesterol and low density lipoproteins have decreased statistically significant. We also observed the improvement of carbohydrate metabolism, and a significant decline of the HOMA-IR index. Conclusions. Multi-target therapy (indole-3-carbinol-200 mg, epigallocatechin-3-gallate-45 mg) provides a complex effect, which manifests itself in inhibiting pathological hyperplastic processes in hormone-dependent

organs and tissues of the female reproductive system on the background of obesity, as well as promotes the normalization of lipid and carbohydrate metabolism in these very patients.

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P1133

Serum anti-Müllerian hormone is significantly associated with higher luteinizing hormone level in polycystic ovary syndrome

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Background
Recent data highlight the role of anti-Müllerian hormone (AMH) to trigger the neuroendocrine abnormalities involving GnRH and secretion of gonadotropins in polycystic ovary syndrome (PCOS).
Aim
To study factors significantly correlated with neuroendocrine dysfunction in PCOS, with focus on AMH.
Subjects and methods
We performed a cross-sectional study in 137 patients with PCOS selected by Rotterdam 2003 criteria and 166 controls age matched, recruited at the National Institute of Endocrinology, Bucharest, Romania. Clinical and biochemical parameters, including BMI, fasting glucose and insulin, serum LH, FSH, AMH and TT were determined and the values are expressed as mean ±S.E.M. HOMA-IR was calculated to quantify insulin resistance.
Results
LH values were 11.24±0.79 UI/l in PCOS and 5.97±0.41 UI/l in controls; FSH values were 6.23±0.22 UI/l in PCOS and 7.65±0.53 UI/l in controls; and AMH was 69.16±3.29 pmol/l in PCOS and 25.24±2.93 pmol/l in controls. LH and AMH were significantly higher ($P< 0.0001$, $P< 0.0001$) and FSH significantly lower ($P=0.03$) in PCOS than in controls. In PCOS, LH was positively correlated with AMH ($P< 0.0001$) and TT ($P=0.0006$) while BMI ($P=-0.1009$), fasting-Ins and HOMA-IR were not significantly correlated with LH in these patients. In stepwise linear regressions including as effects AMH, TT, BMI, fasting-Ins or HOMA-IR and age, AMH remained a significant independent predictor for LH values in PCOS ($P=0.0002$). FSH had no significant correlations in PCOS. There were no significant correlations for gonadotropins in controls.
Conclusions
These data reveal AMH as a significant positive independent predictor for higher LH values in PCOS and support the role of AMH in maintaining high levels of LH in PCOS.

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P1134

Hyperandrogenism in postmenopausal women

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Introduction
The presentation of new onset hyperandrogenism is extremely rare in postmenopausal women. In premenopausal women, the most common cause of androgen excess is polycystic ovary syndrome. In contrast, when hyperandrogenism develops in postmenopausal women, it is usually associated with other causes, such as ovarian hyperthecosis or an androgen secreting tumor. We describe 5 patients with hyperandrogenism (Table 1). Total Testosterone 0.06–0.86 ng/ml, free testosterone 2–12.8 ng/dl, DHEA-S 0.3–2.5 µg/ml, Androstendiona 0.21–4.5 ng/ml, FSH postmenopausal 26–139 U/l, LH postmenopausal 20–65 U/l, Estradiol postmenopausal <49 pg/ml, Hemoglobine 12–15.3 g/dl, Hematocrite 35–46%
Conclusion
Diagnosing the source of hyperandrogenism in postmenopausal women remains a clinical challenge. In post menopausal women with progressive hirsutism or virilization, it may be reasonable to consider bilateral oopherectomy in the setting of normal ovarian imaging and biochemical evidence of ovarian source of the hyperandrogenism. The combination of a detailed history, proper clinical assessment and appropriate laboratory and imaging evaluation is required for the accurate differential diagnosis and management.

Table 1

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	61	51	68	51	57
Ferriman Galleway	25	36	13	12	12
Total testosterone	4.41	3.16	13.2	6.9	0.68
Free testosterone	86.2	64.2	160.9	190.2	16.1
DHEA-S	0.61	1.71	0.34	55.2	1.63
Androstenodione	2.1	3.6	2.4	10	3.9
FSH/LH	61.8/20.1	23.5/19.1	52.6/40.6	31.9/14.5	31.9/18.5
Estrogen	25.7	29.5	31.9	50.2	13.4
Nugent	0.9	1.1	1.2	26	1.2
Hb/Hemotocrite	17.3/51.4	17.8/52.1	16.1/48.9	16/47.2	13.1/41.4
Ovaric US	Normal	Normal	Tumor in Right ovary	Normal	Bilateral Solid tumor
Adrenal TC	Bilateral Adenoma	Bilateral Adenoma	Normal	Adrenal Carcinoma	Normal
Surgery	Bilateral Oophorectomy	Bilateral Oophorectomy	Bilateral Oophorectomy	Unresectable	Bilateral Oophorectomy
AP	Leydig Tumor	Leydig Tumor	Leydig Tumor		Hyperthecosis
Normalization Androgenism	Yes	Yes	Yes	No	Yes

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P1135

Assessment of the feasibility and safety of a novel transvaginal ovarian drilling method in a bovine model: ovarian rebalancing

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Polycystic Ovary Syndrome (PCOS), the most common endocrinopathy affecting reproductive-aged women, is characterized by oligo-/anovulation, hyperandrogenism and polycystic ovaries. In PCOS women with anovulatory infertility, the accepted first-line treatment is clomiphene citrate (CC). For patients resistant to CC, laparoscopic ovarian drilling (LOD) is recommended as a second-line therapy. Whilst very effective, LOD is an invasive technique requiring general anaesthesia and associated with a significant risk of postoperative adhesions. The aim of the study was to evaluate the feasibility and safety of a new transvaginal ovarian drilling procedure in a bovine model. Thirteen female cattle aged 3–8 years were selected to have ovarian morphology and size similar to human PCOS ovaries. The procedure was performed under light epidural anaesthesia using the *AblaCare Kit*, comprising a device (an ablation catheter deployed through a needle) mounted on a vaginal ultrasound probe, and a radiofrequency energy generator. After transvaginal introduction of the probe, the needle was inserted into each ovary and the catheter released to deliver 4–6 ablations/ovary. Animal sacrifice or ovariectomies were performed on day 0, 7, 36, 69–72 of the procedure to harvest ovaries and reproductive tract. The procedure was successfully completed in all animals without any sign of pain or significant discomfort. Before performing ablations, the needle and catheter were easily visualised and located within the ovary by ultrasound. No adverse events or significant technical difficulties occurred during or after procedure, demonstrating good feasibility. From a safety standpoint, the macroscopic analysis of the harvested ovaries showed no adhesions or damage to the ovarian surface aside from the needle puncture. Thermal lesions were confined to the ablation zones at days 0 ($n=3$) and 7 ($n=4$) and their volume amounted to 5.74% and 5.20% of the total ovarian volume respectively, in line with target volume reduction known to achieve efficacy of ovarian drilling. No lesions were visible at days 36 and 69–72 ($n=3$ both, $P<0.001$). The ovarian structure was conserved, and no damage secondary to ablation or puncture was found in surrounding organs. All animals, monitored by ultrasound after procedure, maintained normal cycles with no disruption of folliculogenesis/corpus luteum development. The technical feasibility and safety of this novel procedure, ovarian rebalancing, using a dedicated device were successfully assessed in the bovine model. These preclinical results need to be validated in a clinical trial in anovulatory PCOS women, that will additionally allow to evaluate the efficacy in terms of ovulation induction.

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P1136

Kisspeptin in regulation of menstrual function in patients with resistant hyperprolactinemia

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Introduction
Patients with resistant prolactinomas have reduced fertility todue to chronic anovulation and hypoplasia of uterus and ovaries. SERM tamoxifen demonstrates a recovery of menstrual function and ovulation and reverses the hypoplasia of the uterus. The mechanism of its action in case of hyperprolactinemia is not clear yet.
Aim
To study the role of kisspeptin in restoration of reproductive function in patients with prolactinomas treated by tamoxifen.
Materials and patients
This pilot study included 2 women of reproductive age (30 and 27 years old) with resistant prolactinomas treated by maximal doses of cabergoline 4.5 mg per week. Patients had amenorrhea for 6 and 8 months. Tamoxifen was administered as adjuvant therapy in dose of 10 mg per day for 3 months. Hormonal and pelvic ultrasonic parameters were evaluated before and after complex treatment.
Results
Before addition of tamoxifen, prolactin level was 2658 U/l and 3001 U/l, LH and FSH levels were normal. At ultrasonography, patients presented symptoms of anovulative menstrual cycle. There were no any differences between kisspeptin levels before and after tamoxifen treatment and its levels varied from 0.041 to 0.053 in first patient and from 0.069 to 0.077 in second, $P=0.18$. Normal menstrual cycle was recovered in 1 month after start of tamoxifen in both women. Prolactin levels decreased by 4.4% and 6.5%. Dynamics of ultrasound picture at 3 months revealed significant improvement of the state of reproductive organs with signs of ovulation, presence of corpus luteum and dominant follicle.
Conclusion
Tamoxifen recovers menstrual function without changes of kisspeptin and normalization of prolactin levels which may be explained by direct activation of estrogen receptors and positive affects at the levels of ovaries and endometrium without recovering of the hypothalamic regulation.

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P1137

Clinical and para-clinical characteristics of Klinefelter syndrome diagnosed in adulthood

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Klinefelter syndrome (KS) is the most frequent sex chromosomal disorder and affects approximately one in 660 newborn boys. The phenotype is variable ranging from 'nearnormal' to a significantly affected individual. Typically, diagnosis is delayed with the majority of patients identified during fertility workup in adulthood, and only 10% of patients diagnosed prior to puberty.
Patients and methods
This is an 8-year retrospective study of the clinical and paraclinical characteristics of patients with Klinefelter syndrome diagnosed in the Department of Cytogenetics and Reproductive Biology at Farhat Hached University Hospital Center at Sousse.
Results
The study involved 129 patients with a mean age of 35.7 years [21–55]. The reason for consultation was infertility in 88.4% of cases (117 patients), signs of hypogonadism in 7% of cases (9 patients), erectile dysfunction in 2.3% (3 patients) and missing in 3 patients. All patients had bilateral testicular hypotrophy. Eighty-two patients (63.6%) had normal secondary sexual characteristics. One hundred and nineteen patients (92.2%) had azoospermia and 2 patients (1.6%) had oligozoospermia. In 8 patients, the spermogram result was not available. Twenty-eight patients had a hormonal assessment. Testosterone was normal low between [2.7–5.67] ng/ml in 13 patients and low in 15 patients.
Conclusion
The diagnosis of KS should be suspected in patients with bilateral testicular hypotrophy associated with primary infertility in adults. Clearly, the earlier the diagnosis is made, the greater the benefits. Thanks to the new medically assisted procreation techniques, based essentially on the techniques of testicular extraction and sperm, these patients' chances of procreation have become real.

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P1138

Abstract Unavailable.

P1139

Androgen steroids profile in follicular fluid of Polycystic Ovary Syndrome (PCOS) women

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Polycystic Ovary Syndrome (PCOS), the most common endocrinopathy of reproductive-age women, was initially defined by the association of anovulation and clinical and/or biochemical hyperandrogenism (1990 NIH). Since Rotterdam Consensus Conference in 2003, its diagnosis requires the presence of at least two of the following features: oligo-/anovulation, hyperandrogenism and polycystic ovaries on ultrasound. However, since its introduction, this definition was strongly challenged by Androgen Excess Society, as they supported a central role of hyperandrogenism in PCOS pathogenesis, thus considering it as an essential diagnostic criterion. Indeed, theca cells of PCOS women appear to have the intrinsic property of synthesizing excessive amounts of androgens because of a possibly genetically determined hyperexpression and/or hyperactivity of steroidogenesis enzymes, notably cytochrome P450c17α, the limiting step in androgens biosynthesis in the ovary and adrenal gland. Hyperandrogenism may in turn promote adipose tissue accumulation at abdominal level, typically accompanied by insulin resistance. Compensatory increased insulin levels at the ovary can further stimulate androgens synthesis, thus creating a vicious circle. The aim of the study was to characterise androgen steroids profile in follicular fluid (FF) of PCOS women. Three groups were evaluated ($n=20$, each), PCOS patients diagnosed according to Rotterdam criteria, women requiring a Medically Assisted Reproduction procedure for another infertility cause (control group) and women presenting ≥ 12 follicles/ovary on ultrasound without other PCOS characteristic features (ECHO group). Each group of patients equally included normal weight (BMI 18-25 kg/m^2) and obese (BMI >30 kg/m^2) women. Androgen steroids were measured in FF by mass spectrophotometry. Follicular concentrations of testosterone, dehydroepiandrosterone (DHEA) and delta4-androstenedione were significantly higher in PCOS women ($P<0.01$ compared to controls). A significant difference between PCOS and ECHO groups was found for 17-OH pregnenolone ($P<0.05$), DHEA and delta4-androstenedione ($P<0.01$). Concerning adrenal androgens, PCOS patients presented lower 11-deoxycorticosterone (DOC) levels compared to controls ($P<0.01$). No difference was found respecting corticosterone, cortisol, 11-OH cortisol and 17-OH progesterone. Interestingly, follicular levels of testosterone, DHEA and delta4-androstenedione were positively correlated with cycle duration ($P<0.05$), while a negative correlation was observed between DOC concentration and plasmatic Anti-Müllerian Hormone levels ($P=0.02$) as well as ovarian follicles number ($P=0.03$). Follicular concentrations of androgen steroids seem to be increased in PCOS women independently of the presence of a systemic hyperandrogenism. Notably, we found a selective increase in ovarian androgens, further suggesting that PCOS pathogenesis is strongly linked with an initial alteration of theca cells leading to an excessive androgens biosynthesis.

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P1140

Low levels of kisspeptin in patients with acromegaly

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Introduction
Acromegaly impairs the hypothalamic-pituitary-gonadal (HPG) axis and reproductive function that causes amenorrhea and infertility. The mechanism of these disturbances is not clear. Kisspeptin and neurokinin B are very important neuropeptides regulating cyclic LH release from pituitary due to stimulation of GnRH.
Aim
The purpose of this study was to assess the role of key reproductive neuropeptides in regulation of menstrual function in patients with acromegaly.
Materials and methods
The study included 30 patients of reproductive age with acromegaly, the average age was 37 [30;42] years, BMI – 26.1 [24.7;30.5], the period from first symptoms to operation was about 5 [3;8] years. The control group consisted of 17 healthy women with regular menstrual cycle of similar age and BMI. Blood samples for neurokinin B and kisspeptin were collected into tubes containing EDTA and aprotinine, immediately centrifuged and stored at −80°C until measurement. Neuropeptides were detected by EIA (with previous extraction procedure for kisspeptin).
Results
Macroadenoma was confirmed in 26 patients, 4 patients had microadenomas. Only 16 women presented with normal menstrual cycle, 8 – amenorrhea, 2 – oligomenorrhea, 2 - menorrhagia. The levels of gonadotropins and inhibin B were statistically lower in the group of acromegaly compared to control, FSH 3.9 [2.4; 5.0] and 6.5 [5.2; 7.9], $P<0.001$; LH 2.9 [1.3; 4.1] and 4.6 [4.1; 5.9], $P=0.002$; inhibin B 32.9 [19.7; 76.7] and 79.1 [65.6; 98.6], $P=0.004$. Kisspeptin was also reduced in patients 7.2 [0,1;11,7] ng/ml and 12.5 [11.8;13.6], $P<0.001$, but there were no differences in neurokinin B level. The same trend in hormonal characteristics was revealed during analysis by groups depending on menstrual function. The presence of negative correlations was noted between kisspeptin and IGF-1, ($r=0.66$, $P=<0.001$) kisspeptin and GH ($r=0.54$, $P=0.02$) and positive correlation between kisspeptin and LH ($r=0.35$, $P=0.006$). Hyperprolactinemia was registered in 50% of patients but without correlation between prolactin and neuropeptides studied.
Conclusion
Kisspeptin plays a significant role in regulation of menstrual function in patients with acromegaly. The decrease of kisspeptin secretion is dependent on the severity of the disease and is not related to prolactin level.

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P1141

Ovarian expression of adipokines in polycystic ovary syndrome: characterisation of the 'ECHO' condition

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Introduction
Polycystic Ovary Syndrome (PCOS) is a very common endocrinopathy affecting 6 to 13% of women of reproductive age and one of the leading causes of female poor fertility. It was initially defined by the association of anovulation and clinical and/or biochemical hyperandrogenism (1990 National Institutes of Health-sponsored conference). Since Rotterdam ESHRE/ASRM Consensus Conference in 2003, polycystic ovaries morphology on ultrasound (ECHO condition) was added as a supplementary diagnostic criterion, although not mandatory. Indeed, PCOS is currently defined by at least two of the three features mentioned above. Despite some discordant results, ECHO condition seems to be associated with higher levels of androgens and major insulin resistance. Further, a large number of ovarian follicles is a known risk factor of ovarian hyperstimulation syndrome during a Medically Assisted Reproduction (MAR) procedure.
Objective
Since adipokines role in reproductive function is well known, the aim of our study was to characterise the ovarian mRNA expression of some adipokines and their receptors in PCOS women and compare it with the ECHO condition.
Methods
PCOS patients ($n=20$) were compared to women presenting ECHO condition ($n=19$) or another infertility cause requiring a MAR procedure ($n=22$). Each group equally included normal weight (BMI 18–25 kg/m^2) and obese (BMI > 30 kg/m^2) women. Adipokines expression was studied both in follicular fluid (ELISA) and granulosa cells (qPCR) obtained during the oocyte retrieval preceding *in vitro* fertilisation. Hormonal profile and reproduction outcomes were also collected for all patients.
Results
Ovarian expression of all adipokines varied according to weight profile, with chemerin, resistin, visfatin, omentin and apelin levels higher in obese patients. Compared to controls, PCOS women presented a higher expression of chemerin, apelin and omentin ($P<0.001$), while ECHO group was characterised by lower levels of omentin ($P<0.01$). Same results were found in follicular fluid and granulosa cells. Interestingly, compared to PCOS group, ECHO women had a greater number of mature oocytes and embryos ($P<0.01$) and lower concentrations of plasma Anti-Müllerian Hormone ($P<0.05$). No difference was observed concerning adiponectin, resistin and visfatin expression.
Conclusion
Ovarian expression of chemerin, apelin and omentin is higher in PCOS patients compared to controls. Interestingly, the regulation of these adipokines seems to be different in women presenting only polycystic ovarian morphology, who seem to be characterised by a different hormonal profile and better IVF outcomes. Thus, ECHO could be an independent physiopathogenic condition whose metabolic and reproductive profile remains to be clarified.

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P1142

Changes of steroid hormones in pregnant ex-smokers and their newborns

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Smoking has many effects on human health and reproduction. Women are generally recommended to quit smoking before conception. Cessation improves fertility and helps avoid many health risks for the mother and the child and plays an important role in the future development and health of the offspring. We have decided to perform a study following changes in the production of steroid hormones in pregnant smokers and ex-smokers compared to non-smokers. In physiological pregnancies, there are differences in the levels of steroid hormones in a pregnant woman depending on the sex of the fetus, and there are differences in the steroids of newborns depending on their sex and the type of delivery. We have focused on changes in steroidogenesis in the blood of mothers in their 37th week of pregnancy and in mixed cord blood of their newborns. The study included 47 healthy women, of which 14 were active smokers, 11 ex-smokers (smoking cessation lasts more than a year), and 22 non-smokers. All women had physiological course of gravidity, gave birth spontaneously, and carried female fetus. Selected steroid hormones (cortisol, cortisone, dehydroepiandrosterone (DHEA), 7α-hydroxy-dehydroepiandrosterone, (7α-OH-DHEA), 7β-hydroxy-dehydroepiandrosterone, (7β-OH-DHEA), 7-oxo-dehydroepiandrosterone (7-oxo-DHEA), pregnenolone, 17α-hydroxy-pregnenolone (17-OH-pregnenolone), testosterone, androstenedione, progesterone, 17-OHprogesterone, corticosterone, estrone, estradiol, and estriol) were measured using methods LC-MS/MS. Local ethical committee approved the study. We found higher levels of androstenedione and lower levels of 17-OH-pregnenolone at the 37th week of pregnancy in smokers and ex-smokers compared to non-smokers. The levels of 7β-OH-DHEA, 7-oxo-DHEA were lower in smokers compared to ex-smokers and non-smokers. Other measured steroids did not differ for ex-smokers or smokers. We have measured lower levels of 7α -OH-DHEA in female newborns delivered by non-smokers compared to other groups, while other measured hormones showed no significant differences. Even a history of smoking can induce changes in the production of steroids during pregnancy. Our study shows that hormonal dysbalances found in pregnant ex-smokers could be similar to pregnant smokers for some steroids, while levels of other steroids will normalize with abstinence. This finding correlates with our data from previous studies and studies of other authors about long lasting influence of smoking on steroid metabolome. However, the results of our study are limited by the smaller number of participants.

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P1143

AdipoRon, an adiponectin receptor agonist, reduces the proliferation and secretion of steroids by human granulosa cells

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Diet, and especially metabolic dysregulation such as obesity can influence the ovarian activity. Adipose tissue plays an important role since it is known to be one of the most important endocrine organs producing hundreds of cytokines, such as adiponectin. Our team has observed that adiponectin modulated steroid secretion by the ovarian granulosa cells and its concentration in the follicular fluid was influenced by the metabolic status. Recently, a small adiponectin mimetic synthetic molecule, called AdipoRon, has been developed. In this study, we have the objective to study its role on human granulosa cells. The experiments were performed on the KGN cell line, a human granulosa line (Nishi et al., 2001), as well as on primary granulosa cells prepared from IVF protocol. The cells were exposed to AdipoRon (2.5 μM and 25 μM) for 48h and 96 h. The dose of 25 μM has been described in the literature and observed in the laboratory, as being activator of the adiponectin pathway (10 μg/ml). After 96 hours of AdipoRon (25 μM) exposure, primary granulosa cells and KGN showed a 30% reduction in cell proliferation with no change in cell mortality, observed by BrDU incorporation and PCNA protein expression. AdipoRon also modified cell metabolism (lactate increase), reduction in steroid secretion and in the Reactive Oxygen Species production, which is a marker of cellular stress. In conclusion, these results indicate that AdipoRon is able to modify the metabolism of granulosa cells and could be a potential compound in the development of new therapeutic strategies requiring the reduction in cell proliferation or steroid production of the granulosa cells.

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P1144

The impact of vitamin D supplementation on HOMA IR and ovulation in patients with polycystic ovarian syndrome

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Introduction
Polycystic ovarian syndrome (PCOs) is a common cause of ovarian dysfunction in women with anovulation. Vitamin D plays a physiologic role in reproduction including ovarian follicular development and luteinization via altering anti-müllerian hormone (AMH) signalling, follicle-stimulating hormone sensitivity and progesterone production in human granulosa cells. Low vitamin D levels may exacerbate the symptoms of PCOS, including insulin resistance, ovulatory, menstrual irregularities, infertility, obesity and elevate the risk of cardiovascular diseases.
Aim
Aim of the study is to estimate the impact of vitamin D supplementation on insulin resistance, using HOMA IR calculation, in PCOs patients.
Materials and methods
The study includes 60 patients with PCOs and normal levels of vitamin D (between 50–100 ng/ml) divided in four groups. Before treatment, we measured fasting glucosae and insulin levels and calculate HOMA IR to all patients. Then we divided patients in four treatment groups: MD- treated with MET (metformin) plus LGD(low glycaemic diet-1800 Kcal), MDW- treated with MET plus LGD plus vitamin D supplementation 14000 ij/weekly, MDD2- treated with MET plus LGD plus vitamin D supplementation 2000 ij/daily and MDD4- treated with MET plus LGD plus vitamin D supplementation 4000 ij/daily. During period of six months we followed progesterone levels on 21th day of menstrual cycle. After six months of treatment we evaluated fasting glucosae, fasting insulin and HOMA IR.
Results
After treatment mean values of HOMA IR in MD group was reduced from 2.93 ± 1.43 to 2.31 ± 1.01(reduced for 21%), in MDW group was reduced from 2.84 ± 0.93 to 2.30 ± 1.22 (reduced for 19%), in MDD2 group was reduced from 2.89 ± 1.21 to 2.19 ± 1.44 (reduced for 24%) and in MDD4 group was reduced from 2.99 ± 1.40 to 1.97 ± 0.95(reduced for 34%) ($P < 0.05$). Also number of biochemical confirmed ovulations, during six months of treatment, was the highest in MDD4 group, 2.45 ovulations per patients, then in MDD2 group, 1.61 ovulations/patients, while in the MD i MDW groups were similar 1.14 and 1.11 ovulation/patients.
Conclusion
In patients with metformin and diet treated polycystic ovarian syndrome, weekly supplementation with vitamin D have no additional effect on the reduction of insulin resistance. However, daily supplementation with vitamin D has a significant effect on the additional reduction of insulin resistance, especially at a dose of 4000 IU per day. Also, the same dose significantly improves ovulation in patients who are already treated with metformin and diet.

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P1145

Prevalence of equol production capacity in women with polycystic ovary syndrome (PCOS) and association with reproductive, hormonal and metagenomic parameters before and 3 days after isoflavone challenge

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Objective
Polycystic ovary syndrome (PCOS) is characterized by biochemical and clinical androgen excess and disturbed ovarian function and is associated with disorders of glucose and lipid metabolism. Isoflavones are phytoestrogens exerting endocrine effects on human hormone and metabolic signaling and may influence symptom penetrance in PCOS. We investigated whether women with PCOS and healthy controls have alterations in their capacity to metabolize hormonally active dietary isoflavones to produce the metabolite equol and whether this capacity is associated with PCOS-typical clinical, biochemical and metagenomic pathways.
Methods
Urine isoflavone and equol levels were measured by mass spectrometry in women with PCOS ($n = 24$) and non-PCOS controls ($n = 20$) before and after 3 days of soy challenge. Bacterial equol production was evaluated using the log(equol: daidzein ratio). Group size was calculated according to the effect of equol. Metagenome analyses were performed using PiCRUST (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States), LEfSe (Linear discriminant analysis effect size) and QIIME1.9 (Quantitative Insights Into Microbial Ecology).
Results
The prevalence of equol producers was 21% in the PCOS group and 42% in controls; however, this difference was not statistically significant due to the pilot study sample size. In the whole cohort, larger equol production was associated with lower serum total and free testosterone, androstenedione and anti-Müllerian hormone (AMH) levels, but only AMH remained significant in both groups separately. After isoflavone challenge, stool metagenome pathway groups primarily associated with PCOS phenotypes aligned with the pattern of the control group.
Summary and Conclusions
We conclude that a reduced capacity to produce equol is likely not a driving factor in the pathophysiology of PCOS but might rather modulate several aspects of PCOS. These women might therefore benefit from consuming isoflavone-rich foods, as their stool metagenome findings shifted to the control pattern after isoflavone ingestion.

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P1146

Recurrent reversal of male congenital hypogonadotropic hypogonadism and atypical fertility: A case report.

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Abstract
Congenital hypogonadotropic hypogonadism (CHH) is characterized by isolated GnRH deficiency in the absence of central anatomical causes. Classically considered to be a permanent disorder, CHH reversal has been reported in up to 15% of cases. However, reversal may not always be life-long, as hypogonadism relapse can occur in a subset of patients. Criteria for reversal normalization of circulating sex steroids, and spontaneous fertility. We report a 26-yrs-old man, who presented with incomplete pubertal incomplete pubertal development, infertility, low libido, sporadic sexual activity with no ejaculation and normal sense of smell, as confirmed by a formal smell test. Physical examination revealed eunuchoid body proportions, pubic hair tanner stage 3, penis length, 4 cm, and testicular sizes 2.8×1.7 cm (right), and 2.7×1.5 cm (left). Hormonal evaluation showed testosterone (T), 35 ng/dl, LH, 0.8 U/L FSH: 1.53 U/L (IFMA), and otherwise normal pituitary function. Hypothalamic-pituitary imaging was normal. Genetic analysis revealed a homozygous GnRHR mutation (p.Q106R/p.Q106R), previously known to be partially inactivating. He was diagnosed with normosmic CHH and started on testosterone replacement therapy (TRT) with intramuscular testosterone cypionate 200 mg every 3 weeks. After one year his wife was pregnant while he was still on TRT. Treatment was discontinued, and further evaluation showed an increment in the testicular size (4,0×2,5 cm, bilaterally), T, 209 ng/dl, LH, 4.2 U/L, FSH, 8.1 U/L, sperm count of 17×10^6/ml. One year after therapy withdrawal he complained again of low libido and lack of energy, suggesting relapse of the hypogonadism. Hormonal evaluation showed T, 66 ng/dl, and LH, 3.8 U/L. Three years after proper TRT with intramuscular testosterone cypionate 200mg injections every 14 days, his wife had a new spontaneous pregnancy. After discontinuation of testosterone replacement, a new spermogram confirmed fertility in addition to normal sexual hormones level. This case shows a recurrent atypical spontaneous fertility in the course of TRT in a CHH patient. Unlike hCG therapy, TRT is not supposed to induce gonadal maturation or fertility in these patients, by the significant negative regulatory effect of GnRH pulse frequency. Nevertheless, it has been speculated that testosterone exposure could act as a trigger to reversal, by stimulating GnRH neuronal plasticity in predisposed patients. Spontaneous testicular growth and/or fertility are indicatives of CHH reversal. Long-term follow-up with physical examination, assessment of the possibility of reversal, relapse and counselling about fertility is necessary for all CHH patients.

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P1147

Acne in girls and young women with hyperandrogenism

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Introduction
Acne vulgaris is the most common skin disorder, which may be sometimes the only early clinical manifestation of hyperandrogenemia. Main role in its pathogenesis play: genetical predisposition as well as hormonal and environmental disturbances, which may begin in puberty. It has been widely discussed at what age and what kind of diagnostics should be performed in this area.
Aim of the study
Was to evaluate concentrations of selected hormones and their impact on skin changes in girls and young women with hyperandrogenism.
Material and methods
250 girls and young women, aged 16–36 years, were evaluated. We assessed body height, weight, BMI, concentrations of hormones: TSH, fT3, fT4, FSH, LH, estradiol, prolactin, dehydroepiandrosterone sulfate (DHEA-S), androstenedione, testosterone, sex hormone binding globulin (SHBG), 17-hydroxyprogesterone. Furthermore, we analyzed glucose and insulin concentrations, both fasting and in oral glucose tolerance test. Statistical analysis was made with Statistica 9.0pl.
Results
Subjects presented significantly higher concentrations of androgens: testosterone ($P<0.000$), DHEA-S ($P<0.000$), androstenedione ($P=0.007$) and high Free Androgen Index ($P=0.016$) comparing to the control group. There was a significant negative correlation ($r=-0.420$; $P<0.000$) between concentrations of testosterone, androstenedione, DHEA-S and concentration of SHBG ($r=-0.391$; $P<0.000$).
Conclusions
Acne is a significant clinical marker of hyperandrogenism and cannot be considered as a temporary sign of puberty in female teenagers.

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P1148

Improvement of bone microarchitecture after 30 months of testosterone substitution therapy in young patients with Klinefelter Syndrome

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Background
Klinefelter Syndrome (KS) patients, defined by a 47 XXY karyotype, suffer from osteoporosis, with an increased risk of mortality after femoral neck fracture. The mechanisms underlying this bone alteration remain unclear.
Patients and methods
In KS patients naïve from testosterone substitution therapy (TST), we assessed bone microarchitecture at distal radius and tibia by High Resolution peripheral Computed Quantitative Tomography, and body composition by Dual-energy X-ray absorptiometry, before and after 30 months of TST. At baseline, we measured sex steroids: total testosterone (tT) by radio immunology assay (RIA) after diethylether extraction, bioavailable testosterone (bio-T) by RIA after ammonium sulphate precipitation, and total 17β-estradiol (17βE2) by RIA.
Results
Between February 2014 and November 2015, we included 34 KS patients (mean ± SD age: 23.7 ± 7.8 years and BMI: 20.9 ± 3.4 kg/m^2). They were paired with 72 age-matched controls. We found low levels of tT (<10.4 nmol/l), bio-T (<2.25 nmol/l), and 17βE2 (<66.0 pmol/l) in respectively 10 (42%), 15 (62%) and 17 (71%) KS patients. Compared to controls, patients with KS had lower Relative Appendicular Lean Mass (RALM, 7.53 ± 1.28 vs 8.65 ± 1.05 kg/m^2, $P<0.01$), and higher fat mass percentage (22.3 ± 6.8 vs 14.1 ± 6.2, $P<0.01$). They presented impaired cortical and trabecular compartments, particularly at the tibia, especially in KS patients with low levels of sex steroids or low RALM. After a median 30.4 [29.7–31.0] months of TST, 16 (67%) of KS patients were reassessed. We observed an increase of cortical volumetric Bone Mineral Density and cortical thickness, respectively at the radius 787 ± 81 to 838 ± 46 mg/cm^3; $P<0.01$ and 0.75 ± 0.25 to 0.86 ± 0.18 mm; $P<0.05$ and at the tibia 847 ± 49 to 862 ± 44 mg/cm^3; $P<0.01$ and 1.15 ± 0.25 to 1.26 ± 0.24 mm; $P<0.05$. Trabecular areas decreased at both radius and tibia ($P<0.05$).
Conclusions
Young TST naïve KS patients have an early bone impairment at both radius and tibia, which improve after 30 months of THS. KS patients should benefit from TST before the achievement of peak bone mass especially if they are hypogonadic.

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P1149

Predictive factors of testosterone-induced erythrocytosis on transgender males

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Background
Testosterone therapy (TTh) may produce various side effects, particularly erythrocytosis, with short-acting testosterone (T) injections presenting the greatest risk. Other causes are smoking and obesity. Erythrocytosis increases blood viscosity, which may lead to thromboembolic complications. Aim: to study the frequency of erythrocytosis induced by TTh and its predictive factors on transgender males (TM) in the Gender Unit of our hospital.
Methods
A retrospective study on TM on TTh for $\geq$ 3 months was conducted. Age, age at treatment initiation (ATI), months on treatment, anthropometric measures, hematocrit and hormonal levels at last visit, and the highest value of hematocrit (MaxHt) measured were recorded. Additionally, T formulation, smoking status, and previous hysterectomy and mastectomy procedures were also documented. Hematocrit $\geq$ 50% was considered erythrocytosis and $\geq$ 53% was indication for phlebotomy.
Results and conclusions
140 TM were included (M$\pm$EEM, min-max): age (29.29$\pm$0.82, 15–62 years); ATI (24.06$\pm$0.70, 14–54 years); months on treatment (63.07$\pm$4.11, 4–276); weight (70.27$\pm$1.28, 40–117 kg); height (162.10$\pm$0.48, 146–179 cm); BMI (26.72$\pm$0.49, 14.9–49 kg/m^2); waist perimeter (85.45$\pm$1.12, 59–121.5 cm); hip perimeter (98.53$\pm$0.87, 74.5–136 cm); waist-hip ratio (0.87$\pm$0.01, 0.72–1.13); body fat % (29.40$\pm$0.71, 9–49); hematocrit (46.93$\pm$0.34, 37.0–59.3%); MaxHt (48.44$\pm$0.32, 26.7–55.1%); total T (5.13$\pm$0.35, 0.2–22.7 ng/ml); SHBG (23.89$\pm$1.44, 5.3–139.6 nmol/l); estradiol (38.34$\pm$1.50, 20–107 pmol/ml); FSH (19.33$\pm$2.96, 0.1–214 mUI/ml); LH (9.84$\pm$1.41, 0.1–73.7 mUI/ml) and PRL (12.30$\pm$0.83, 2.83–83.2 ng/ml) levels. The number of smokers, those undergone hysterectomy and mastectomy were 51, 76 and 80 respectively. There were 9 TM on transdermal T gels, 100 on short-acting IM T injections and 31 on extended-release IM T injections. Hematocrit and MaxHt were $\geq$ 50% in 31 and 46 (30%) persons, and $\geq$ 53% in 5 and 14 (10%) persons respectively. Hematocrit (47.73$\pm$0.45 vs 45.96$\pm$0.50%, $P=0.01$) and MaxHt levels (49.69$\pm$0.35 vs 46. 96$\pm$0.52%, $P=0.0001$) were higher in hysterectomized persons, while in smokers only MaxHt was higher (49.03$\pm$0.42 vs 48.10$\pm$0.45%, $P=0.006$). On the other hand, nor hematocrit nor MaxHt were related to T formulation, mastectomy or BMI. Moreover, there was no difference in the hormones levels between the three T preparations. In conclusion, erythrocytosis frequency was high (33%), and 10% of treated TM required phlebotomy. Hematocrit values were independent of BMI and type of T preparation, possibly due to the small number of individuals in two of the three treatment groups.

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P1150

Evolution of referrals for gender dysphoria and trends in the sex ratio: Data from the Trans'Est Gender Identity Centre of the University Hospital of Nancy (2002–2018)

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Background
During the last decennium, an increase in the number of persons referred to gender identity centres has been observed. Epidemiological data have not yet been formally studied in France. Here we report the experience from the Trans'Est Gender Identity Centre of the University Hospital of Nancy.
Aim
To study the number of people seeking transgender care, the age at referral and the trends in the sex ratio.
Methods
The authors reviewed retrospectively medical records of all subjects who were referred for gender dysphoria to the Department of Endocrinology of the University Hospital of Nancy from January 2002 to December 2018.
Results
271 subjects (165 birth-assigned male) were referred to our gender identity centre from 2002 to 2018. The mean number of persons evaluated per year increased from 8.1 (2002–2013) to 37.2 (2014–2018). The median age at first assessment was significantly lower in birth-assigned females (21.7 years; range 15.1–50.9) than in birth-assigned males (31.9 years; range 15.9–61.4) ($P<0.05$). Seventy-three percent of persons self-identified as binary. The sex ratio of birth-assigned males to birth-assigned females decreased from 1.9 in 2002 to 0.9 in 2018 with a change in the sex ratio since 2016 in young subjects aged $<$ 25 years, favouring birth-assigned females.
Limitations
This study is retrospective and some data could be missing. The Trans'Est Gender Identity Centre is among the largest in the Grand-Est region of France; however, these observations cannot be generalized to the whole transgender population in France.
Conclusion
Manifestation of gender dysphoria appears to be different in birth-assigned males and birth-assigned females. In concordance with the literature data, our results indicate a change in the sex ratio of young people referred for gender dysphoria, favouring birth-assigned females. The underlying reasons are not well understood and warrant further studies.

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P1151

Psychological issues in turner syndrome

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Introduction
Turner syndrome (TS) affects 1/1700 female, is due to total/partial lack of an X chromosome and besides short stature and gonadal dysgenesis, is associated with several comorbidities. No defined psychiatric condition has been related to TS. However, several case-reports have appeared in psychiatric literature, and TS is reported to be three times more prevalent in schizophrenia compared with the general female population.
Aim
To evaluate the prevalence of psychological issues in a population of TS attending a specialist adult TS-clinic.
Methods
140 TS women were retrospectively studied. Data on psychiatric history were collected using self-reporting and/or reported diagnoses, along with karyotype, age of TS-diagnosis, height, spontaneous menarche and autoimmune disease. To evaluate the patients' own perception of psychological morbidity, questionnaires were submitted to women seen during a 6-months period ($n=57$), asking for their views on their need for psychological support.
Results
A total of 23/140 (16.4%) TS women had a DSM-5 defined mental-health related condition. Nine (39%) had 45,X, mean age at TS-diagnosis was 12 years, mean height 150.4 cm, two had spontaneous menarche and seven had Hashimoto thyroiditis. Six/23 had a diagnosis of major depression, one attempted suicide and one had a history of self-harm. All were treated pharmacologically, one with psychologist support. Six had a diagnosis of anxiety, one associated with panic attacks and two with depression. Two had to stop working due to anxiety. Two were referred to a psychologist; one with significant improvement in her symptoms. Four with diagnosis of alcoholism. Three diagnosed with anorexia, coexisting with depression in two. One needed multiple hospitalization. One with catatonic-schizophrenia and 1 with obsessive-compulsive disorder. One had attention-deficit hyperactivity disorder, one social awkwardness. Comparing women with and without a psychological diagnosis, no differences were found regarding karyotype, age of diagnosis, height, spontaneous menarche and autoimmune disease. Psychological support had been received by 26.3% (15/57), but 38.6% (22/57) considered it would be helpful now.
Conclusions
A high prevalence of mental-health disorder was found among adult TS with the majority of disorders being of depressive type. These results may underestimate the actual prevalence since a systematic assessment for psychological morbidity was not performed. Based on the patient's own assessment almost 40% would find it helpful to receive psychological counselling. Clinicians should assess psychological comorbidity alongside annual monitoring for other associated conditions during the longterm follow-up of TS patients. Psychiatric consultation should be available as part of routine clinical practice.

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P1152

Effects of paroxitine on biochemical parameters and reproductive function in male rats

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Selective serotonin reuptake inhibitors (SSRI) are a class of molecules used in treating depression, anxiety, and mood disorders. Paroxetine (PRT) is one of the mostly prescribed antidepressant which has attracted great attention regarding its side effects in recent years**.** This study was planned to assess the adverse effects of paroxitine on the biochemical parameters and reproductive system. Fourteen male wistar rats were randomly allocated into two groups (7 rats or each): control and treated with paroxitine at dose of 5 mg/kg.bw for two weeks. At the end of the experiment, blood was collected from retro orbital plexus for measuring the biochemical parameters, whereas the reproductive organs were removed for measuring semen quality and the histological investigations. Results showed that paroxitine induced significant changes in some biochemical parameters and alteration of semen quality including sperm count, spermatids number and sperm viability, motility and abnormalities. The histopathological examinations of testis and epididymis revealed an alteration of spermatogenesis, cellular disorganization and vacuolization, enlargement of interstitial space, shrinkage and degenerative changes in the epithelium of seminiferous and epididymal tubules with few to nil numbers of spermatozoa in their lumens. In conclusion, paroxitine treatment caused changes in some biochemical parameters and sperm profile as well as histopathologic effects in the reproductive organs.

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P1153

Relationship and sexual experiences in young women with oestrogen deficiency: comparison between women with Turner syndrome and premature ovarian insufficiency

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Background
Ages at first date and sexual encounter have been observed to be delayed in women with Turner's syndrome (TS), with late presentation and delayed puberty induction being the main culprits. There is no equivalent data in women with premature ovarian insufficiency (POI).
Objectives
We sought to assess whether age at start of oestrogen replacement therapy (ERT) and amenorrhoea status affected the age at first relationship and sexual experience and whether this differed between women with TS and POI.
Methods
This cross-sectional observational study formed part of the Reproductive Life Course Project carried out at University College London Hospitals and comprised 268 women with TS and 50 women with karyotypically normal POI. A questionnaire was used to collect data on menarche, age at diagnosis and at ERT start, whether they have been on a date, had a romantic relationship or sexual intercourse and the respective ages at first such experiences.
Results
Women with TS were older than those with POI (36.7 ± 12.8 vs 29.0 ± 9.4, $P = < 0.001$), were diagnosed earlier (9.6 ± 8.1 vs 16.3 ± 3.9, $P = < 0.001$) and started ERT at a younger age (15.5 ± 6.1 vs 17.2 ± 3.3, $P = < 0.001$). There was no difference in the number of women with TS compared to POI who had been on a date (81.0% vs 72.0%, $P = 0.25$), had a romantic relationship (67.6% vs 72.0%, $P = 0.39$) or sexual intercourse (60.5% vs 70.0%, $P = 0.15$). Moreover, there was no difference in the mean ages at first such experiences (romantic relationship 19.3 ± 5.2 vs 18.3 ± 2.8, $P = 0.54$; sexual intercourse 20.9 ± 5.8 vs 19.1 ± 2.7, $P = 0.19$). In TS and POI, women suffering from primary amenorrhoea (77.6% and 66.0% respectively) compared to those undergoing spontaneous menarche (20.5% and 34.0%), had a significantly delayed median age at first romantic relationship (19 ± 0.3 vs 17 ± 0.2, $P = < 0.001$) and at first sexual intercourse (20 ± 0.3 vs 18 ± 0.4, $P = < 0.001$). In women with primary amenorrhoea, the age at first romantic relationship/sexual intercourse was related to age of starting induction of puberty. A significantly lower percentage of women with POI and TS had their first sexual intercourse < 16 years compared to that found in UK reference data (Natsal-3; 3.6% *vs* 18.0%, $P = < 0.001$).
Conclusion
Primary amenorrhoea, which is often associated with later pubertal maturation, results in a delayed relationship and sexual experience in both TS and POI alike. Women undergoing puberty induction have an overall delayed mean age at first relationship and sexual experience compared to the general population.

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P1154

A rare cause of secondary amenorrhea in a patient with non-classical CAH due to a uterine middle-line developmental defect: Case report

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Introduction
The female genital developmental defects are not common in non-classical congenital adrenal hyperplasia (CAH). The causes of amenorrhea are multifactorial and are due to the incomplete control of hyperandrogenism as well as the increased progesterone, acting in various modes: blunted LH mid-cycle surge, lack of progestin withdrawal action and antagonise the estradiol action on the endometrium. The overtreatment with glucocorticoid results in the suppression of gonadotropins and iatrogenic Cushing syndrome.
Clinical case
We report a 33-year-old female patient with a history of delayed puberty and two menses in her lifetime. She stated she has secondary amenorrhea non-responsive to progestins and previous treatment with oral contraceptive for two years without menstrual bleeding. The diagnostic of 21 hydroxylase deficiency emerged from her clinical appearance and basal levels of 17-hydroxyprogesterone of 18.44 ng/dl. We obtained control of the disease with a maximum target for 17 OH progesterone level below the double of the upper limit of the reference range with dexamethasone at bedtime. Adding an oral contraceptive the menses doesn't resume, despite ultrasound evidence of an endometrium above 7 mm. We addressed her to extensive gynaecology evaluation. The hysteroscopy describes the bicornuate uterus and an incomplete intrauterine septum conformed by magnetic resonance of the pelvis.
Discussion
Congenital malformations of female genitalia appear in the classical CAH as part of virilisation of the external genitalia and sexual ambiguity. Abnormalities of genital development are not commonly described in non-classical CAH. The literature mentions a phenotype that included malformations of genitalia and CAH, apart of virilisation, due to an association between CAH due to 21 hydroxylase deficiency and Ehlers-Danlos Syndrome– the two coding genes for CYP21A2 and tenascin gene (TNXB), respectively located within the HLA complex on Chromosome 6. In this report, we described the occurrence of the bicornuate uterus with an incomplete intrauterine septum in a patient with non-classical CAH, regarded as a middle line malformation because of the failure of fusion of the müllerian ducts.

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P1155

Metabolic and hormonal improvement after ketogenic VLCD diet (VLCK): Case report

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Obesity has become one of the most important public health problems. Considered as one of the many adverse consequences of overweight and obesity,

the maleobesity-associatedsecondary hypogonadism (MOSH) is a very prevalent and undervalued condition. Is characterized by low total testosterone (TT) levels associated to low or inappropriately normal luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Increased aromatase activity, imbalance in the testosterone/estradiol ratio and the state of low-grade inflammation are the major factors involved. Low levels of testosterone may have important long-term negative health consequences, related to earlier death owing to cardiovascular disease and all causes. Low testosterone levels contribute to increase in fat mass and waist circumference, aggravating obesity. Increased aromatase activity, imbalance in the testosterone/estradiol ratio and the state of low-grade inflammation are the major factors involved. Current evidence supports the association between the fast loss of weight following bariatric surgery and reversal of hypogonadism, associated to obesity, while a hypocaloric diet and lifestyle change does not produce the same results. As an alternative for non-invasive substantial weight loss, very low-calorie ketogenic diet (VLCK) provide similar results as bariatric surgery. When used under proper medical supervision, is safe and effective in promoting significant short-term weight loss, with concomitant improvement in obesity-related conditions. In this report, we describe clinical and laboratorial features of 4 obese man with metabolic syndrome (MS) and MOSH, who had a significant improvement in metabolic and hormonal parameters after VLCK. Pre and post-treatment parameters are described below: P1- 42y, VLCK 28 days; Weight 98/87; BMI 30,2/26,8; Fat% 23,2/17,8%; waist circumference (WC) 119,5/109 cm, Triglicerides 202/118; HDL 38/41; HOMA IR 3,38/2,15; Total testosterone (TT)215/440; E2 40,9/33,3. P2- 47y, VLCK 112 days; Weight 106,4/83,1; BMI 33,9/26,5; Fat% 28,8/24,3%; waist circumference (WC) 120/97 cm, Triglicerides 162/78; HDL 33/39; HOMA IR 4,54/1,9; Total testosterone (TT)287/575; E2 0,9/4,1. P3- 42y, VLCK 120days; Weight 128/95,8; BMI 43,7/32,8; Fat% 50,7/40%; waist circumference (WC) 120/97 cm, Triglicerides 160/80; HDL 25/43; HOMA IR 6,7/2,0; Total testosterone (TT) 275/598; E2 6,0/3,6. P4- 42y, VLCK 90 days; Weight 96,2/83,1; BMI 30,7/32,8; Fat% 28,3/18,9%; waist circumference (WC) 106/95 cm, Triglicerides 372/135; HDL 31/39; HOMA IR 5,12/2,5; Total testosterone (TT)273/479; E2 3,3/3,6.

Conclusion

VLCK appears to be a promissing method to improve testosterone levels in obese hypogonadal men. Further larger controled studies are required.

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P1156

Sex hormone-binding globulin (SHBG) as a marker of aggressive prostate cancer

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Background

Sex hormone-binding globulin (SHBG) is a dimeric glycoprotein synthesized in, and secreted from, hepatocytes. SHBG is also expressed in, but not secreted from, the prostate, where its role is unclear. The expression of SHBG is linked to lipid metabolism, and it also modulates transport and availability of androgen. Given its expression in the prostate and role in the androgen signalling axis, we postulated that expression of SHBG will increase in prostate cancer (PCa), distinguishing it from both normal prostate and benign prostate hyperplasia (BPH), and reflect aggressiveness of disease.

Methods

We utilized tissues and data from existing South Australian PCa Registries. *SHBG* mRNA was measured by qRT-PCR ($n=47$: 7 BPH and 40 PCa of varying Gleason score (GS)). SHBG protein was measured by immunohistochemistry and quantified by Image J software ($n=125$: 8 normal, 32 BPH and 85 PCa of varying GS). The expression of *SHBG* transcript variants was analysed by qRT-PCR from an independent set of PCa samples of varying GS ($n=12$ 1 with GS ≤ 6, 9 with GS ~ 7 and 2 with GS ≥ 8) that had been treated with the androgen receptor antagonist Enzalutamide (10 uM MDV) or vehicle control.

Results

SHBG mRNA and SHBG protein are barely detectable in normal prostate epithelium or in BPH but increase in PCa epithelial cells ($P<0.001$; compared to both). SHBG protein concentration was highest in with GS ≥ 8 compared to GS ≤ 6 and ~ 7 ($P=0.002$). PCa with GS ≤ 6 ($n=1$) and GS ≥ 8 ($n=2$) expressed unique coding transcripts of 1382bp and 1311bp respectively. However, within PCa of GS ~ 7($n=9$), there was marked heterogeneity of SHBG transcripts; 463 bp, 522 bp (non-coding), 526bp and 1146bp transcripts predominated, none expressed the 1311 bp and 1382 bp transcript. In response to 10 uM MDV, PCa with GS ≤ 6 ($n=1$) did not express, 522 bp transcript predominated in GS ≥ 8 ($n=2$) while GS ≥ 7 ($n=9$) expressed unique coding transcripts of 1382bp and 973bp respectively but 522 bp transcript predominated.

Conclusions

SHBG protein abundance and/or transcript size are markers of advanced disease and may be a novel marker for aggressive tumor behavior in early-stage disease.

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P1157

Klinefelter syndrome in adults: variability in clinical findings

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Introduction

Klinefelter syndrome (KS) is the most common congenital abnormality causing primary hypogonadism. It occurs in about 1 in 660 live male births. The clinical manifestations include tall stature, small testes, gynecomastia and neurocognitive impairment. Nevertheless, the KS phenotype varies greatly, which might be one of the reasons why the syndrome is highly underdiagnosed. KS is associated with several clinical conditions and increased morbidity/mortality. Testosterone replacement therapy helps to prevent or eventually treat some of these abnormalities. Our aim was to study a population of adult patients with KS, by evaluating clinical and anthropometric parameters, as well as their diagnostic features, treatment options and related comorbidities.

Methods

Retrospective study including patients older than 18-years old diagnosed with KS currently followed at the Endocrinology Department at Hospital de Braga.

Results and Discussion

We identified 17 subjects with KS. The average age at diagnosis was 28.6 years (minimum 3 years and maximum 66 years). In general, in children ($n=3$) the diagnosis was established because of cognitive/linguistic impairments, whereas in adolescence ($n=3$) the main referral reason was gynecomastia or delayed puberty. Eleven patients were diagnosed at adult age: gynecomastia was also a relevant feature between these subjects ($n=3$); of the remaining, 2 cases were diagnosed during infertility screening, 1 because of sexual dysfunction symptoms and 1 at the Obesity Clinic. Only 2 subjects presented with genotypic variants (47,XXY/48,XXXY and 48,XXYY); the others presented the classic karyotype (47,XXY). Three of them are currently under psychiatric guidance due to behavior, impulsivity and anxiety problems. We documented 1 case of mediastinal germ cell tumor; no history of breast cancer was reported. Regarding other related comorbidities, the prevalence of type 2 diabetes and hypertension was similar (23.5%); whereas the prevalence of dyslipidemia was higher (35.3%). Obesity, obstructive sleep apnea syndrome and peripheral vascular/coronary disease were also described in our sample. On physical examination, 76.5% presented small testes and 64.7% had gynecomastia. The average stature was 178.0 cm, a wingspan of 182.5 cm and BMI of 25.9 kg/m^2. Blood biochemistry revealed the following mean results: FSH 34.5 mUI/ml, LH 16.3 mUI/ml and total testosterone 293.37 ng/dl. Five patients performed spermogram, all with azoospermia. Bone densitometry showed osteopenia in 7 cases and lumbar spine osteoporosis in four patients. Testosterone replacement therapy was initiated in 12 subjects (70.6%). Only 1 of them presented a documented side effect (high hematocrit). This descriptive analysis reflects several of the classic features reported in the literature in patients with KS.

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Thyroid 3

P1158

Cosmetic complaints in patients with thyroid disease

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Introduction
Patients with benign thyroid disease may present an impaired Quality of Life (QoL). However, evidence of cosmetic complaints in patients with thyroid disease is limited. The aim of the current study was to investigate the cosmetic complaints of patients with thyroid disease and determine any associations with specific clinical characteristics.
Methods
A cross-sectional study was performed. Patients with benign thyroid disease who attended the Endocrinology Outpatient Clinic of Hippokration General Hospital during 2017–2018 were included. Thyroid-related quality of life was measured by the Greek translated and cross-cultural validated version of ThyPRO. ThyPRO includes nine subscales for nine different aspects of quality of life. Each score is constructed by the summation of relevant items and linear transformation to a range of 0–100, where 100 indicates most symptoms/impact on QoL.
Results
In total, 376 patients with thyroid disease were included in the analysis, of which 151 patients had a non-toxic nodular goiter, 13 had a toxic adenoma, 40 had Graves' disease, 128 were diagnosed with Hashimoto thyroiditis and 44 patients had non-autoimmune hypothyroidism. Among all patients, those with Graves' orbitopathy presented higher scores in the ThyPRO cosmetic complaints scale, followed by patients with Graves' disease, without orbitopathy. Cosmetic complaints were higher in both hypothyroid and hyperthyroid patients vs. euthyroid patients (20 and 26 vs 13 respectively, $P=0.012$). Levothyroxine (Lt4) supplementation was correlated with a higher cosmetic complaint scale score in comparison to no medication.
Conclusion
Not only hyperthyroidism but also hypothyroidism seem to negatively affect the appearance-related aspect of QoL. Not surpisingly, patients with Graves orbitopathy have more cosmetic complaints in comparison to all other patients with benign thyroid disease.

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P1159

Features of depression in patients with hypothyroidism

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Introduction
In everyday practice, doctors often have to deal with patients who show features of depression - it has been proven that in 20–30% of cases it may be related to the ocurrence of another disease, such as hypothyroidism.
Aim of study
The aim of the study was to verify the frequency of occurrence features of depression (based on Beck's scale) in the population of patients with hypothyroidism and comparison to the general population.
Materials and methods
In the study, we used original questionnaire form, containing record questions and questions based on Beck's scale (standardized for the diagnosis of depression). 1155 respondents took part in the study - 631 (54.63%) suffered from hypothyroidism (239 - 20.69% hypothyroidism with Hashimoto's thyroiditis).
Results
The results indicating an increased propability of depression (Beck's score >11 points) concerned 69.88% of total number of respondents - significantly more frequently it concerned patients with hypothyroidism (75.12% vs 63.55%; $P<0.001$) and patients with hypothyroidism in the course of Hashimoto's thyroiditis (79.50% vs 67.36%; $P=0.003$).
Conclusions
The Beck's scale is an element of the complex diagnosis of depression, but due to the high incidence of depression's features (both in the hypothyroid and general population) it is reasonable to consider more frequent mental health tests performed by specialist medical personel.

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P1160

Stress induced cortisol release depresses the secretion of triiodothyronine in patients with anterior wall myocardial infarction

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Stress is any uncomfortable emotional experience accompanied by predictable psychological, physiological and behavioral changes. A sudden and severe stress generally produces an increase in the heart rate and blood pressure and induces a state of alertness in an individual. Evidence indicates that chronic stress depresses thyroid function, resulting in low levels of T_3 and T_4, which affects cardiomyocytes' function and leads to development of cardiovascular diseases (CVDs). The present study aimed to determine the effect of stress on thyroid function in terms of release of cortisol and its effects on T_3 and development of hypertension and related CVDs. Hundred hypertensive CVD patients and hundred normotensive subjects between the age of 21 and 60 years were included in the study. Blood samples were collected and plasma cortisol and T_3 concentrations were determined by using RIA systems. Data were analyzed using Student's t-test, ANOVA and Pearson correlation r. Our results indicated that 68% patients had high cortisol levels demonstrating that they were experiencing some kind of stress. Moreover, 69% patients had low T_3 levels indicating that most of our hypertensive CVD patients were suffering from hypothyroidism. In addition, a negative correlation was observed between cortisol and T_3 levels, whereas a positive correlation was witnessed between cortisol concentrations and BP and blood glucose levels. A negative correlation was observed between T_3 and BP and blood glucose levels. The majority of patients fell between the age group of 41–50 years, had primary level of education, belonged to low income socio-economic status, had exercise free lifestyle with no diet plan, were overweight, married, smokers, had disease duration of <1 year, without family history of hypertension and had anterior wall myocardial infarction. In conclusion, the current investigation demonstrated that most of CVDs patients had high cortisol and low T_3 concentrations irrespective of any or no treatment.

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P1161

Do patients with differentiated thyroid cancer (DTC) harboring TERT promoter mutation require a more intensive treatment and follow-up? – proposal of a prospective study

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Introduction
The importance of telomerase reverse transcriptase promoter (*TERTp*) mutations in DTC is widely discussed. It has been demonstrated that the presence of *TERTp* mutations is associated with higher cancer aggressiveness, reflected by lymph node metastases, distant metastases, advanced tumor stage, recurrence, and even disease-specific mortality. Nevertheless, there is no clear evidence-based data demonstrating how to manage these patients. Therefore, we decided to carry out a single-center, prospective, pilot study. Its primary aim is to evaluate the predictive value of *TERTp* mutations in DTC. Secondary aim is to answer the following questions:

- Whether the sensitivity of Sanger sequencing in diagnostics *TERTp* mutations in FNAB specimen is sufficient to make clinical decisions?

- Whether the presence of *TERTp* mutations influence RAI avidity in DTC?
- Whether the presence of *TERTp* mutations justify broader indications for RAI complementary treatment?
- Whether more aggressive treatment and follow-up influences long term outcomes?

Material and the study scheme
The study group will involve 60 DTC patients, 30 TERTp positive and 30 TERTp negative. The aim of the first stage is to evaluate the sensitivity of Sanger sequencing in diagnostics of *TERTp* mutations in FNAB specimen and to compare the impact on RAI avidity by comparison of TERT negative and TERT positive groups. The purpose of the second part is to compare treatment outcomes, based on ATA response criteria, in TERTp positive group between patients treated according to standard protocol and those subjected to more intensive therapy and follow-up.

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P1162

Microvascular blood flow measurements of the thyroid nodules by diffuse optics

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Background
The most common tool to test malignancy in the study of thyroid nodules (TN) is ultrasound and fine needle aspiration biopsy (FNAB). However, the sensitivity and specificity of the methods and the effectiveness in thyroid cancer are limited; therefore new methods to study thyroid nodules are required. In this way our goal is to introduce hybrid diffuse optical instruments that are capable to measure and discriminate altered microvascular blood flow, blood volume and tissue scattering coefficients of TN. Near-infrared diffuse optical technologies aim to overcome the shortcomings of present techniques while screening for malignant thyroid nodules for early and fast diagnosis of cancer. This idea was based on the previous experience in breast cancers with diffuse optical techniques.
Methods
We have developed a device based on near-infrared diffuse correlation spectroscopy (DCS), which is a technology aimed at retrieving the microvascular flow of a certain region of tissue by mean of low power near-infrared laser light, and used in combination with a commercial ultrasound system (US). In order to combine these devices, we have developed a probe enabling multimodal data acquisition and subsequently we have analyzed the optical properties and the blood flow index in the thyroid lobes of eleven subjects who presented a thyroid nodule.
Results
Four subjects have required FNAB: P4 and P7 were reported as being malignant (Bethesda VI and IV respectively) while P6 and P8 were evaluated as being benign (Bethesda II). Surgical removal confirmed papillary thyroid carcinoma in P4, while denied the result of FNAB for P7 (Multinodular thyroid hyperplasia). We have considered the contralateral lobe as intra-subject reference to validate the feasibility of the DCS system in a very absorbing tissue as thyroid is. The difference between the blood flow index of the nodule and the contralateral lobe is maximum for subject P4, while the difference in benign subjects is lower. T-test showed no significant difference between benign nodules and contralateral lobes. Subject P7 showed a small difference as for other benign subjects despite the FNAB results indicating presence of malignancy.
Conclusion
Apparently diffuse optics technologies would be able to differentiate malignant thyroid nodules from benign thyroid nodules, but more measurements require confirming our preliminary results as that diffuse optical technology can complement the current techniques such as US and FNAB. A new measurement campaign is being scheduled with a completed, fully integrated device that was developed within the LUCA project (http://www.luca-project.eu).

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P1163

Atypical hyperthyroidism in a case of neutrophilic dermatosis (Sweet's syndrome)

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Introduction
Sweet's syndrome is a rare, acute febrile neutrophilic dermatosis, associated with a variety of inflammatory and neoplastic conditions, drug reactions and rarely with a spectrum of thyroid dysfunction. A possible link between thyroid autoimmunity and Sweet's syndrome has been previously suggested by rare reports of Hashimoto's thyroiditis, subacute thyroiditis and classic Graves' disease. We describe a case of 'atypical' hyperthyroidism coinciding with the presentation of Sweet's syndrome.
Case Report
A previously healthy 34-year-old woman presented with pyrexia up to 40°C for three weeks, followed by a tender papulovesicular eruption on the forearms, lower legs and chest, with intact mucosae. Laboratory testing revealed WBC 11.64×10^3 /μl, neutrophils 78.9%, lymphocytes 11.8%, Hct 29%, Hb 11.8 gr/dl, Platelets 346×10^3 /μl, ESR 110 mm/1 hr, TSH 0.025 μIU/ml, FT3 4.4 ng/dl (1.8–4.2 ng/dl), FT4 1.83 ng/dl (0.84–1.76 ng/dl) negative anti-TG, anti-TPO and TSI 0.89 U/l (Φ.T. <1.75 U/l). The thyroid gland was enlarged and firm to palpation. ^{99m}Tc scintigraphy showed diffusely increased uptake 6.16% (1.7 ± 1.3). On thyroid ultrasound the parenchyma was distinctly nodular, consisting of multiple, uniform, solid, slightly hypoechoic, adjoining nodules 10–15 mm in diameter, with predominantly peripheral vascularity and increased vascularity in the intermediate tissue. Several reactive cervical lymph nodes were noted bilaterally. US-guided fine needle aspiration of one such nodule was consistent with Bethesda II. A skin biopsy from the right forearm was consistent with acute neutrophic dermatosis without vasculitis and the patient was treated with oral methylprednisolone tapering, with rapid resolution of the symptoms and rash. She was also started on thiamazole 10 mg and soon became euthyroid. Twelve months later, she remains euthyroid on 7.5 mg/d. CT scan of the abdomen showed a lipid-rich, left adrenal incidentaloma 3.1 cm in diameter, which was found nonfunctional on testing.
Conclusion
This unusual presentation of hyperthyroidism in association with Sweet's syndrome has not been previously described and is notable because it features characteristics shared between Graves' disease and multinodular goiter, displaying a true overlap or unclassified form of thyrotoxicosis.

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P1164

A rare and particular form of goiter to recognize: The dyshormonogenetic goiter

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Introduction
Thyroid dyshormonogenesis continues to be a significant cause of congenital hypothyroidism occurring due to a lack of enzymes necessary for the synthesis of thyroid hormones. Treatment can be medical or surgical. Early treatment is important to avoid mental retardation and growth abnormalities.
Case reports
We report 3 cases of dyshormonogenetic goiter occurring in 1 female and 2 males. The medium age of the patients was 12 years ranging from 7 to 20 years. Family history was significant for consanguinity; the patient's parents were first cousins. On examination, the thyroid gland was enlarged ad multinodular in the 3 cases. There was no significant lymphadenopathy. Hypothyroidism was documented before the histological diagnosis was made in all cases. Ultrasonography revealed a diffuse enlargement of the thyroid in all cases. Both of the lobi and the isthmus contained confluent nodular masses. All patients underwent total thyroidectomy. The post-operative course was uneventful. The histologic examination concluded to a benign dyshormonogenetic goiter. Since thyroidectomy, all patients has been stable, with levothyroxine doses adjusted as needed to maintain a euthyroid state.
Conclusion
Dyshormonogenetic goiter is considered as a form of thyroid hyperplasia due to enzymatic defects in hormone synthesis. The architectural polymorphism and cellular atypia may mimic thyroid neoplasms and cause diagnosis difficulties. So this entity must be recognized in patient with history of hypothyroidism since infancy.

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P1165

Thyroid carcinoma in *Struma ovarii*: two case reports

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Introduction
Struma ovarii is a rare form of ovarian teratoma mostly composed of thyroid tissue. In about 5% of the cases, well-differentiated thyroid carcinoma may arise in *struma ovarii*. As this medical entity is so exceptional, there is still no consensus on diagnosis and treatment.
Case Reports
A 52-year-old old woman was submitted in 2009 to total hysterectomy with bilateral adnexectomy and pelvic lymphadenectomy. Histopathology revealed papillary thyroid carcinoma with 2.5 cm arising in *struma ovarii*, with no lymph node metastasis. It was decided not to perform thyroidectomy and the patient was kept under surveillance. Nine years after the surgery, there is no evidence of imaging relapse, with thyroglobulin levels of 22.71 ng/ml (<77 ng/ml). A 53-year-old woman underwent total hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy in 2010. The histopathology result showed a 7 cm papillary carcinoma arising in *struma ovarii*. The patient was subsequently treated with total thyroidectomy and radioactive iodine. Eight years after, she remains disease free with undetectable serum thyroglobulin levels.
Discussion
Both our cases of thyroid carcinoma in *struma ovarii* showed favourable outcomes, as usually described. Performing total thyroidectomy and therapy with radioactive iodine should be considered, bearing in mind the initial risk and the clinical, analytical and imaging follow-up data. Long-term follow up is recommended, as late recurrences are known to occur.

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P1166

Hyperthyroidism in children: About 3 cases

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Introduction
The majority of thyroid diseases in adults can also affect the child. Graves' disease is characterized by the association of signs of hyperthyroidism and exophthalmia. It is a rare condition in pediatrics and especially affects the big child. Easy to diagnose, Graves' disease in children requires strict management. We report 3 clinical cases of baseline disease, 2 of which required radical treatment.
Case 1
A 9-year-old child consults for signs of hyperthyroidism. History ans physical examination found signs of thyrotoxicosis (weight loss, tachycardia); bilateral exophthalmia, homogeneous vascular goiter. The biological assessment reveals an FT4 level of 30 ng/L; TSH at 0.09 mIU/L. Cervical ultrasound notes homogeneous diffuse thyroid hypertrophy. These clinical and para-clinical data support the diagnosis of Graves' disease. The patient was put under Dimazol.
Case 2
A 10-year-old boy consults for signs of hyperthyroidism. We noted on his history and examination: signs of thyrotoxicosis (weight loss, tachycardia); bilateral exophthalmia, homogeneous vascular goiter and statural delay. The biological assessment reveals a level of FT4 at 40 pmol/L; TSH <0.05 mIU/L. The cervical ultrasound shows a homogeneous hypervascularized thyroid hypertrophy. The patient was put under Dimazol then iratherapy, patient currently presents a hypothyroidism under levothyrox.
Case 3
An 8-year-old child presented with abdominal pain, vomiting, physical asthenia, palpitations, diarrhea and weight loss for the past 6 months. On examination, his blood pressure was 100/60 mmhg, heart rate 100 bpm, a diffuse homogeneous goiter with vascular trill, a bilateral exophthalmia and lesions of vitiligo. The thyroid assessment showed a T3: 27.3 pmol/l T4l: 69.5 pmol/l TSH: 0.05 uUI/ml. The cervical ultrasound showed hypoechogenic heterogeneous thyroid, increased in size, without visible nodule with important vascularization, the patient was put on B blockers and dimazole with intolerance manifested by neutropenia at 660, the reason why the patient received iratherapy at 6mCi with good evolution.
Conclusion
Although rare in children, Graves' disease remains the leading cause of hyperthyroidism in young patients. It remains easy positive diagnosis but its management may cause huge problems.

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P1167

Effect of maternal thyroid function on neonatal thyroid screening results

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Evidence on whether neonatal thyroid screening results are dependent on maternal thyroid function is limited.
Objectives
To study the relationship between iodine status and maternal thyroid function in pregnancy, and neonatal screening results in a Northern Spanish population.
Methods
Prospective, longitudinal study of 297 pregnant women recruited in 2 obstetric centers of Pamplona (Spain) at the first antenatal visit, and their neonates. Serum thyrotropin (TSH), free thyroxine (fT4) and thyroid antibodies were measured in the three trimesters of pregnancy, and urinary iodine concentration (UIC) was measured in the first one. Neonatal TSH screening was performed in heel-puncture blood samples collected on filter paper, at 48–72 hours after birth. We analyzed the association between neonatal TSH values, and maternal UIC and thyroid function through pregnancy.
Results
Most pregnant women were caucasian (92.9%), mean age was 33.5±4.0 years-old, and 48.8% were nulliparous. Thyroid autoantibodies were positive in 63 women (21.2%). The maternal UIC in the first trimester was 243 mcg/L (133.5–395.5). The mean neonatal TSH was 1.7±1.4 mUI/L with 1.7% of neonates having TSH>5 mUI/L. Newborn TSH was higher in boys, and in offspring from older women (>30 year-old). Neonatal TSH values were correlated with maternal TSH only in the second trimester ($P=0.043$), and with maternal age ($P=0.007$). We found no association between neonatal TSH values and maternal thyroid function in the first and third trimester, maternal UIC, BMI, parity, birth weight or gestational age at delivery. We found no statistical differences in neonatal TSH values according to maternal iodine status, or according to thyroid autoimmunity.
Conclusions
In our population, only maternal TSH values in the second trimester correlated with newborn TSH. Maternal UIC was not associated with neonatal TSH at screening.

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P1168

The role of GLP-1, IGF-1 and leptin in thyroid cancer

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Aim
The aim was to assess the expressions of GLP-1, IGF-1 and leptin in the paraffin sections of operated thyroid cancer and non-thyroid cancer patients, and show the relationship of GLP-1, IGF-1 and leptin receptor expressions with thyroid cancer, comparatively.
Materials and Methods
This study was carried out retrospectively. The case groups consisted of 20 medullary thyroid cancer (MTC), 20 follicular thyroid cancer (FTC), 20 classical papillary thyroid cancer (PTC-kl) and 20 follicular variant papillary thyroid cancer (PTC-fv). The control group consisted of 40 patients with Hashimoto thyroiditis or nodular goitre. The IGF-1 receptor (IGF-1R), GLP-1 receptor (GLP-1R), and leptin receptor (leptin-R) expressions were examined by immunohistochemical staining using thyroid gland paraffin blocks.
Results
GLP-1R expression was positive in 17.5% of the controls, 15.0% of the FTCs, and 5.0% of the MTCs, whereas no GLP-1R expression was detected in any of PTC-kl and PTC-fv. The difference between the groups was not statistically significant ($P=0.064$). In addition, in 9 cancer cases (5 MTC, 4 PTC-KL), 5% GLP-1R

expression was detected in normal tissues. While IGF-1R expression was positive in 7.5% of the controls, 5.0% of the FTCs and 10.0% of the MTCs; IGF-1R expression was not detected in any one of the PTC-kl and PTC-fv. This difference between the groups was not statistically significant ($P=0{,}618$). The mean leptin score was 1.75 ± 1.81 (median:2) in the control group, 3.0 ± 2.62 (median:4) in FTC, 1.15 ± 1.87 (median:0) in MTC, 1.80 ± 2.12 (median:0) in PTC-kl, and 1.05 ± 1.79 (median:0) in PTC-fv. Leptin scores were statistically significantly higher in FTC group than in the control, MTC and PTC-fv groups ($P=0.037$, $P=0.014$, $P=0.014$). Leptin score was significantly higher in the presence of vascular invasion ($P=0.002$).

Conclusion

GLP-1R staining was not statistically significant in the FTC, MTC, and PTC groups compared to the control group. However, the presence of GLP-1R positivity in the control group and the detection of GLP1-R expression in surrounding normal tissues in the presence of cancer suggests that GLP1 may play a role in tumorigenesis and loss of receptor expression after tumor development. Contrary to previous studies, our study detect negative expression of IGF-1R. Leptin-R expression was found to be significantly higher in the FTC than in the control group. It was also found that high levels of leptin expression were associated with vascular invasion. It is thought that leptin may be associated with FTC formation and poor prognosis.

Keywords: Thyroid cancer, Leptin, IGF-1, GLP-1

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P1169

Surprizing diagnosis of congenital adrenal hyperplasia in a young infertile patient

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Congenital adrenal hyperplasia (CAH) is a group of diseases which develop as a result of deficient enzymes or co-factor proteins required for cortisol biosynthesis. Depending on the defect, the manifestations range from life-threatening salt-wasting syndrome to almost no symptoms. Nevertheless, some subclinical subtypes can cause impediments in particular situations. This case brings to light a possible manifestation of CAH, revealed in the process of in-vitro fertilization. We present the case of a 32 year old woman who was referred for endocrinological evaluation from a Reproductive Medicine Department with suspicion of CAH. She was previously diagnosed with idiopathic infertility and started an IVF procedure, but during controlled ovarian stimulation (COS) high progesterone levels (5–6 ng/mL) were observed. Therefore, all the embryos were frozen and additional blood tests were performed. A high value of 17-hydroxiprogesterone (11.42 ng/ml) in association with low morning serum cortisol (5 microg/dL) and high ACTH levels (>2000 pg/mL) were found. She had no significant family history. Her gynecologic history included menarche at the age of 14 and periods of oligomenorrhea alternating with regular menstrual cycles throughout her life. She also had autoimmune thyroiditis with hypothyroidism and was using adequate L-thyroxin replacement therapy. The physical exam was unremarkable. During the endocrinological evaluation we found a low blood sodium concentration (130 mmol/l), low serum testosterone levels (6.38 ng/dl), high 11-deoxicorticosterone (0.26 ug/L), low DHEA-S (6.3 ug/dl), high 17OHP, low normal cortisol level (5.68 microgr/dl) and ACTH > 2000 pg/ml. An ACTH stimulation test was performed which showed unstimulated cortisol levels 5.35 micrograms/dl, high 11-deoxicorticosterone 0. 36 ug/L and 17 (OH) progesterone (12.92 ng/ml) one hour after stimulation. Because not one enzymatic defect could explain all of the biochemical anomalies, we suspect a mixt enzymatic defect of 17,20 lyase and 11 hydroxylase. Hydrocortisone treatment in doses of 20 mg/day was started. After two months of treatment her ACTH values declined to 631.3 pg/ml, but serum progesterone remained high. The hydrocortisone dose was augmented to 25 mg/day. Besides underlying the pathophysiologic mechanisms, our aim is to find the most suitable treatment for infertility, as high progesterone levels throughout controlled ovarian stimulation is a well-recognized cause of implantation failure.

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P1170

Carcinoma showing thymus-like differentiation (CASTLE) - a case report

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Carcinoma showing thymus-like differentiation (CASTLE) is a rare malignancy, localized in the thyroid parenchyma. As far as we know, only a few CASTLE cases are described in literature. The diagnosis is based on immunoreactivity, the main characteristic is positivity to CD5, which reveals a thymic differentiation. We report the case of a 63-years-old male, who presented with a 3 cm solid, hypoechoic nodule in the lower part of the left thyroid lobe, with underlying structures fixation. The ipsilateral lymph node involvement was noted. The mass was irregularly shaped and adherent to the tracheoesophageal area, with a mass effect on the trachea, in his cervical superior mediastinal portion. Vessel displacement was recorded, as the tumor was in contact with the left common carotid artery in posterior, with jugular vein in posterolateral, and right common carotid artery inferior. He was surgically treated by a subtotal thyroidectomy with central neck dissection. The histopathologically and immunohistochemically exam revealed carcinoma, showing thymus-like differentiation (CASTLE) with cluster of differentiation 5 (CD5) (+), tumor protein p63 (p63) (+). Postsurgical chemotheraphy was applied (6 cycles with carboplatin and paclitaxel), afterwards external beam radiation (66 Gy/33 fractions/50 days). The diagnosis of CASTLE is a challenge for the physician, as there is a great resemblance with anaplastic thyroid carcinoma and squamous-cell carcinoma of the thyroid. A correct diagnosis is essential because the treatment and prognosis is different. CASTLE is an indolent and slow-growing malignancy, with a great response to chemo and radio therapy. In our case, extrathyroidal infiltrations and nodal metastasis are risk factors that are seriously decreasing the patient life expectancy.

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P1171

Obesity and differentiated thyroid cancers: What prognostic impact?

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Introduction

According to the literature, there is a link between obesity and thyroid cancer. A high body mass index (BMI) increases the risk of thyroid cancer and its progression, although their mechanism is still unknown.

Objective

To evaluate the association between obesity and the clinical-biological profile of differentiated thyroid cancers.

Materials and methods

We conducted a retrospective study carried out in the Endocrinology Department of Ibn Rochd University Hospital of Casablanca concerning the patients followed for a differentiated thyroid carcinoma between January 2010 and January 2019. The patients were divided into 2 groups: G1 having an obesity (62 cases), and G2 control (120 cases), by comparing the clinical-biological data and the evolutionary profile of the 2 groups.

Results

182 patients were included in our study. The average age was 35 ± 6.5 years with a female predominance (sex Ratio F/H: 4.6). The average BMI was 28.5 kg/m^2. Papillary carcinoma was the predominant histological type (89.4%), classified as high risk in 34% of cases. Over an average follow-up of 4.8 years, in the obese group, 49% were in remission (Tg <1 µg/l, negative antithyroglobulin antibody and no morphological abnormality), 24% in persistent disease (detectable Tg and/or morphological abnormality), without a significant difference between the 2 groups ($P=0.72$). The analytical study showed that prognostic factors: tumor size, multifocality, capsular invasion and distant metastases were not significantly elevated in the obese group compared to the control group ($P>0.54$). only the presence of vascular emboli was strongly associated with obesity ($P<0.005$).

Conclusion
The significant association between obesity and the presence of vascular emboli during thyroid cancer increases its aggressiveness.

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P1172

Graves' disease associated with severe pancytopenia; case report

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Introduction
Thyrotoxicosis may be associated with anemia (10–34% of thyrotoxic patients), leucopenia (15–30%) and thrombocytopenia (2–5%). We present the case of a 13-year-old girl with Graves' disease associated with severe pancytopenia.
Case presentation
The patient presented with menorrahgia and symptoms suggestive of an upper respiratory tract infection. On examination she was afebrile with a pulse rate of 100/min at rest. She had a small goiter with no signs of thyroid eye disease. There was no organomegaly or lymphadenopathy but the presence of petechiae and bruising was noted. She was admitted to the Pediatric Department and a blood count revealed pancytopenia (Hct 28.8%, Hb 9.7 g/dl, MCV 76.6 fl, MCH 25.4 pg, WBC 2010/μL, Neut:703/μL, PLT: 39500/μL). Serum ferritin, folate and B12 levels were normal and hemolysis screen was negative. Bone marrow aspiration showed reactive changes and granulocyte and platelet antibody screening was consistent with the diagnosis of autoimmune neutropenia and thrombocytopenia. On admission, there was subclinical hyperthyroidism [TSH: 0.07 μIU/ml, (0.34–5.6)] with positive anti-TPO, anti-TG as well as TRAb (TSH receptor antibodies) thyroid autoantibodies. Thyroid scintigraphy revealed increased uptake with a diffuse pattern. ACTH stimulation test was normal. During her hospital stay, her peripheral blood count worsened (Hct 23.1%, Hb 7.9 g/dl, WBC 1360/μL, Neut 136-430/μL, PLT 15000/μL); she received blood and platelet transfusions and was treated with antibiotics, glucocorticoids and i.v.immunoglobulin. Oral prednizolone was continued with gradual tapering over the subsequent three months. Five months later the patient developed overt hyperthyroidism [TSH $<$ 0.03 μIU/ml, FT4 2.27 ng/dl (0.6–1.37), T3 3.3 ng/ml (0.56–1.56)] and antithyroid treatment with methimazole was initiated. Management of the hyperthyroidism with antithyroid drugs proved challenging due to fluctuations in the neutrophil and platelet counts; therefore, thyroidectomy was recommended as a definitive therapeutic option.
Discussion
Although rare, an association of immune thrombocytopenia and neutropenia with autoimmune thyroid disease has been reported in several studies. Pancytopenia in association with Graves' disease has been described in 23 cases in the literature. Hematologic values tend to normalize with recovery from thyrotoxicosis. Evaluation of thyroid function tests and thyroid antibodies should be part of the work-up of patients who present with thrombocytopenia, neutropenia or pancytopenia.

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P1173

Biotin thyroid interference an emerging problem with a practical solution: beyond a case report

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Introduction
Biotin is a water-soluble vitamin involved in several and important metabolic processes, recommended daily intake for adults is 30–100 μg/day and normal plasma concentrations are 0.4–1.2 ng/day. Nowadays biotin is being used in inherited metabolic diseases, multiple sclerosis and as a supplement in, over the counter multivitamins widely used for common hair and skin problems. The supraphysiologic biotin intake has produced emerging problems with biotin-based immunoassays, producing interferences in different assays.
Case report
Our first case was a 55-year-old woman with progressive multiple sclerosis (PMS) referred to our Endocrinology Unit because a screening thyroid function test revealed a severe biochemical hyperthyroidism with TSH: 0.01 mUI/L (0.27–4.20 mU/L), FT4 $>$ 7.7 ng/dL (0.93–1.7 ng/dL), FT3: 10.9 pg/mL (2.0–4.4 pg/mL). The patient was admitted and methimazole with propranolol treatment was initiated, although clinical signs of thyroid disorder were unspecific and not clear, which made us doubt and continue with further investigations. Thyroid function tests were repeated and similar results were obtained with negative anti–thyrotropin receptor antibodies. Then we found that patient was using biotin 300 mg/d, therefore, an interference was suspected. When biotin was measured revealed a plasma concentration of 3830 ng/mL, (more than 1000-fold of normal concentration). The patient sample was also quantified by a biotin-free method and results confirmed biotin interference in our patient. Consequently, we tried to find a practical solution and applied a simple method described by Piketti and cols, to overcome the biotin interference. In addition, we designed an *in vitro* approach by adding biotin to a control serum-pool (with euthyroid status) increasing its concentration up to 1150 ng/mL simulating biotin intakes between 2.5–300 mg per day.
Conclusion
We confirmed that in competitive immunoassays [FT4 and FT3] excess biotin in the specimen competes with the biotinylated analogue for the binding sites on streptavidin, resulting in falsely high values. In contrast, when the sandwich immunoassay formats are used (TSH determination) excess of biotin in the sample displaces biotinylated antibodies, resulting in falsely low results. Therefore, the streptavidin-based method described, successfully eliminates biotin from de samples, avoiding false hyperthyroidism.

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P1174

Intra-tumoral necrosis after Sorafenib in a patient with radioactive iodine-refractory differentiated thyroid cancer: what's next?

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Introduction
Radioactive iodine-refractory differentiated thyroid cancer is a rare form of advanced thyroid cancer (approximately 4 cases per million population per year) defined by persistent disease after administration of a cumulative radioiodine dose of 600 mCi or at least one tumor without radioactive iodine uptake or by progression of the disease within one year after RAI treatment. Therapeutic options in this case include molecular-targeted therapies, like tyrosine kinase inhibitors, selective BRAF inhibitors, treatments directed at the VEGFR and even immunotherapy that may control thyroid progression and prolong progression-free survival.
Case Report
We present the case of a 69 year old female who was admitted in our endocrinology department with history of papillary thyroid carcinoma for which she had undergone total thyroidectomy in 2007, followed by three surgical reinterventions for local regrowth in 2011, 2013, 2014 and a cumulative dose of 1200 mCi of radioiodine. A CT scan performed in March 2018 identified a cervical tumor of 33/20/30 mm that which grew up to 23.2/54.5 mm during the next 6 months, associated with multiple metastases in local lymph nodes and both lungs. At that point a new surgery was refused by the patients. Taking into account the progression of the disease despite high cumulative dose of radioiodine already received by the patient there was no indication for I131 treatment. In this scenario, indication for thyrosine kinase inhibitor was recommended so the patient received 400 mg of sorafenib per day. In January 2019, at 3 months of therapy, she had clinically local progression of the disease and the CT scan shows a tumor of 43.4/54.8 mm with massive intra-tumoral necrosis and persistent lymph nodes and pulmonary metastases with newly developed left pleuresy. The thyroglobulin levels under LT4 treatment decreased 3 months of sorafenib from 4034 ng/ml to 2277 ng/ml.
Discussion
Despite significant reduction of thyroglobulin levels and tumor necrosis after 3 month of tyrosine kinase inhibitors that would make our patient a good responder, the local progression of the disease in the surrounding tissue will have an important impact on the patients' survival.

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P1175

Familial autoimmune polyglandular syndrome: a case report

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Introduction
Autoimmune polyglandular syndrome (APS) is an autoimmune disorder that affects many endocrine glands. Until now four categories of APS are identified: APS-I includes at least two out of: mucocutaneous candidiasis, hypoparathyroidism and adrenocortical failure. APS-II, the most frequent, comprises of Addison's disease, autoimmune thyroid disease and/or type 1 diabetes. APS-III is defined by the presence of autoimmune thyroid disease and other autoimmune disorders, type 1 diabetes (IIIa), biermer disease (IIIb) and alopecia (IIIc) and the absence of Addison's disease and hypoparathyroidism, while PAS IV includes non-endocrine autoimmune disorders and Addison's disease, but not hypothyroidism.
Presentation: We describe a case of a 40 years old man born of non-consanguineous parents who is followed in our endocrinolgy departement for a probable autoimmune polyendocrine syndrome; association of type 1 diabetes and hyperthyroidism.The patient's medical family history includes a total of four siblings: a sister with vitiligo a brother with type 1 diabetes and vitiligo and a brother with adrenocortical insufficiency, hypoparathyroidism and type 1 diabetes. His father, had type 2 diabetes and hypertensien. His mother had type 2 diabetes and hypothyroidism. For our patient we report the onset of type 1 diabetes in 1993, at the age of twelve, with reccurent hospitalisations due to diabetic ketoacidosis. The most recent in january 2019. For this patient adrenocortical insufficiency was suspected in 2010 but excluded by a normal Synacthen test. We report the onset of hyperthyroidism in 2017. He is suspected to be a case of autoimmune polyendrocrine syndrome type 3 (APS3).
Discussion
In this case, the patient and his family's medical history is full of autoimmune involevement that leads us to think of familal APS. However in this case we find different associations of autoimmune diseases, particulary the sibling with the association of surrenal insufficiency and Hypoparathyroidism that can be classified as APS-I. Anyhow for our patient APS-III is more probable. This variation in presentation within the same family makes the diagnosis of APS and its classification challenging.

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P1176

Coexistence of primary mucosa-associated lymphoid tissue lymphoma of thyroid and papillary thyroid microcarcinoma in a background of hashimoto's thyroiditis

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Introduction
Papillary thyroid carcinoma (PTC) is the most common endocrine cancer however extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT) of the thyroid gland is quite rare. The simultaneous association of both cancers is much more rare.
Case report
65-year-old woman underwent a thyroid ultrasound examination due to palpable thyroid nodules. Thyroid ultrasound revealed thyroiditis and multiple nodules on the right and left sides. The results of routine laboratory tests were normal and serum hormone measurements showed a thyroid-stimulating hormone (TSH) value of 1.80 mU/l (reference range 0.27–4.2), free T4 value of 0.85 ng/dl (reference range 0.58–1.6), thyroglobulin antibodies of 133 IU/ml (reference range 0–4), and peroxidase autoantibody of 1.3 IU/ml (reference range 0–9). Although the biopsies were benign, total thyroidectomy was performed due to the presence of multiple nodules and therefore with the concern that the subsequent follow-up would be difficult. Histopathology examination revealed a papillary thyroid microcarcinomas in the right lobe was 0.45 cm and in the left lobe 0.6 cm in diameter a predominant follicular pattern (Figure 1A) accompanied with MALT lymphoma showing transformations to diffuse large B-cell lymphoma (Figure 1B and 1C). She reported no systemic B symptoms related to lymphomas. The staging procedures with contrast enhanced computed tomography of neck, thorax and abdomen revealed no evidence of metastasis but bone marrow biopsy was consistent with marginal zone lymphoma metastasis. Thyroid tissue or pathological lymph node was not detected in post-operative 3rd month ultrasound.
Conclusion
Herein, we presented a case with concomitance of thyroid papillary microcarcinoma and MALT in a background of hashimoto's thyroiditis. In contrast to published cases and despite transformation to DLBCL our patient was asymptomatic. The prognosis of the extranodal marginal zone lymphoma of MALT localized to the thyroid is excellent; however, its known that patients with extrathyroidal invasion or transformation to high-grade lymphoma have poor prognosis. As a result, extranodal marginal zone lymphoma of the thyroid gland is rare and its pathogenesis is not fully understood. Despite the rarity of PTL, it can simultaneously exist with PTC, especially in patients with Hashimoto thyroiditis and the treatment has to prioritize the tumor with worse stage and condition.

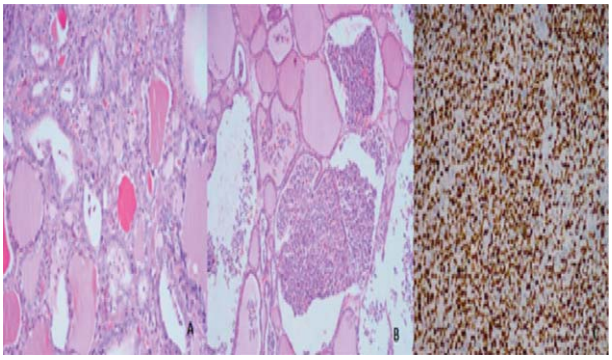

Figure 1 (A) Hematoxylin-eosin staining showing follicular variant papillary microcarcinoma (200×magnification) (B) lymphoid infiltrate filling the follicle lumen (100×magnification) and (C) Ki-67 proliferation index of the tumor was 90% (200×magnification)

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P1177

Single thyroid amyloidosis: a case report

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Introduction
Thyroid amyloidosis is defined as amyloid protein and fat deposition within the thyroid gland. It is classified as either primary (idiopathic) or secondary to inflammatory/chronic disease. Albeit deposition of amyloid protein in thyroid tissue is frequent, amyloidosis affecting exclusively the thyroid gland without evidence of other organs involved is extremely rare. We report a clinical case of a patient who underwent lobectomy due to a toxic adenoma, whose histology revealed thyroid amyloidosis, without further evidence of systemic involvement, to date.
Clinical case
A 78-year-old male presented to the endocrinology department in January 2018 with thyreotoxicosis, with the laboratory workup confirming a primary hyperthyroidism (TSH 0.05 uU/ml, free T4 1.92 ng/dl, thyroid peroxidase and thyroglobulin antibodies negatives, TRAb 0.80 U/l). There were no other positive findings on the evaluation, namely signs or symptoms of a systemic disease. Thyroid ultrasound revealed a heterogenous thyroid gland, with a single solid nodule with 45 mm on the right lobe. The diagnosis of toxic adenoma was made and the patient underwent right hemithyroidectomy after thyroid function normalization. The histology showed a nodular micro and macrofolicular hyperplasia of the thyroid gland, stroma enlargement, and marked thickening

of thyroid vessels wall, with amyloid deposits (positive for Congo red and birefringent in polarized light). The immunohistochemistry was positive for amyloid AA and lambda light chains, and negative for calcitonin and beta 2 microglobulin. Based on morphology and histochemical findings, the diagnosis of thyroid amyloidosis was rendered. Further investigations were carried to check for systemic involvement, including complete autoimmunity panel and biochemical markers of other inflammatory or chronic diseases, all of which were negative. Plasma amyloid precursor was in the normal range. Fat abdominal biopsy was negative for amyloid proteins. The final diagnosis was single thyroid amyloidosis, and the patient maintains a regular follow-up.
Conclusion
Thyroid amyloidosis presented in this clinical case was diagnosed as an incidental finding. Exclusion of systemic involvement is mandatory in this setting, as well as exclusion of a secondary cause of amyloidosis, because most cases of thyroid amyloidosis coexist with involvement of other tissues or organs. This case highlights the rarity of a single thyroid amyloidosis, and the importance of a multidisciplinary approach following a rare diagnosis with an unknown prognosis.

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P1178

Malignant melanoma and papillary thyroid carcinoma: a case report

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Introduction
Patients with either papillary thyroid carcinoma or melanoma have an increased risk of developing the other cancer as a second primary malignant neoplasm. We report a rare case of malignant melanoma (CM) and papillary thyroid carcinoma (PTC) that were diagnosed and treated simultaneously.
Observation
We report a case about a 46-year-old male, in whom examination of a skin biopsy that was obtained from a lesion in the right big toe revealed the lesion to be consistent with malignant melanoma. The patient underwent radical inguinal node dissection upon the detection of malignant melanoma metastasis to the sentinel lymph node. Papillary thyroid carcinoma was then diagnosed, revealed by a solitary nodule and a total thyroidectomy was indicated. High-dose followed by moderate-dose interferon-α therapy for the treatment of malignant melanoma were administred. The patient also received concurrent radioactive iodine therapy for the treatment of papillary thyroid carcinoma, at the same time as the interferon therapy. The two primary tumors of the patient were treated successfully. During therapy, no serious side-effects were observed.
Conclusion
Malignant melanoma and papillary thyroid carcinoma may occur concurrently, although this is rarely observed. More studies are needed to better define the associated genetic predisposition between PTC and CM.

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P1179

Sonographic-pathologic correlation of thyroid nodules: TI-RADS vs EU-TIRADS

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Background
Several ultrasound (US) scoring systems have been proposed to provide rules for standardizing risk stratification of thyroid nodules and to select which nodules should have a fine needle aspiration (FNA) biopsy performed. TI-RADS classification is one of the most used in the daily practise. Recently, EU-TIRADS scoring system has been published to simplify the evaluation of thyroid nodules and to integrate previous classifications into a single system. We aimed to compare these two scoring systems (TI-RADS and EU-TIRADS) and to assess the correlation between the ultrasonography TI-RADS/EU-TIRADS classification systems and histopathology.
Methods
Observational, retrospective study of patients with thyroid nodules who underwent thyroidectomy at our centre between January and October 2018. Nodules were categorised according to TI-RADS and EU-TIRADS classification. After thyroidectomy, histopathological results were correlated with the US findings.
Results
We included 61 patients (79% females, age 55.4 ± 14.6 years old) with 89 nodules. Of all the nodules, 74 (83%) were benign, whereas 15 (17%) were malignant. The benignity percentages of TI-RADS category 2, 3, 4A, 4B and 5 were 100%, 100%, 91%, 68% and 0%, respectively. No malignant nodules were classified in category 2 or 3 ($P < 0.001$). In relation to EU-TIRADS, the benignity percentages of category 2, 3, 4 and 5 were 100%, 97%, 91% and 0%, respectively. No malignant nodules were classified in category 2 ($P < 0.001$). The size of the the malignant nodule classified as EU-TIRADS 3 was 40 mm, so FNA would have been indicated in this nodule. When compared with histopathological results, sensitivity, specificity, positive predictive value and negative predictive value were 100%, 39%, 25% and 100%, respectively, for TI-RADS; and 94%, 72%, 40% and 98%, respectively, for EU-TIRADS.
Conclusion
Our results show that TI-RADS demonstrated a higher sensitivity, whereas EU-TIRADS had a higher specificity; besides, it is easier to use in daily practice. Moreover, EU-TIRADS also considers the nodule size as a criterion for FNA, which increases the sensitivity of this classification.

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P1180

Long-term results in elderly patients with differentiated thyroid carcinoma

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Introduction
Differentiated thyroid cancers are rare (less than 1% of cancers), and generally have a positive prognosis: Their mortality rate increases steadily with age.
Objective
To assess the biologic behavior of differentiated thyroid carcinoma in patients aged 65 years or older and evaluated factors that influenced long-term survival..
Patients and methods
We conducted a retrospective study of elderly patients (>65 years) followed for papillary thyroid carcinoma at the endocrinology department of Ibn ROCHD University Hospital of Casablanca from 1986 to 2019, based on clinical features, histology and their evolutionary profile. Statistical analysis was univariate for all variables, using SPSS software version 22.0.0.
Results
Among the 713 patients treated for papillary thyroid carcinoma, advanced age was found in 90 patients with an average age of 68.7 years (65–81), a sex ratio F/H: 6.5 (78 women, 12 men), and a history of familial thyroid neoplasia in 29% of cases. The most common clinical symptom was a solitary nodule (31.2% of cases). All patients underwent total thyroidectomy with lymph node dissection in 33%. Complementary totalization by iratherapy was indicated in 97.7% of patients. Papillary carcinoma with vesicular differentiation was the predominant histological type (59.8%), classified as high risk in 36% of cases. The follow-up (average of 6.8 years) includes 34% of locoregional metastases, and distant ones in 42% of patients, with a survival rate of 46%.
Conclusion
Thyroid cancers in the elderly patients are infrequent, characterized by their advanced stage at the diagnosis' time, its prognosis does not seem to be influenced by just histological diagnosis, but also by its association with other prognostic factors: age, female predominance and locoregional or distant metastases.

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P1181

Ethanol ablation of cystic thyroid nodules: an effective and not aggressive treatment

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Introduction
Simple aspiration is the first-line treatment used for benign cystic thyroid nodules. However, a high recurrence rate has been reported with this procedure. When this happens, percutaneous ethanol injection into the nodules has proven to be an effective technique which can reach a volume reduction of about 85% (Kim *et al.*, Eur Radiol. 2012 Jul;22(7):1573–8).
Material and methods
Descriptive analysis of percutaneous 96° ethanol injection into mainly cystic thyroid nodules with a benign cytology (Bethesda 2) and an ineffective simple aspiration, performed in our centre between 2015–2018. Eight patients were included (women 87.5%; mean age 49.1 ± 14.0 years). Thyroid function was normal and anti-thyroid antibodies were negative in all the cases. Thyroid nodule volume was estimated with three diameters, obtained by ultrasound, in exams practised before and at 3 and 6 months after ethanol injection. Results are given as median (P_{25}-P_{75}) and as mean ± S.D.
Results
The amount of ethanol injected was 5 ml (3–7.5). Initial thyroid nodule volume was 13.4 cc (8.0–22.8). Final thyroid nodule volume was 1.7 cc (0.2–2.6), which means a 84.6% (78.7–99.3) reduction in our cohort ($P < 0.05$). During procedure, only one patient presented local pain that responded to non-estheroidal anti-inflamatories and low dose corticotherapy. Recurrence was not detected in any case in a 8 month (5–9) follow-up and only one patient needed to repeat the procedure.
Conclusion
Percutaneous 96° ethanol ablation in cystic thyroid nodules is a very effective treatment to reach a permanent volume reduction with both a low complication rate and a low recurrence rate. Our results are similar to those reported previously with wider series from experienced centres.

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P1182

Cured medullary thyroid carcinoma after surgical treatment: does initial presentation matters?

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Background
Surgery is the standard treatment in patients with medullary thyroid carcinoma (MTC), 43% being biochemically cured postoperative in a large series, the most important prognostic factor being the stage of the disease.
Material and methods
We present 3 cases of biochemical cured patients after surgery with different preoperative presentation. Calcitonin and carcinoembryonic antigen (CEA) were measured by chemiluminescence. Histological examination and immunohisto-chemistry (IHC) were used for the analysis of the thyroidectomy specimen.
Cases presentation
Case 1. A 41 years old female patient with high calcitonin levels (> 2000 pg/ml), normal CEA (3.02 ng/ml), bilateral suspicious lymph nodes on US evaluation of the neck. A total thyroidectomy with dissection of cervical lymph node compartments was performed and a 3/2.1 cm MTC was identified. No RET mutations were identified. She had normal calcitonin (< 2 pg/ml) at 3 month after surgery and after 9 years of follow-up (< 1 pg/ml). Case 2. A 56 years old female patient with high levels of calcitonin (4339 pg/ml), high levels of CEA (115.84 ng/ml), no suspicious lymph nodes on ultrasound (US) evaluation of the neck, negative MEN2 biochemical screening, RET mutation analysis is pending. A total thyroidectomy with dissection of cervical lymph node compartments was performed and a 3.8/2.6 cm MTC with 2 ipsilateral lymph node metastases were identified. She had high calcitonin levels after surgery (80.6 pg/ml) that continued to rise during 1 year of follow-up (203.5 pg/ml). The tumor stained positive at IHC for SSTR2. An Octreoscan was performed, showing 2 lesions in the left lateral cervical area. A second surgery was performed with successful normalization of calcitonin levels at 3 month after surgery (5.58 pg/ml) and at 1 year follow-up (9.1 pg/ml). Case 3. A 63 years old female patient with modestly elevated calcitonin levels (39.1 pg/ml), normal CEA (2.5 ng/ml), no suspicious lymph nodes on ultrasound (US) evaluation of the neck. A total thyroidectomy without dissection of cervical lymph node compartments was performed. Morphological examination showed a 0.4/0.3 cm microMTC. No RET mutations were identified. She had normal calcitonin (1.07 pg/ml) at 3 month after surgery and after 5 years of follow-up (0.5 pg/ml).
Conclusion
We aim to highlight the importance of adequate surgical treatment, pre and postoperative evaluation.

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P1183

Challenges of thyroid cancer management in amiodarone treated patients: a case report

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Introduction
Thyroid carcinoma (TC) is the most common endocrine malignancy. Although the overall prognosis for patients with TC is good, up to 20% of patients develop recurrent or persistent disease after conventional therapy by total thyroidectomy and radioactive iodine (RAI). Amiodarone is a highly efficient anti-arrhythmic drug with a very long half-life, so it may interfere with RAI many months after the drug withdrawal. This case report mirrors the challenges of thyroid cancer management in an amiodarone treated patient.
Case
A 65 years-old man, with a well-differentiated papillary cancer (T3N1aMx), underwent total thyroidectomy in 2013, followed by RAI therapy. The I 131-whole body scan (WBS) failed to indicate uptake, in discordance to high TG levels 927.4 ng/ml and low Tg Ab 26 IU/ml and presence of lateral cervical lymph nodes at ultrasound (US). In view of prior use of amiodarone for the past 2 years, which was interrupted 6 weeks before RAI therapy and negative WBS, in March 2014 the serum amiodarone concentration was < 0.01 mg, but associated with high serum 192 µg/l and urinary iodine 782 µg/levels, showing excessive iodine body load. The head,neck and thorax CT scan were negative, despite the abnormal TG 393.3 ng/ml. 18FDG-PET showed left latero-cervical and supraclavicular lymphadenopathy, and no distant metastases. In July 2014, TG increased to 863 ng/ml and therefore, the patient received an additional dose of 76.4 mCi I 131. The post-therapeutic WBS showed RAI uptake in the neck. In October 2014 the Tg level was still elevated at 1105 ng/ml, so the patient received another completion dose of 118.8 mCi I 131, followed in March 2015 by another dose of 100 mCi I 131, at a Tg level of 766 ng/ml. Pathological lymph node uptake was confirmed at WBS and no uptake in the thyroid bed or distant secondary disease was evidenced. Neck US confirmed multiple left latero-cervical and supraclavicular round, hypo-echoic, intensely, vascularized lymphadenopathies. In view of lack of adequate response of the disease to RAI treatment, and no organic metastases, the patient was proposed to therapeutic lymph node dissection.
Discussion
In high amounts, iodine saturates the thyroid gland, blocking further absorption of both non-radioactive and radioactive iodine. As in the presented case, iodine uptake blockade is prolonged for several months after high iodine exposure by amiodarone intake and may explain lack of RAI image on WBS in our patient, despite increased Tg levels and US data.

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P1184

Screening of thyroid dysfunction in diabetic pregnant women

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Introduction
Thyroid disorders are quite common during pregnancy complicated by diabetes mellitus.

Objective
The aim of our study was to detect thyroid disorders in a group of diabetic pregnant women.
Patients and methods
Rétrospective study involving 243 pregnant women with diabetes followed in consultation or hospitalized in Endocrinology and Diabetology department of Ibn Rochd University Hospital of Casablanca, over a period from January 2016 to Octobre 2018. Data collection was done from medical records. All women had been interrogated for personal and family history of dysthyroidism and a complete physical examination. They had benefited from a biological assessment including the couple FT4-TSH. The evaluation of thyroid status referred to the 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum.
Résults
Mean age of women was 32 years old (18–49). They have on average 4 gestations, 2 parities and 2 live children. 36.6% of patients had gestational diabetes and 63.6% had pre-gestational diabetes (43.62% type 2 diabetes, 19.75% type 1 diabetes). The average term at first consultation was 21.6 weeks of amenorrhea (5–37): 49.5% were in the first trimester of pregnancy while 37.7% and 12.6% were respectively in the 2nd and 3rd trimester. The average TSH was 1.44 ± 0.96 uIU/mL (0.28–5.28) while FT4 was 11.35 ± 1.94 pmol/l (6.16–15.74). 25.10% of women suffered from some form of thyroid disorder, mostly (55.73%) hypothyroidism. Thyroid dysfunction was not associated with the type of diabetes mellitus (GDM or PGDM) ($P < 0.05$). Nearly half of these patients had been put on L-thyroxine. This treatment was recommended in patients with a thyrotropin level higher than 2.5 mui/l. Hyperthyroidism was noticed in 44.26% of our patients and was dominated by gestational transient thyrotoxicosis (62.96%).
Conclusion
The study findings warrant routine screening for thyroid abnormalities in diabetic pregnant women. These women have increased rate of maternal and neonatal complications.

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P1185

Goiter and hashimoto's thyroiditis

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Introduction
Hashimoto's thyroiditis is known to induce nodularity in the thyroid and in some cases to coexist with papillary thyroid carcinoma. However, the effect of the development of Hashimoto's thyroiditis on the course of nodular goiter is not known.
Aim
The aim was to describe the effect of the development of Hashimoto's thyroiditis in the course of nodular goiter.
Methods
A cohort of 12 patients, female, aged 22 to 50 years old is described. The patients presented with nodular goiter. The goiter was not causing obstructive symptoms, the patients being followed up. In the course of the disease they developed antithyroid antibodies, anti-thyroglobulin and anti-thyroid peroxidase antibodies. The patients developed overt hypothyroidism over a period of 2–5 years.
Results
Thyroxine was administered for the treatment of hypothyroidism. Three years after the development of hypothyroidism the patients were evaluated. Ultrasound examination revealed the absence of nodules within the thyroid gland. In 3 of the patients the thyroid was smaller than normal while in the rest of the group the thyroid was of normal size.
Conclusions
Goiter is known to be associated with iodine deficiency, on the contrary Hashimoto's thyroiditis being associated with iodine sufficiency. Iodine sufficiency seems to have altered the epidemiology of thyroid disease. In the present study we report the effect of the development of Hashimoto's thyroiditis on thyroid nodularity in a cohort of female patients. It appears that the development of Hashimoto's thyroiditis, overt hypothyroidism and the subsequent treatment with thyroxine may modulate thyroid nodularity.

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P1186

Graves' disease in asssociation with common neoplasms – a retrospective study

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Introduction
Graves' disease is an autoimmune disease that leads to a generalized overactivity of the entire thyroid gland – hyperthyroidism. Although the link between Graves' disease and thyroid carcinoma was widely explored, we cannot undermine the relationship between this condition and other common neoplasms.
Materials and method
The retrospective analysis was performed using clinical data of 295 adult patients (225 women and 70 men) from our endocrine department in the last five years. Among them, we evaluated 21 with any type of carcinoma (7.11% of all patients with hyperthyroidism, 18 woman and 3 men, aged between 37 and 89 years old) and 79 patients with Graves' ophtalmopathy. The data was analyzed using IBM SPSS Statistics 20.
Results
The most frequently found 4 types of neoplasms were of thyroid, uterus, breast and dermatological. The prevalence of thyroid cancer in patients with hyperthyroidism varies widely in the literature – from 1.6% to 21.1%. The majority of carcinomas reported in these studies were papillary microcarcinomas. In our analysis we found four cases of thyroid cancer, all four patients being women (19% of all types of cancer) – three papillary microcarcinomas and one papillary-like (NIFPT). Another association mentioned in literature is between hyperthyroidism and breast cancer, as more studies reports the onset of breast cancer especially within three years from the thyropathy diagnosis. In our study, we discovered three cases of breast malignant tumors (14.28% of all types of carcinoma), aged between 52 and 61. Epidemiologic studies also show an association between ovarian cancer and hyperthyroidism, although no mechanism of association was demonstrated. In our analysis, three cases of malignant tumors of the uterus were found (14.28% of all types of carcinoma), aged between 44 and 62. Other malignant tumors were dermatological (three cases – 14.28% of all types of neoplasm), colo-rectal (two cases), pulmonary, renal, prostatic, gastrointestinal (a neuroendocrine tumor), Kaposi Sarcoma and meningioma. Among the 21 patients diagnosed with neoplasms, seven of them (33.33%), all woman, also associated Graves' ophtalmopathy. A positive statistical correlation was made between the presence of thyroid nodules associated with any type of cancer ($P = 0.003$, $r = 0.372$).
Conclusion
The relationship between common neoplasms (not only thyroid carcinoma) and Graves' disease is a subject of great interest, our results being limited by the small number of patients. Further investigations, especially between the link to Graves' ophtalmopathy and pathogenical mechanism should be considered in future studies.

Keywords: Graves' disease, Graves' ophtalmopathy, neoplasms
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P1187

Pretibial myxedema in Graves' disease: about two cases

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Introduction
Grave' disease is associated with extra thyroid auto-thyroid manifestations such as basal ophthalmopathy and/or. We report the case of two patients presenting with extrathyroid manifestations of the basic illness hospitalized at the

department of diabetic endocrinology and metabolic diseases of Ibn Rochd University Hospital of Casablanca.
Case 1
This is a patient aged 53 years, chronic smoking at 20 years, for low weight disease since 5 years, under Dimazole 05 mg/day. Clinical examination found moderate ophthalmopathy with grade 2 exophthalmos and a clinical activity score of 4 with a pretentious myxedema of digital clubbing. Paraclinically, anti-reactive TSH Ab above 40 U/l, orbital MRI showed Hypertrophy occulomotor muscles, while the ultrasound of the parties was demonstrated distal third infiltration of the two legs, and the biopsie confirmed yhe diagnosis. Patient receved oral corticosteroid in ordre to prepare him for Iratherapy. During follow-up, inflammatory signs of ophthalmopathy disappeared, whereas pretitibial myxedema stably persisted at 2 years after irathérapie.
Case 2
This is the 37-year-old patient, followed by grave's disease under 25 mg of progressive Dimazol for 12 years, with the appearance of pratibial myxedema since 2 years. Clinical examination found moderate ophthalmopathy with a clinical activity score of 4 with pre-tibial myxedema. On the paraclinical TSH level, is free, the Ab anti-powers of TSH are greater than 40 U/l, orbital CT is a hypertrophy of right muscles, nerves, normal optics, absence of exophthalmos. The patient took a bolus of corticosteroids to manage her orbitopathy, with titration of doses of Dimazol, waiting for euthyroidism to receive radical therapy with Iratherapy.
Conclusion
Dermopathies are a rare manifestation in the Grave's disease, of preferential localization pretibial. Myxedema is almost always associated with ophthalmopathy. Treatment is mainly based on corticosteroid therapy.

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P1188

Tuberculous lymphadenitis mimicking nodal metastasis in papillary thyroid carcinoma: a diagnostic dilemma

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Introduction
Cervical lymphadenopathy is often a diagnostic challenge to medical professional due to its varied etiologies. Malignancies and infections are the main causative factors that should be included in the differential diagnosis. Cervical lymphadenitis is a common manifestation of extra-pulmonary invasion of the tuberculosis. A cervical tuberculous lymphadenitis could be confused with metastatic lymph node of thyroid cancer.
Case reports
Case 1: A 37-year-old man complained of a tow months swelling in the left side of the neck. On examination, a solitary nodule in the right lobe of the thyroid with multiple painless enlarged left cervical lymphnodes were identified. Ultrasonography of the neck suggested a suspicious nodule in the right lobe of the thyroid with a 3 cm left cervical metastatic lymphadenopathy. The patient underwent total thyroidectomy with neck dissection. Histopathological analysis were performed on the total thyroidectomy specimen, the left side neck nodes (from level II to level VI) and the central compartment neck nodes. A papillary thyroid carcinoma in the right lobe was confirmed. The isthmus and left lobe were uninvolved. The lymph nodes isolated from the left chain (levels II-V) revealed tuberculous lymphadenitis. The lymph nodes isolated from the central compartment were free of tumor deposits. The patient was put on anti-tubercular therapy for 6 months. The radioiodine ablative treatment was given as per the protocol.
Case 2: A 48-year-old female presented to our department with a 4-months history of a gradually enlarging lateral mass of the neck. On examination a mass measuring 4 $\times$ 3 cm was palpated at the left thyroid lobe. An associated 3 cm lymphnode was also palpated at the left cervical area.The rest of the examination was otherwise unremarkable. A thyroid ultrasound showed a solid mass at the left lobe with multiple cervical lymph nodes of the left level II chain. The patient underwent total thyroidectomy with neck dissection. Histopathological examination confirmed papillary thyroid carcinoma at the left thyroid lobe associated with tuberculous lymphadenitis. The patient was put on anti-tubercular therapy for 6 months. The antimycobacterial therapy was well-tolerated. She underwent adjuvant high-dose radioactive iodine treatment with no untoward complications and she is currently on levothyroxine suppression therapy.
Conclusion
These cases show that cervical lymphadenopathy in a patient with papillary thyroid carcinoma may not always indicate metastatic spread from the disease. In developing countries, tuberculosis should be considered as an important differential diagnosis of cervical lymphadenopathy in a patient with papillary thyroid carcinoma.

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P1189

High activity range and longer follow up duration have better success rate in Radioiodine treated hyperthyroidism

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Purpose
To evaluate the outcome of different Radioactive iodine-131 activity range for the treatment of hyperthyroidism assessed at 6 and 12 months.
Material/method
We retrospectively reviewed data of patients who received Radioiodine treatment for benign thyroid disorder at our center between 2013 to 2015. Indication for treatment, radioiodine activity administered, type of hyperthyroidism, and biochemical outcome of thyroid function at 6 and 12 months post treatment points were collected and analysed. Primary diagnosis was Grave's disease in 37 patients, Toxic Multinodular goiter in 15 patients, autoimmune negative thyrotoxicosis seven patients, Hashitoxicosis two patients, subclinical hyperthyroidism two patients and recurrent autoimmune thyroiditis 1 patient.
Results
Sixty four patients with mean age 54 years, 49 (77%) females, received radioactive iodine treatment between 2013 and 2015. Grave's disease was the commonest underlying pathology in 37 (58%) of patients. Dose of radioactive iodine received had mean activity of 582 Mbq (distribution 400mbq–800mbq), and 19 out of 64 (30%) patients received radioactive iodine as primary treatment. At 6 months post treatment 40 (63%) patients were hypothyroid, 13 (20%) were euthyroid, 5 (8%) were hyperthyroid, and remaining 6 (9%) subclinical. At one year after treatment 44 (68%) were hypothyroid, 12 (19%) were euthyroid, 3 (5%) were hyperthyroid and remaining 5 (8%) were subclinical. When split by activity, 30 (75%) of patients who received 600 Mbq were hypothyroid in 6 months, 7 (17.5%) were euthyroid, and only 1 (2.5%) were hyperthyroid who later reverted to subclinical hypothyroid by 12 months. 2 (5%) patients remained subclinical both at 6 and 12 months. In comparison, 6 (42.8%) of those who received 400 Mbq were hypothyroid in 6 months, 4 (28.5%) were euthyroid, and 4 (28.5%) were Hyperthyroid. By 12 months 9 (64.2%) were hypothyroid, but still 3 (21%) remained hyperthyroid and required a second radioiodine dose. Only 1(7%) patient remained euthyroid and 1(7%) were subclinical.
Conclusion
Despite the small sample there were clear indications for better outcome and less failure rate when radioiodine is used at the higher suggested activity and follow-up extended to 12 months.

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P1190

Clinical case: follicular thyroid carcinoma metastasis in pubic bone without primary tumor

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Introduction
Follicular thyroid carcinoma (FTC) is the second most common malignancy of the thyroid gland. Distant metastasis, usually in bones or lungs, can be found in about 10%–15% of cases. A clinical case of FTC distant bone metastasis is presented.
Case
A 62-year-old male came to endocrinologist for annual follow-up (FU) of multinodular goiter, euthyreosis in 2010. Two years before prostate carcinoma (T1N0M0) was also diagnosed for the patient and brachytherapy was adjusted. At

that time small pelvis computed tomography (CT) scan showed a focal lesion with cortical bone destruction in the upper ramus of the right pubic bone. Management and outcomes: thyroid ultrasound scan (US) showed nodes in both thyroid lobes up to 23 mm of diameter. After fine needle aspiration (FNA) only benign follicular epithelium changes were found. Blood test showed normal thyroid-stimulating hormone (TSH) 0.71 mU/l, but highly elevated thyroglobulin (Tg) 2030 mcg/l. In 2011 Tg increased (4920 mcg/l), during thyroid US nodes with calcifications were diagnosed, therefore FNA was performed and benign follicular epithelium changes were found again. After 6 months blood tests were performed: Tg 6888 mcg/l, TSH, TPOAb and TgAb were within the normal range, FNA was repeated for the third time and follicular epithelium proliferation was found. Total thyroidectomy was recommended, but surgeon refused it. Thyroid US showed no significant changes during FU period, but Tg was markedly elevated ($>30{,}000$ μg/l). In 2014 the patient had a pubic bone fracture and bone biopsy revealed metastasis of follicular thyroid carcinoma (TTF-1: 100% tumor cells had strongly positive nuclear staining; Tg: 90% tumor cells had strongly positive cytoplasmic staining). Total thyroidectomy was performed in 2014, the histology showed benign thyroid hyperplasia with no signs of follicular carcinoma. SPECT and low dose CT scan of pelvis was performed after 1 month and radioactive iodine-131 (I-131) accumulation was found in the thyroid bed and intensive accumulation on the right side of pelvis (around 75×65 mm lesion). I-131 therapy was indicated and cumulative 28,8 GBq dose was adjusted since 2014. The patient is still followed-up and Tg levels after I-131 were decreasing for 3 years till 56.9 μg/l, unfortunately in 2018 Tg levels increased (1345 mcg/l) and primary tumor is still not found.

Conclusion

This case is exceptional because of its rarity and also due to the incapability to find the primary tumor.

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P1191

Differentiated thyroid cancer treated with lobectomy: assessment of response to therapy

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Background

Assessment of response to therapy is a valid tool for dynamic risk stratification in patients with differentiated thyroid cancer (DTC). It is well documented in patients treated with total thyroidectomy and radioiodine ablation therapy (RAI), but data is still sparse regarding patients treated with lobectomy. Our study aimed to evaluate response to therapy in patients with DTC treated with lobectomy.

Methods

We performed a retrospective study of 69 patients identified from our institutional database, who underwent lobectomy for DTC between 2000 and 2015. All patients had apparent complete tumour resection, without clinically apparent lymph node or distant metastasis at diagnosis and nonaggressive histologic variant. Excellent response to therapy was defined as stable, nonstimulated thyroglobulin (Tg) <30 ng/ml and negative imaging and indeterminate response was defined by nonspecific findings on imaging studies or rising Tg levels. Statistical analysis was performed using SPSS v23.0.

Results

All patients were followed for a minimum of 3 years post-operatively (79.5 ± 44.3 months). Forty patients (57.9%) had microcarcinomas and mean tumour size was 11.7 ± 11.5 mm. Twenty patients (28.9%) had completion thyroidectomy and RAI in the first year after lobectomy due to the presence of contralateral nodules or extra-thyroidal extension, and half of these had malignant disease. These patients had a similar level of post-surgery (Tg) (22.1 ng/ml versus 18.3 ng/ml; $P=0.646$) to patients who did not undergo completion thyroidectomy. All of these patients had excellent response to therapy. At the end of the follow-up, 51% of the patients who did not undergo completion thyroidectomy, had contralateral nodules and these patients had a higher level of Tg at the end of the follow-up than patients who had no nodules (13.2 ng/ml versus 3.9 ng/ml; $P=0.02$). Eleven patients (15.9%) had indeterminate response to therapy at the end of the follow-up, based on ultrasound findings or rising Tg levels. These patients had similar levels of post-surgery Tg levels (19.4 ng/ml versus 17.6 ng/ml; $P=0.451$) to patients with excellent response to therapy but higher Tg levels at the end of the follow-up (13.1 ng/ml versus 6 ng/ml; $P=0.03$).

Conclusion

Outcomes are excellent in selected patients with DTC treated with lobectomy. Indeterminate response to therapy does not seem to affect overall survival and post-surgery Tg levels do not seem to predict response to therapy. In this study, a threshold lower than 30 ng/ml might be more accurate to define excellent response to therapy or even indeterminate response.

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P1192

Amiodarone-induced thyrotoxicosis: which type?

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Introduction

Amiodarone is a widely used antiarrhythmic drug for refractory atrial or ventricular tachyarrhythmias. Amiodarone-induced thyrotoxicosis (AIT) occurs in up to 6% of patients taking this medication in iodine-sufficient areas of the world and in up to 10% in iodine deficient areas. AIT can be divided into two types: type 1 is a form of iodine-induced hyperthyroidism whereas type 2 is a drug-induced destructive thyroiditis. Type 1 AIT tends to occur in patients with underlying thyroid autonomy in a nodular goitre, or Graves' disease, while type 2 AIT appears as a result of direct damage or induction of apoptosis in thyrocytes by amiodarone.

Case report

A 69-year-old man admitted in Cardiology department for ventricular tachycardia (VT), presented a 3-week history of unintentional weight loss (10 kg), fatigue and lethargy. VT was diagnosed five years before and he started amiodarone. Thereafter, patient needed an implantable cardioverter defibrillator. He denied previous personal or familiar history of thyroid dysfunction. On examination, he presented tachycardia (120 bpm) and a small thyroid goitre. Thyroid function tests showed thyrotoxicosis (TSH 0.008 μU/ml, FT3 9.20 pg/ml, FT4 >7.76 ng/dl), negative TRAb (0.9 U/l) and positive anti-Tg antibody (486 U/ml). Given the previous medical history of amiodarone use, AIT was assumed. His cardiologist prescribed methimazole 20 mg qd, propranolol 40 mg tid and stopped amiodarone. However, significantly thyroid dysfunction persisted. An iodine uptake scan was not performed as patient had already been started on methimazole. Ultrasound revealed a heterogeneous and hyperechogenic thyroid gland, with a 1 cm nodule in the left lobe. At this point, methimazole dosage was increased to 30 mg qd and oral prednisolone 30 mg qd was co-administered. Approximatively 1 month later, biochemical re-evaluation showed TSH <0.005 μU/ml and FT4 >7.76 ng/dl. Given the severity of his presentation and lack of clinical or biochemical improvement, methimazole and prednisolone were increased to 50 mg ($15+15+20$) and 60 mg qd, respectively. His symptoms subsequently improved. Prednisolone was tapered and stopped while methimazole was progressively reduced to 20 mg qd. After 6 months, methimazole was stopped since thyroid function evolved to hypothyroidism. At the last visit, patient remains in subclinical hypothyroidism.

Conclusion

This patient presented severe AIT and needed administration of high dosage of both antithyroid medication and corticosteroids before improvement occurred. He presented features of both types of AIT, proving the diagnosis and management of this condition is sometimes challenging.

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P1193

Surgical outcome of thyroid nodules with atypia of undetermined significance in fine needle aspiration biopsy

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Thyroid nodules have 3–7% freuquency in general population. FNA biopsy is an important diagnostic tool for patients with thyroid nodules. There are many reporting systems for FNA biopsy and Bethesda system is the most common one. The aim of this retrospective study, detect the atypia of undetermined significance (AUS) rates in the patients who performed FNA biopsy and evaluate the concomittant biopsy results of this patients and malignancy rates in the patients

who were candidate and performed surgical operation. In this study 5958 patients who was performed thyroid FNAB between 2012 and 2017 in Ankara University Hospital evaluated retrospectively. Frequency of AUS has been found as 9.82%. When FNAB and final pathology results evaluate together and FNAB's sensitivity is found as 50% and spesivity is 59.5%. The frequency of atypia of undetermined significance in patient series on the literatüre is between 3-10% and in our study we found this rate as 9.82%. The malignancy rates according to final pathology reports are between 22–35% and we found this rate as 52.5%. When the sample divided into three groups as 1) whose 1 fnab cytology result in AUS 2) whose 2 fnab cytology results in AUS, 3) whose 3 fnab cytology results in AUS, malignancy rates were 54%, 44% and 60%, respectively. There was no significant difference between the groups regarding the incidence of malignancy. This findings suggest that repeated FNABs have no predictive value in patients with AUS on thyroid cytopathology. New studies with larger patients series is necesary about this topic. In this study no significant relationship was found between preoperative sonographic features and malignancy risk in patients with AUS on thyroid cytopathology.

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P1194

Papillary thyroid carcinoma revealed by retro spinal adenopathy

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Introduction
Cases of spinal ganglionic chains invasion due to a thyroid carcinoma are exceptional. We are reporting the observation of a patient with thyroid papillary carcinoma, with insular component, revealed by retro-spinal lymphadenopathy.
Observation
Our patient is 55-year-old with no particular pathological history, consulting due to the development of a posterior cervical swelling gradually increasing in volume. A cervical ultrasound was performed, showing the appearance of several retro-spinal lymphadenopathies associated with a nodular goiter. An excisional biopsy of the largest lymphadenopathy found lymph node metastasis of a necrotized and moderately differentiated carcinoma, originating from the thyroid gland, with images of vascular emboli. The patient underwent total thyroidectomy with the excision of the cervical lymph node, including right lateral and cervical, jugulo-carotidian superior and inferior, and retro-spinal. Anatomopathological examination of the operative specimen found a right thyroid carcinoma with an unencapsulated insular component of 2 cm, capsular intrusion and lymph node metastasis. The patient finally benefited from a radioactive iodine treatment at 100 mCi. Three years after the surgery, the evolution was marked by the reappearance of multiple hypodense and necrotic bilateral cervical adenopathies, whose cytological study suspected a malignancy. Lymph node excision was the treatment of choice.
Conclusion
The discovery of spinal adenopathy should not rule out the diagnosis of a lymph node metastasis of a thyroid carcinoma even if it is not the preferred drainage region of these tumors.

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P1195

Amiodarone-induced thyrotoxicosis: when combined treatment is an option

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Introduction
Amiodarone is an effective drug in the management of supraventricular arrhythmias. Due to its composition rich in iodine and pharmacological properties can cause thyroid dysfunction in 15–20% of the treated patients. Clinically it can present in the form of amiodarone-induced hypothyroidism or amiodarone-induced thyrotoxicosis. This latter situation may result from an excess of iodine supply, glandular destruction or both pathogenic mechanisms.
Clinical case
A 58-year-old male with a history of ischemic stroke with cardioembolic etiology, paroxysmal atrial fibrillation requiring ablative therapy and electrical cardioversion, who has been treated with amiodarone for three years. He started with exuberant tremor of extremities, tachycardia, palpitations, irritability, heat intolerance and asthenia with about 6 weeks of evolution associated with involuntary weight loss of 13 pounds in 4 months, initially requiring hospitalization for control and monitoring of symptoms. In thyroid function tests, thyroid stimulating hormone (TSH) $<$ 0.008 μUI/ml (0.4–4.0), triiodothyronine-L (T3L) $>$ 20 pg/ml (1.8–4.2), thyroxine-L (T4L) $>$ 6.0 ng/dl (0.8–1.9), anti-TSH receptor antibodies (TRABS) 2.4 U/l ($<$1.0) and anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies were negative. The Colour-flow Doppler sonography showed a gland of increased dimensions, heterogeneous texture, without thyroid nodules, with reduced vascularity but not negligible. He started therapy with thiamazol a daily dose of 30 mg, prednisolone 40 mg, bisoprolol 2.5 mg and stopped amiodarone. During the 6 months of treatment, there was a symptomatic improvement, with reestablishment of euthyroidism – TSH 0.008; 0.012; 2.3; 1.6 uUI/ml; T3L$>$ 20; 9.7; 5.0 pg/ml; T4L 6.0; 5.0; 2.4; 1.0 ng/dl; TRABS 2.4; 1.9; 1.4; 0.6 U/l. It is currently asymptomatic, without treatment with thionamides or glucocorticoids. He did not restart treatment with amiodarone and maintains an annual monitoring of thyroid function tests.
Conclusion
This case is an example of the approach of amiodarone-induced thyrotoxicosis of mixed/indefinite cause, in which the best therapeutic strategy remains controversial.

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P1196

Stressful life events induce graves' disease: further evidence for the role of stress as an inducing factor in graves' disease

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Introduction
Stress is a known risk factor for the development of Graves' disease. We have previously described the role of bereavement as an inducing factor for Graves' disease. Bereavement as an inducing factor for Graves' disease was shown to affect primarily female patients after the loss of a loved one. However, it appears that other stressful life events may also cause Graves' disease.
Aim
The aim of the study was to describe two cases of patients developing Graves' disease after job related events.
Case reports
A male patient, aged 42, presented with hyperthyroidism and Graves' ophthalmopathy affecting both eyes. The patient had also severe pretibial myxedema. Within the previous month he had lost a good job and had suffered the subsequent financial loss. He had also experienced fraud from a job partner. The patient was treated with methimazole and corticosteroids for Graves' ophthalmopathy. Hyperthyroidism improved. Pretibial myxedema also improved. Graves' ophthalmopathy stabilized. However, two years later the patient suffered a relapse of hyperthyroidism. The patient had a family history of Graves' disease from the maternal side. A female patient, aged 56, presented with hyperthyroidism and mild Graves' ophthalmopathy affecting both eyes. The patient had suffered a job loss within the previous two months. She was treated with methimazole and hyperthyroidism improved. The patient had a family history of Graves' disease from the maternal side.
Conclusions
It appears that stressful life events such as a job loss with severe financial impact may be followed by disease, in particular, an autoimmune thyroid disease, such as Graves'. Bereavement has been previously described to induce Graves' disease. However, in this report we show that stressful life events related to financial loss may also be an inducing factor for Graves'.

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P1197

Hyperthyroid Graves' disease without detectable thyrotropin receptor antibodies

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Introduction
Detection of TSH-receptor autoantibodies in the diagnosis of graves disease is well established. however these autoantibodies may not be always present in some forms of correctly observed autoimmune hyperthyroidism. Here, we describe a patient with hyperthyroid Graves' disease without detectable thyrotropin receptor antibodies.
Case report
She was A 55-year-old woman, presented with a 2 years history of increased sweating, palpitations, polyphagy and insomnia with weight loss of 10 kg. Clinical examination revealed exophthalmos and lid lag, a fine tremor of her fingers, the pulse was 100/min and a small diffuse goiter without trill. Blood tests demonstrated high FT4 = 55.3 pmol/L (NR 12–22), FT3 = 29.2 pmol/L (3.1–6.8), TSH < 0.005 mIU/L (0.27–4.2), Measurement of her thyroid-stimulating hormone was négatif. Thyroid scintigraphy shows an enlarged gland with homogeneous uptake of radiotracer in both lobes.
Discussion
Immunogenic hyperthyroidism (Graves or Basedow's disease) is a consequence of pathological stimulation of the thyroid gland by stimulating TSH-receptor autoantibodies (TSAbs). In Differentes studies The results show that it is extremely rare to have negative TSH receptor autoantibody in patients with active hyperthyroid Graves' disease. In our case palpation, clinical findings, and the data of thyroid sintigraphy were sufficient to establish the diagnosis of Graves disease despite of TSH receptor autoantibodies were undetectable. Other mechanisms can also activate graves disease than antibody-dependent ones or a local production of antibodies within the thyroid can be suggested.

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P1198

Radioiodine-avid bone metastases from differentiated thyroid cancer without structural abnormality, a singular entity with heterogeneous outcomes

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Bone radioiodine (RAI) uptake without structural abnormality in thyroid cancer (TC) patients may be related to false positive or to microscopic foci of metastatic tissue. In such cases, outcome is reported to be excellent. Mrs D. had been operated for a pT3(m) poorly differentiated TC at the age of 43. The first post-therapeutic whole body scan revealed 3 foci of bone uptake (right clavicle, L2, L3). The elevated level of thyroglobulin (157 ng/mL) favoured the hypothesis of bone metastases despite the absence of any structural lesion on CT and MRI. She received 7 courses of radioiodine therapy. The right clavicle RAI uptake persisted, and subsequent CT disclosed an osteolytic lesion which was treated by radiofrequence and external beam radiation. Twenty-five years after the diagnosis, she has a persistent morphological disease with a 30 × 8 mm progressive lesion on the right clavicle, for which surgery is planned. In the Nuclear Medicine Departement database, we identified 13 other cases of RAI-avid bone metastases without structural correlation on CT or MRI between 1993 and 2018. After a median follow-up of 3.9 years (range 0.6 to 25 years), 13 patients were alive, one patient had died from a breast cancer. Patients received on average 2.3 courses of radioiodine (median 2, sd 1.5). At last follow-up the disease status was: complete remission in 9 patients (64%), persistance of bone RAI uptake in 1 patient (7%), and structural residual disease in 4 patients (28.5%). Among these 4 patients, 2 had relived from bone metastases, but developed soft tissue metastasis consisting of supra sternal mediastinal nodes (the patient who died from a breast cancer) and lung metastases. One patient had a multimetastatic disease (7%), and Mrs D. had a structural bone metastase with skeletal-related event. Robenshtok et al. reported a similar series of patients with RAI-avid bone metastases of TC without structural abnormality on imaging studies. They concluded that this subgroup of bone metastatic patients have more favorable long-term prognosis than those harbouring structurally visible bone metastases and do not undergo skeletal-related complications. Based on our experience, we agree that most of these RAI-avid bone metastases with no structural correlate often resolve following RAI treatment without serious prognostic significance. However some patients do no achieve remission, and may in rare cases suffer from unfavourable outcomes with skeletal-related complications. In the absence of identified prognosis factors, close follow-up of these patients seems reasonable.

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P1199

Delayed de novo onset orbitopathy after radio-iodine treatment of Graves' thyrotoxicosis

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Background
Delayed new-onset Graves' orbitopathy (GO) or worsening of existing GO occurs in approximately 15–20% of patients following radioiodine treatment (RAI), mostly within 12 month.
Case Report
A 57-years-old woman was referred in April 2016 to our endocrinology department for Graves' disease hyperthyroidism. Relevant medical history included chronic lymphocytic leukemia (2004), fludarabine-related interstitial pneumonia with temporary tracheotomy (2009) and cytomegalovirus pneumonia secondary to rituximab (2013). Disease was in remission since 2013, requiring monthly intravenous immunoglobulins. The patient was ancient smoker (stopped 2008). At presentation, there were no symptoms of GO, TSH was undetectable, T4 58 ng/l (10–16), T3 25.4 ng/l (2–4.4), TRAbs 18.1 U/l (< 1.5). Propylthiouracil (PTU) and betablockers were introduced. Six days after introduction of PTU 200mg/day, agranulocytosis and meningitis developed. After clinical stabilization of infectious disease, RAI (500MBq) was administered. Simultaneously, prednisolone (0.5 mg/kg) was introduced and gradually decreased over 4 weeks. Two months post-RAI, hypothyroidism occurred (TSH 38 mU/L, T3 1.37 pmol/l (3.1–6.8), T4 6.4 pmol/l (12–22)) despite the introduction of 50 µg thyroxine. The supplementation was increased to 100 µg to achieve euthyroidism. The evolution was eventless until February 2018 (22 months), when she presented to the ophthalmology department with a sudden orbital swelling and redness, prevailing in the right eye associated with multidirectional diplopia. Visual acuity was 10/10 bilaterally, there was a minimal proptosis, (18 mm right eye and 17 mm left eye), NOSPECS score at 4, Clinical Activity score (CAS) at 3/7. Orbital magnetic resonance imaging (MRI) showed extraocular muscle edema with a bright signal from the lateral and inferior recti muscles at gadolinium-enhanced image consistent with GO and mild right proptosis. TSH was 7.75 mU/l (vs 2.5 mU/l, December 2017), T4 11.9 ng/l (10–16), T3 2.4 ng/l (2–4.4) TRAbs: 10.4 U/l (VN < 1.5). High-dose systemic methylprednisolone was administrated, cumulative dose 3.5 g (6 weekly 0.5 g infusions, then 2 weekly 0.25 g infusions). Topical lubricants and selenium supplementation were introduced. Clinical control after 6 weeks showed CAS 2/7 with persistent vertical diplopia, with no significant improvement at MRI. Patient refused radiotherapy. CAS was 3/7 at 3 months, 2/7 at 6 months. Ocular motility improved and conjunctival chemosis decreased. At 9 months patient showed no activity signs. All clinical symptoms resolved, except for a small bilateral lid retraction. TSH was 0.45 UI/l, surprisingly TRAbs were 34.4 U/l (< 1.75). 12-month clinical assessment remained unchanged.
Conclusion
De novo orbitopathy may occur several months after radioiodine treatment in Grave's disease despite glucocorticoid prophylaxis. Close monitoring and

screening for orbitopathy can lead to early treatment and improved long-term eye prognosis.

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P1200

Clinical, ultrasonographic, cytological and histological correlation in the diagnosis of thyroid nodules

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Background
The discovery of a thyroid nodule is a problem in thyroid cancer screening. Thus, the analysis of the criteria of malignancy remains the first step of study of a thyroid nodule. The objective of our study was the correlation between the clinical, ultrasonographic and cytologic malignancy criteria and the anatomo-pathological study results of the operative specimen.
Materials and methods
For this we conducted an analytical cross-sectional study including 198 patients presenting a nodule or a nodular goiter admitted during the year 2012–2018 to the endocrinology department of Ibn Rochd University Hospital of Casablanca and having benefited from a fine needle aspiration biopsy of thyroid nodules then a surgery.
Results
This series accounted for 55.5% of cancers. The median age of our patients was 41 years (18–75) with a clear female predominance. The study showed a significant statistical relationship between hard consistency, clinical presence of cervical lymphadenopathy and signs of locoregional compression with nodular malignancy ($P<0.001$). On ultrasound, the malignant nodules had an average size of 3.45 cm (1.5–7 cm), they had in 45% of cases a hypoechoic appearance, blurred outlines in 30% of cases, one of the microcalcifications in 47% of them. The TIRADS score had a sensitivity, specificity, a positive predictive value and a negative predictive value of 88.6%, 58%, 39.6% and 94.3% respectively. The sensitivity of the needle aspiration was 94% and the specificity was 70%, with a positive predictive value of 72.5% and a negative predictive value of 94%.
Conclusion
According to our study, the evidence for malignancy was advanced age (>50 years), hard nodule consistency, dyspnea, presence of reccurential paralysis, poorly limited ultrasound, microcalcifications and the presence of lymphadenopathies on clinical examination and ultrasonography and suspicious cytology. The association of clinical and ultrasound criteria for suspicion of malignancy nodular, with cytological findings can improve the screening sensitivity of nodular carcinomas, so a better selection of patients to operate.

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P1201

Pitutary apoplexia: a cause of spontaneous remission of cushing's disease with cyclic secretion

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Introducion
Pituitary apoplexy is an endocrine emergency that is a rare complication of pituitary adenomas and exceptional in ACTH adenomas. We report a case of apoplexy on corticotropic adenoma with intermittent secretion.
Case report
The patient was 41 years old woman, she presented in 2012 a period of symptomatic hypercortisolism. Urinary free cortisol was elevated to 113 µg/24H, Low-dose dexamethasone testing was negative, ACTH was elevated to 40.2 pmol/l, the high-dose dexamethasone suppression test was positive, a pituitary MRI and a thoraco pancreatic scanner were normal; These finding led us to a Cushing disease with normal MRI. The patient was revaluated 5 months later, she was clinically better and biochemically presented an eucorticism. 1 year later she presented relapsed symptoms and a biochemical recurrence of hypercortisilosm (high urinary cortisol: 125.7 µg/24H and negative Low-dose dexamethasone testing). an intermittent cushing was suggested. Brutally the patient presented a sudden tumor syndrome, pituitary MRI revealed an intrasellar arachnoidocele approving the apoplexy of an adrenocorticotropic pytuitary adenoma that was unnoticed on the previous pituitary MRI. Endocrine and ophthalmological examinations were normal.The patient was revaluated 6 months later and she was clinically better, The Urinary free cortisol and pituitary function testing showed a good pituitary hypothalamic function.
Conclusion
Apoplexy adenomatosis is a rare complication. Evolution can be marked by a cure of Cushing's disease, a persistence of Cushing's syndrome due to a tumor residue, or a remission followed by a recurrence of Cushing's disease. In our case, the clinical, biological and radiological evolution was in favor of an intermittent cushing syndrome spontaneously regressive by apoplexy of a corticotropic adenoma.

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P1202

Predictive factors of malignancy in thyroid nodules categorized as atypia of undetermined significance or follicular lesion of undetermined significance

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Introduction
Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) of Bethesda system for reporting thyroid cytopathology has emerged as most controversial category due to its heterogeneity and inconsistent usage. Initially associated risk of malignancy was estimated to be about 5–15%, but eventually different results have been obtained across institutions due to variable follow-ups and interpretation. The objective of this study was to determine the risk of malignancy for nodules classified as atypical of undetermined significance/follicular lesions of undetermined significance (AUS/FLUS) and to study the predictive factors of malignancy.
Materials and methods
For this we conducted an analytical cross-sectional study including all patients presenting a nodule or nodular goiter admitted during the year 2012–2018 to the endocrinology department of the Ibn Rochd University Hospital of Casablanca and having benefited from a cytopuncture then a thyroid surgery. All nodules diagnosed as AUS/FLUS during a thyroidal cytosis performed between 2012 and 2018 were examined retrospectively. Clinical data, ultrasound characteristics and final pathological findings were recorded. After further exclusion, only surgically operated nodules were included in the final analysis. Clinical and ultrasound characteristics were examined to determine the predictive factors for malignancy.
Results
During the study period, 198 nodules were analyzed, of which 89 were diagnosed as AUS/FLUS so a prevalence of 45%. The median age of our patients was 56 years (30–68) with a clear female predominance. No patient had cervical radiation antecedents or familial thyropathy. Of the nodules operated on, 63% had malignant histology. The main predictors of malignancy were age >55 years, hard nodule consistency ($P<0.001$), isthmic localisation ($P<0.001$), and microcalcifications on ultrasonography ($P<0.001$).
Conclusions
According to our study, the overall cancer rate of nodules diagnosed as AUS/FLUS was high, especially in patients>55 years old, with nodules of hard consistency, isthmic site with microcalcifications on ultrasound. It is therefore suggested that the current recommendations be re-examined in order to establish more specific criteria for a better therapeutic orientation.

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P1203

Raynaud's phenomenon as a primary symptom of the thyroid carcinoma

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Paraneoplastic manifestations of well-differentiated thyroid carcinoma are not so common but they can be the first signal of cancer. We present a case of a man with Raynaud's phenomenon in the area of the lower limb fingers. Clinical signs of

Raynaud's phenomenon with ulceration and gangrene of fingers of both lower limbs appeared several months before the diagnosis of papillary microcarcinoma of the thyroid was made. The diagnosis of carcinoma of the thyroid was determined based on histological examination. Both serum thyroglobulin and antiperoxidase antibodies were negative. Basic rheumatologic screening was negative. Thyroid cancer was already visible on preoperative ultrasound which showed nodular structure in atrophic thyroid gland. The Raynaud's phenomenon disappeared after treatment which included total thyroidectomy and application of radiioactive iodine I-131 3700 MBq. Raynaud's phenomenon was marked as paraneoplastic for obvious connection with thyroid carcinoma. Suspicion of paraneoplastic syndrome can be pronounced on the basis of certain anamnestic and clinical features, however a definitive diagnosis can be determined after recognition of a tumor. Late manifestation of symptoms after the 50th year of life with acute onset, rapid progression and atypical development belongs to the most important traces of paraneoplasia.

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P1204

TP53 and *FLT3* may become candidate markers for detecting malignancy in follicular lesions

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Introduction
The aim of the present study was to compare follicular thyroid adenoma (FTA) and follicular thyroid carcinoma (FTC) using the wide oncological molecular panel and identify differences in mutational status which may aid in the preoperative differentiation between these two related thyroidal pathologies, as well as in an understanding their pathways of origin.
Material and methods
We analyzed formalin-fixed paraffin-embedded (FFPE) samples acquired from 70 patients diagnosed with follicular lesions: 35 with FTA and 35 with FTC, 8 men and 62 women, Caucasians (median age at diagnosis: 56). Both groups were adjusted for age and sex. Genomic DNA was isolated from FFPE. The *Ion AmpliSeq Library Kit v2* was used to amplify DNA and the *50-gene Ion AmpliSeq Cancer Hotspot Panel v2* was used with the *IonTorrent™ PGM platform* to perform next-generation sequencing. The obtained data from genomic experiments was subjected for analysis using dedicated software and compared with clinical data.
Results
Any possibly pathogenic mutation was found in 14 out of 35 patients diagnosed with FTA (40%) and 24 out of 35 patients diagnosed with FTC (69%) (OR: 3.27; 95% CI: 1.22–8.75; $P=0.03$). The number of detected mutations was significantly higher in patients with FTC in comparison with those diagnosed with FA ($P=0.03$). The majority of the mutations occurred with the same frequency in FA and FTC. *SMAD4* and *STK11* mutations were present only in patients diagnosed with FA. *FBXW7, JAK3, KIT, NRAS, PIK3CA, SMARCB1*, and *TP53* were detected exclusively in FTC patients. However, only *TP53* made patients significantly more prone to be diagnosed with FTC (OR: 29.24; 95% CI: 1.63–522.03; $P=0.0009$). The most common mutation in FA was *RET*, followed by *FLT3* (39% and 27% of all FA) and the most common FTC mutation was *FLT3*, followed by *RET* (51% and 31% of all FTC). *FLT3*-positivity tended to be higher in FTC than in FA (51% vs. 29%; $P=0.054$).
Conclusions
The results may prove that FTA and FTC may share common genetic background which may be more complex in a case of FTC. *TP53* and *FLT3* may become candidate markers for detecting malignancy in follicular lesions. Further understanding of the importance of *FLT3, HRAS,* and *RET* in FA may be required to determine whether they need more careful follow-up. Identification of new genetic factors participating in FTC pathogenesis may bring new knowledge on carcinogenesis and enable appearance of new targeted drugs.

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P1205

Quality of life in patients thyroidectomized for differentiated thyroid cancer

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Background
The evaluation of health-related Quality of Life (QoL) is becoming a key component in clinical assessment of thyreopathic patients, especially those thyroidectomized for differentiated thyroid cancer (DTC) and treated with levothyroxine (LT4).
Aim
To evaluate QoL in different thyroid states in patients treated with total thyroidectomy for DTC and correlate it with thyroid function tests.
Methods
Two hundred subjects (137 F, 63 M, mean age: 50.3 + 14.4 years) waiting to be treated or treated with total thyroidectomy for DTC were enrolled in the study. Thyroid function was investigated by measuring TSH, fT4 and fT3, while symptoms related to hypothyroidism were evaluated through the analysis of three self-reported questionnaires, including the Italian version of the Multidimensional Fatigue Inventory (MFI), the thyroid-specific QoL patient-reported-outcome measure (ThyPRO) and the 36-item Short Form Health Survey (SF-36). According to time (before or after thyroidectomy) and LT4 therapy, patients were divided in 4 groups: euthyroid before total thyroidectomy (T0, $n=17$), hypothyroid before radioactive iodine (RAI) therapy (T1, $n=69$), hyperthyroid on LT4 TSH-suppressive therapy (T2, $n=107$), euthyroid on LT4 replacement therapy (T3, $n=33$). Considering that some patients were evaluated in more times a total of 226 samples and the corresponding questionnaires were analyzed. The non-parametric Kruskal-Wallis test was used for comparison among 4 groups.
Results
TSH, fT4 and fT3 changed among patients stratified in different times ($P<0,05$). However, TSH, fT4 and fT3 levels were not significantly different among patients before thyroidectomy (T0) and after thyroidectomy on LT4 replacement therapy (T3). Considering questionnaire results, the only statistically significant differences among the four groups were found in three domains of ThyPRO (anxiety, impaired social life and impaired daily life). The highest scores (worst QoL) were reported in hypothyroid patients (T1) and a positive correlation between TSH and impaired daily life has been documented. Comparing questionnaires' results of euthyroid patients, before (T0) or after (T3) thyroidectomy, T0 patients presented poorer scores in psychological well-being items than T3 patients. The lowest scores (best QoL) were reported in patients on LT4 TSH-suppressive therapy (T2), documenting also a positive correlation between fT4 and low scores in items of impaired daily life and impaired social life.
Conclusions
In oncological patients, psychological well-being seems to be impaired because of recent diagnosis of DTC rather than for thyroid function alteration. After thyroidectomy and correction of pre-RAI hypothyroidism, QoL is restored. Thus, LT4 therapy seems to adequately replace endogenous thyroid hormone levels, guaranteeing good QoL.

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P1206

Elephantiasic pretiblal myxedema with involvement of the hand

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Introduction
Thyroid dermopathy is a non-frequent manifestation of autoimmune thyroiditis. It complicates a small percentage of patients and is usually associated with ophtalmopathy and acropachy.

Observation
A 46-year-old man presented to our department of endocrinology at the university hospital of Casablanca with 3 years history of Graves' disease, developed gradual onset of exophthalmos and bilateral leg oedema starting from his pretibial areas and rapidly involving the whole legs evolved in elephantiasis, he underwent a thyroidectomy 2 years ago and was replaced by L-thyroxine 200 µg. Physical examination revealed Inactive bilateral exophthalmos according to the Mouritz score, bilateral elephantiasis myxoedema with orange appearance, Indurated swelling of both hands without skin abnormalities, symmetrical bilateral gynecomastia and free thyroidian lodge. Laboratory tests showed elevated serum free thyroxine level (1.6 ng/l, reference range: 0.7–1.4 ng/l) and thyrotrophin receptor antibody level (>40 IU/ml, reference range: <35 IU/ml). A diagnosis of pretibial myxoedema was confirmed by a skin biopsy specimen. The patient received boluses of Methylprednisolone at a rate of 500 mg/week for 6 weeks then 250 mg/week for 6 weeks with adjuvant therapy, pretibial myxoedema remained, with slight improvement in exophthalmos.
Discussion
Elephantiasic thyroid dermopathy is a rare extrathyroidal manifestation of Graves' disease. Literature on therapeutic strategies is scarce. Remarkably, our patient presented with the triad of ophthalmopathy, acropachy, and pretibial myxoedema, thereby completing the classic but extremely rare triad of clinical signs observed in less than 1% of patients with Graves' disease.

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P1207

Clinical, histological and evolutive characteristics of multifocal thyroid carcinomas

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Introduction
Differentiated thyroid carcinoma (DTC) can often be multifocal. However, the multifocal character as associated with a more pejorative prognosis remains controversial. The objective of our study is to describe the clinical, histological and evolutionary characteristics of multifocal DTCs.
Materials and methods
Retrospective study including 159 patients diagnosed with a multifocal CDT, treated at the endocrinology service of the University Hospital of Casablanca between 1986 and 2018. The statistical analysis was performed by the IBM SPSS Statistics 25 software.
Results
The average age of our patients was 47 ± 13 years with a clear female predominance of 153 women against 6 men. All patients underwent total thyroidectomy. Only 6% underwent lymph node dissection. 88% of patients benefited from radioactive iodine treatment. Papillary carcinoma with follicular differentiation was the most common histological type found in 42% of patients, other histological variants were found including classical papillary carcinoma in 45%, oncocyte differentiation in 3 patients and trabecular differentiation in one patient. Two patients had a non-invasive follicular thyroid tumor with papillary nuclei (NIFTP). Tumor foci were found in the 2 thyroid lobes in 62% of cases. Lymph node invasion was found in 9% of cases, 2% of subjects had distant metastases. Complete remission was noted in 65% of patients, a biologically incomplete response in 6%, and morphologically incomplete response in 10% of cases. Bivariate analysis of the factors influencing the occurrence of locoregional or distant metastasis showed a statistically significant difference in the case of male sex ($P = 0.009$) and vascular invasion on the pathological study ($P < 0.001$).
Discussion
In our present study, multifocality was unrelated to an increase in the aggressiveness of differentiated thyroid carcinomas. However, a study with a larger follow-up would be interesting to evaluate the long-term prognosis of these so-called tumors.

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P1208

Thyroid uptake in PET-CT: IPO-porto consecutive case series

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Introduction
Positive radiotracer uptake by the thyroid gland can occur in PET-CT. It's meaning has led to conflicting results mainly resulting from small studies.
Objective
We aim to present a large single institution consecutive case series.
Material and methods
Observational, descriptive and retrospective study of the PET-CT scans performed between the years 2000–2017. We searched the word thyroid in the computer imaging system and created an Excel database with the epidemiological records and the characterization of the findings in respect to the type of radiotracer and the type of uptake. The results were matched with the list of thyroid cythologies and then the histological results. SUVmax and SUVpeak were calculated with respect to the probability of malignancy.
Results
In brief, we characterized 30470 Nuclear Medicine exams corresponding to 20432 patients: 28499 ^{18}F-FDG-PET/CT (93.53%), 1654 ^{68}Ga-DOTANOC-PET/CT (5.43%), 235 ^{68}Ga-PSMA-PET/CT (0.77%) and 82 ^{18}F-Flurocolina-PET/CT (0.27%). Thyroid uptake occurred in 4.96% patients. Fine needle aspiration (FNA) was performed in 443 cases: age average 60.99 ± 13.54; 150 male sex (33.9%), 293 female sex (66.1%); 405 ^{18}F-FDG-PET/CT (91.4%) and 38 ^{68}Ga-DOTANOC-PET/CT (8.6%). Thyroid uptake occurred in 153 ^{18}F-FDG-PET/CT (37.8%), 78 in the right lobe (51%), 53 in the left lobe (34.6%), 4 in the isthmus (2.6%), 13 bilateral (8.5%) and 5 with diffuse uptake (3.3%). Malignant disease was diagnosed in 15.1% of ^{18}F-FDG-PET/CT – FNA cases: 23.5% of those with uptake and 9.9% of those without uptake. SUVmax malignant vs benign: 9.181 ± 4.93 vs 6.447 ± 3.26, *P*: 0.014551 (<0.05); ROC: 0.668; Youden SUVmáx 6.9 (sensitivity (SN) 55.06; specificity (SP) 69.76). SUVpeak malignant vs benign: 6.17 ± 3.47 vs 4.13 ± 1.6; *P*: 0.007618 (<0.05); ROC: 0.708; Youden SUVpeak 4.8 (SN 57.5; SP 74.05). Malignant disease was found in 69.1% of cases in histology.
Conclusions
We present one of the largest and most complete consecutive case series. The incidence of focal thyroid FDG uptake is clinically relevant. It represents an increased probability of malignancy therefore justifying the continuation of the investigation of those cases throught the correlation with other imaging, cythological and molecular biology exams. Despite overlap, an increased SUVmax heightens that suspicion.

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P1209

Severe hypothyroidism, a rare cause of pancytopenia: a case report

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Introduction
Untreated hypothyroidism may lead to decompensation of a patient's homeostasis. While the association between hypothyroidism and anemia has been noted previously, there are very few, cases of white cell lines and platelet counts being affected by hypothyroidism alone. To demonstrate a rare but significant manifestation of hypothyroidism, we present a unique and interesting case of pancytopenia secondary to severe hypothyroidism
Case report
A70-year-old women, with a past history of diabetes and hypertention for 10 years receiving respectively losartan 50 mg and premixed insulin, patient was admitted for a glycemic imbalance with an HBA1c of 16%, we note a, chronic constipation, progressive weight gain, cold intolerance and drowsiness, there were no signs of adrenal insufficiency. Temperature was 37°C, blood pressure 120/70 mmHg, heart rate 60 beats per minute, with facial myxoedema and normal heart sounds. There was no hepatosplenomegaly. The patient's TSH was

92 mIU/l (0.27–4.2), with total T4 of 1.3 pmol /l (12–22).Antithyroid peroxidase antibodies were not detectable. White cell count was 398 000/ml, hemoglobin 11 g/dl, platelet count 98,000/mL, and mean corpuscular volume 82 fL/cell. Blood smear demonstrated absolute neutropenia, thrombocytopenia and normocytic anemia. The cervical ultrasound finds a thyroid gland of heterogeneous hypoechoic echostructure traversed by hyperechoic trabeculae, transthoracic ultrasonography found a left ventricular hypertrophy, ejection fraction preserved at 60% and a dry pericardium. a low dose of levothyrox was started 12.5 µg/day with an increase of 12.5 µg/15J according to clinical and electrocardiographic tolerance, hydrocortisone substitution was started before levothyrox substitution. 4 weeks later, repeated blood counts citrate tube with blood smear and reticulocyte showed resolution of pancytopenia.

Conclusion

We describe a rare complication of severe hypothyroidism, pancytopenia, and its complete reversal after 1 month of thyroid hormone replacement. Mechanisms of this process remain unclear. Interestingly, the lack of detectable antithyroid peroxidase antibodies, like in our case, makes a hematopoietic antigen-antibody reaction a less likely etiology. In cases of unexplained pancytopenia, hypothyroidism should be considered in the differential diagnosis. Further basic studies are needed to determine this underlying disease mechanism.

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P1210

Vesicular thyroid carcinomas: about 27 cases

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Introduction

Follicular or vesicular cancers represent 5 to 10% of differentiated thyroid cancers (CTD) and are therefore the second leading cause of endocrine tumors after papillary thyroid cancer. They can be minimally or massively invasive, and thus represent a more aggressive histological type compared to the papillary. The aim of our work is to describe in our context the clinical and evolutionary features of thyroid tumors of vesicular origin.

Materials and methods

This is a retrospective descriptive study involving 27 patients, treated in the endocrinology department of Ibn Rochd University Hospital, Casablanca, between 1986 and 2018, and affected by a vesicular thyroid carcinoma. The statistical analysis was performed by the IBM SPSS Statistics 25 software.

Results

The average age of our patients was 47.5 ± 13 years old. All patients in our study were women. The circumstances of discovery were in the majority of cases the presence of an isolated goiter (59%), followed by an isolated thyroid nodule (8%). Bone metastasis indicated the diagnosis in a patient. One patient consulted for a nasal voice with progressive aggravation and was diagnosed with a carcinoma on a lingual ectopic thyroid. All our patients underwent total thyroidectomy, lymph node excision was indicated only in one patient. Radioactive iodine treatment was done in 89% of the patients. All carcinomas in our series were uni focal. The size of the tumors ranged from 0.5 cm to 7.5 cm. The appearance of locoregional and distant metastases (bones, lungs) in one and two patients respectively, was noted. Two patients developed ductal carcinoma of the breast during follow-up. Complete remission was observed in 67% of patients. The occurrence of metastases was significantly correlated with vascular invasion ($P = 0.03$)

Discussion

Thyroid tumors of vesicular origin represent the second most common histological type of malignant thyroid tumors after papillary cancers. Vital prognosis is rather good, and it is the risk of local or remote recurrence that will be relevant to guide the treatment. Among these risk factors: the histological variant of the tumor, the existence of local or regional metastases, or vascular or locoregional invasion. Thus, the degree of invasion of follicular cancers makes it possible to classify these tumors as low risk in case of minimal invasion, and as high risk in case of major invasion.

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P1211

Profiling circulating microRNAs as serum biomarkers for thyroid cancer recurrence before and after recombinant human TSH stimulation

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Objective

Owing to their remarkable stability in the serum, microRNAs are being investigated as circulating cancer biomarkers. Several studies have explored their plasma or serum levels in thyroid cancer in order to differentiate benign from malignant nodules preoperatively. However, very few studies have explored the role of microRNAs to detect recurrent disease during postoperative follow-up and none of them used high through-put technologies. Recombinant human TSH (rhTSH) is used to optimize serum thyroglobulin (Tg) stimulation during follow-up. Our aim was to determine through NGS the circulating miRNA profiles of patients with papillary thyroid carcinoma recurrence before and after rhTSH stimulation.

Material and methods

We collected the serum of thyroid cancer patients after total thyroidectomy and raidioiodide ablation. Illumina small RNA sequencing was performed on 7 patients with recurrent/persistent disease and 4 patients in complete remission, both at basal and rhTSH stimulated time points. Mean Tg basal and rhTSH-stimulated levels were 13 ng/ml and 55 ng/ml respectively for patients with recurrent disease. We used miRPara software tool for novel micro RNA discovery. Sequencing results were validated on 16 patients with recurrence and 14 patients in remission using LNA technology-based qPCR assays, currently the most specific qPCR method for miRNA measurement. Thyroid tumour and adjacent normal tissue were used for evaluating the levels of candidate microRNAs. TPC-1 cell line expressing functional TSH receptor was used to demonstrate microRNA regulation by TSH.

Results

MicroRNA sequencing detected 210 circulating miRs. Our analysis did not show any significant differences in the expression of circulating miRs between recurrent and non-recurrent patients or before and after rhTSH. Validation with qPCR confirmed these results. Interestingly, several sequences designated as putative microRNAs showed significantly different levels in patients with recurrence only after rhTSH stimulation. qPCR analysis confirmed particularly higher levels of one putative microRNA after rhTSH. In addition, this putative miR is upregulated in primary thyroid tumors compared to adjacent normal tissue ($P = 0.003$, paired t-test) and is also expressed in TPC-1 cells and upregulated by TSH ($P = 0.0208$, paired t-test).

Conclusions

Our study shows that currently annotated microRNAs cannot be used as serum markers of recurrence. However, our results point to several putative microRNAs that may be upregulated by rhTSH in serums of patients with recurrent disease. One such microRNA seems promising but further functional studies are being performed to confirm that this TSH-induced small RNA is indeed a novel microRNA with a role in thyroid carcinogenesis.

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P1212

Hypothyroidism and lymphoma in a patient with systemic sclerosis

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Introduction

Patients with systemic sclerosis may develop cancer. The development of malignant hematological diseases has also been described in patients with systemic sclerosis. These patients may also be prone to the development of lymphoma, in most cases a B-cell lymphoma.

Aim
The aim was to describe the case of a patient with systemic sclerosis who had a non-Hodgkin's lymphoma and developed primary hypothyroidism.
Case report
A patient, female, aged 39, presented with anemia and fever. Laboratory investigations revealed Hb 10 g/dl, Ht 30.01% and Fe 19 µg/dl. A diagnostic evaluation was performed for the presence of an infection and antibiotics were administered. Four years earlier a non-Hodgkin T cell lymphoma had been diagnosed and was followed up. She had sclerodactyly, telangiectasias in the area of the face and the posterior surface of the trunk. Gastroscopy was performed and showed impaired peristaltic movement of the esophagus and esophagitis. A chest CT revealed fibrosis and pleural effusions bilaterally. Further laboratory evaluation revealed TSH 20.45 µIU/ml (normal values 0.35–4.94 µIU/ml), FT_4 0.6 ng/dl (normal values 0.7–1.48 ng/dl), FT_3 1.5 pg/ml (normal values 1.8–3.7 pg/ml) and positive antithyroid antibodies. Thyroxine was administered.
Conclusions
Systemic sclerosis is a fibrosing systemic inflammatory disease possibly of autoimmune etiology. In the course of autoimmune diseases lymphoma may develop. The development of hematological malignancies has been described in patients with systemic sclerosis, in particular B cell lymphoma. The extremely rare coexistence of primary hypothyroidism, systemic sclerosis and T cell lymphoma is described. This observation shows that follow up and therapeutic management of patients with systemic autoimmune diseases should be performed with caution as these patients are prone to the development of hematological and other autoimmune diseases.

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P1213

Hyperthyroidism and hepatic dysfunction: the impact of congestive heart failure

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Introduction
Hyperthyroidism (HT) has been associated with hepatic dysfunction in the presence or absence of congestive heart failure (CHF). Our objective is to study the correlation between the clinical and biological presentation of hepatic abnormalities and the cardiac status.
Patients and methods
This retrospective study included 17 patients hospitalized in the endocrinology department of Hedi Chaker Hospital in Sfax over 20 years (1997–2017). We included patients with untreated and non-iatrogenic hyperthyroidism among whom biochemical findings noted hepatic dysfunction and excluded those with concomitant liver disease. Our patients were divided into two categories: «HT with CHF» and «HT without CHF».
Results
Our population is composed of 10 men and 7 women. Eleven patients manifested CHF. The average age of the two groups was comparable (45 years). Only patients with CHF had on abdominal examination ascites, splenomegaly and hepatomegaly. However, no significant difference in clinical presentation was noted between the two categories. The most frequent hepatic dysfunction was cholestasis in both groups (6/6 vs 9/11; $P=0.515$). The cytolysis was significatively more observed in the absence of CHF (5/6 vs 2/11; $P=0.035$). The hepatic dysfunction was severe in two cases, both with CHF. The cardiac failure was mainly global (8/11 cases) with an average left ventricular ejection fraction (LVEF) of $37.7\pm 7.7\%$. A negative correlation, yet not significant, between LVEF and ALAT was noted ($P=0.05$).
Conclusion
It seems likely that congestive heart failure is common in this population. There did not appear to be a consistent relationship between the magnitude of hepatic abnormalities and the cardiac status. More studies are needed to further investigate this association.

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P1214

Graves' disease and thrombocytopenia

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Case History
38 year old male presented with thyrotoxic symptoms and exophthalmos with an initial Free T4 of $>$ 100 pmol/l; TSH $<$ 0.01 mIU/l and thyroid receptor antibody positivity. He had a platelet count of $72^* 10^9$ /L at presentation and was started on carbimazole. A month later he had platelet count of $9^* 10^9$ /L with normal white cell count and haemoglobin levels. He was switched to propylthiouracil, but was readmitted with platelet count of $10^* 10^9$ /L. Propylthiouracil was stopped and he was investigated with bone marrow aspiration and diagnosed with immune thrombocytopenic purpura (ITP). He was started on glucocorticoids with no improvement. However, the thyroid tests returned to normal without anti-thyroid drugs. He was later started on rituximab as the platelet count did not respond to high dose glucocorticoids and he later suffered spontaneous intracranial haemorrhage.
Discussion
It was initially assumed that the thrombocytopenia was either related to Graves' itself or due to either carbimazole or propylthiouracil. Mild immune thrombocytopenia is known to be associated with Graves' and improves with treatment. Platelet lifespan is reduced in thyrotoxicois due to increased destruction of the platelets from elevated thyroid hormone levels leading to activation and the reticuloendothelial system. There is an overlap of auto-immune aetiology between Grave's and ITP with platelet associated antibodies found in Graves'. Usually the platelet count imporves with treatment. Here however the thrombocytopenia worsened with treatment. High dose glucocorticoids used to combat ITP however improved thyroid function. Glucocorticoids are known to block the peripheral T4 conversion to T3 as well as restoring euthyroid status in thyroiditis. The evidence for high dose glucocorticoids in Graves' disease is unclear. This case demonstrates the intriguing effects of glucocorticoids in Graves' disease as well as the association of ITP with Graves' and failure to improve with anti-thyroid treatment or glucocorticoids.

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P1215

Black pigmentation seen in thyroid surgery: an indication for total thyroidectomy?

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To our experience the presence of black pigmentation in vive thyroid tissue cervical lymph nodes before ligating the arteries was associated with differentiated thyroid cancer (DTC). The goal of this study was to evaluate the association between black pigmentation and DTC. 615 patients who were underwent thyroidectomy were assessed during operation by a single surgeon during 5 years from 2013 to 2018 and the presence of black pigmentation was evaluated in gross pathology before cuttning the arteries of thyroid. Then the final pathology diagnosis was assessed with presence or absence of this black pigmentation. From 615 patients, 368 patients had black pigmentaion. The sensitivity and specificity was 98% and 96% respectivley the positive predictive value of this finding during operation was 97%. The presence of black pigmentation was significantly greater in DTC group ($P=0.017$). This study showed that black pigmentation can be a good sign as a gross surgical pathology of DTC and whenever it is observed, it can be a good guide for doing the total thyroidectomy by means of cancer surgery.

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P1216

Real-life experience with lenvatinib in iodine-refractory thyroid cancer in a terciary hospital

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Introduction
Lenvatinib is an oral tyrosine kinase inhibitor (TKI) used for treatment of progressive, clinically significant or symptomatic disease in patients with iodine-refractory differentiated thyroid cancer (DTC).
Objective
To describe our clinical experience with lenvatinib in patients with iodine-refractory differentiated thyroid cancer.
Methods
Restrospective cohort study of patients with iodine-refractory differentiated thyroid cancer who received Lenvatinib as a first-line or second-line treatment from 2015 to 2018 in Hospital Universitario La Princesa. Patients with at least one radiographic control after the start of treatment with Lenvatinib were included. Baseline clinical characteristics, response rate to treatment and adverse effects (AE) were collected. Data analysis was carried out with descriptive statistics (G-Stat 2.0.1).
Results
Six patients were included with a mean age at diagnosis of 67(DS 11.2) years (two men/four women). Histologic diagnosis was: papillary thyroid cancer (4) and poorly differenciated folicular thyroid cancer (2). Distant metastasis were present at diagnosis in 2 patients or were delevoped at a median time of 36(IQR18) months in 4 patients, mainly lung metastasis. Lenvatinib was started after 6(IQR36) months from diagnosis of advanced disease (first-line treatment in 4 cases). First radiographic control (3 months after the start of lenvatinib) showed complete response (CR) in 1 case, partial response (PR) in 3 cases, 1 stable disease (SD) case and 1 progressive disease (PD) case with an objective response rate of 83.34%. All 3 cases with a second radiographic control at 8(IQR3) months showed stable disease. Initial Lenvatinib dose was 24 mg per day. Progressive dose reduction was needed in 83.33% of cases due to intolerability (20 mg in three cases, 14 and 10 mg in the remaining two cases respectively). AE (all grades) ocurred in 100% of cases. The most frequent were hyporexia (83.33%, grade 2 in 4 patients) asthenia (66.67%, grade 3 in three patients) and mucositis (50%, grade 3 in 2 patients). Other AE were weight loss (50%), diarrhea (50%), nausea (33.33%), hypertension (33.33%) and 1 case of hepatotoxicity. Oral nutritional supplements were needed in 83.3% of patients. Three patients required definitive withdrawal of Lenvatinib due to progression (1 patient) and severe toxicity (2 patients). Median time of follow-up with Lenvatinib was 12(IQR19) months with two cases of death due to cancer progression.
Conclusion
Our clinical experience shows lenvatinib as a useful treatment for iodine-refractory progressive DCT. AE are frequent needing closely management and dose adjustment.

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P1217

Thyroid dermopathy: clinical features in patients with Graves' disease

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Thyroid dermopathy or pretibial myxedema (PTM) is a rare extrathyroidal manifestation of Graves' disease with diverse presentations. Therefore, information on the clinical data of PTM patients is scarce. In this study, we aimed to evaluate the clinical features of patients with thyroid dermopathy and Graves' disease. A total of 43 patients with pathologically confirmed PTM were retrospectively recruited. According to the diagnosis, the clinical data and laboratory findings were reviewed and analyzed. The mean age at diagnosis of PTM was 54.4 years (range 30–67 years). Diffuse form of the PTM was the most dominant (48.8%), followed by the plaque (27.9%) nodule (18.7%) and elephantiatic (4.6%) variants. All the patients had pretibial distribution of the lesions, 90.6% of them experienced bilateral allocation of dermopathy. The majority of the patients had Graves ophthalmopathy. Mild form was present in 55.8%, moderate in 18.6%, and severe in 9.3%; 88.8% had ophthalmopathy before manifesting PM. The majority of the patients had high levels of anti-TSH receptor antibodies. There was no correlation between anti-TSH receptor antibodies levels and the severity of PTM. Development of pretibial myxedema was usually late, the duration between the onset of Graves' disease and PTM was 5.2 years on average (1–7 years). The later after the diagnosis of hyperthyroidism diagnosis of PTM was made the more severe form of thyroid dermopathy occurred ($P < 0.05$). Exact clinical features on every particular form of PTM remains to be determined on larger groups of patients.

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P1218

Association of polycystic ovary syndrome and graves' disease – case report

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Introduction
Polycystic ovary syndrome (PCOS) is a common endocrine system disorder among women of reproductive age. Although some studies have suggested an association between PCOS and autoimmune thyroiditis, only a few cases indicating association between PCOS and Graves' disease are reported.
Case report
We present a woman aged 29 with Graves' disease certified by suppressed TSH (0.001 mUI/l), high FT4 (6.6 ng/dl) associated with elevated TRAb (32 IU/l) and elevated TPOAb (476 IU/l). BMI was 21.33 kg/m^2, menarche at 12.6 years, oligomenorrhea for about 1 year, waist circumference 76 cm, Ferriman - Gallwey score was 15. Total testosterone was 77.02 ng/dl (25.0–65), LH and FSH was 19 IU/l (2–19) and 7.33 IU/l (4.5–9.31) respectively with LH/FSH ratio 2.59. Prolactin and 17-hydroxyprogesterone was in the normal range. The transabdominal USG was suggestive for PCOS by presence of 10–11 peripheral follicles each 2–7 mm in diameter in both ovaries.
Conclusions
The association of a Graves' disease with PCOS is unlikely to be because of a chance alone and may point to a common aetiopathogenic linkage.

Keywords: Autoimmunity, Graves' disease, polycystic ovary syndrome
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P1219

Primary thyroid angiosarcoma – a case report

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Introduction
Primary thyroid angiosarcoma (TAS) is a rare malignancy that arises from endothelial cells, and nearly all reported cases originate from the Alpine region of central Europe. Most of the patients are female, elderly, with a history of goiter. Generally, TAS arises as a painless infiltrating mass and patients present with compression symptoms due to the brisk tumor growth. Other TAS clinical presentations are varied and highly non-specific. Metastasis occur early in the disease history, and preferential sites include loco-regional lymph nodes, lungs and bone marrow.
Case report
We present a case of a 49 year old portuguese female patient presenting with a painless, rapidly growing cervical mass and complaints of hoarseness. At the physical examination we observed a large, hard mass, occupying the entirety of the left thyroid lobe. The patient underwent a fine needle aspiration of the lesion, but while suggestive of malignancy, the results were inconclusive. The cervical CT scan revealed an increased volume of the left lobe of the thyroid due to an heterogeneous mass with a long axis of 62 mm. The thoracic CT scan identified several bilateral nodules suggestive of metastatic involvement of the lung. The patient was subjected to a total thyroidectomy and central compartment neck dissection. Histologic examination confirmed the diagnosis of angiosarcoma. Immunohistochemical staining was positive for CD31, CD34 and factor VIII but negative for thyroglobulin, calcitonin and TTF-1. The patient was started on chemotherapy with paclitaxel. While undergoing the second cycle of chemotherapy a new left cervical nodular mass appeared adjacent to the internal jugular vein with no surgical indication. At this point the patient started radiation therapy treatment. Eight months after the initial diagnosis the local recurrence is stable and the pulmonary metastasis reduced in size. Currently the patient is undergoing her 22nd cycle of chemotherapy.

Discussion
As is often the case in TAS, in this case the patient presented with metastatic dissemination at the time of diagnosis. Radical surgery was an early option in order to minimize local growth symptoms. Afterwards chemotherapy associated with radiotherapy helped the patient achieve a certain degree of stability. The prognosis is poor and there is no defined management strategy for TAS. Currently the therapeutic gold-standard is radical surgery. Systemic therapy is indicated for disseminated disease control and palliative care. Otherwise, due to an extremely low incidence, therapeutic options remain very much institution-dependent.

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P1220

Retrospective analysis of clinical and laboratory features of patients with Hashimoto Thyroiditis

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Hashimoto thyroiditis (HT) is the most common cause of hypothyroidism in the world with iodine deficiency and its incidence is 0.3–1.5 per 1,000. The aim of this study is to retrospectively evaluate the demographic characteristics, clinical and laboratory findings of the patients with HT who applied to our endocrinology outpatient clinic. The findings were compared with the control group who had hypothyroidism with negative thyroid autoantibodies. For this purpose, a total of 1009 patients with the diagnosis of 788 HT and 221 control groups were included in the study. Age, gender, age of diagnosis, duration of disease, initial clinics of patients (hypothyroidism, euthyroidism, thyrotoxicosis) and thyroid antibody positivity (anti-TPO, anti-Tg, TSH receptor antibody (TRAb)), thyroid US findings were reviewed. If thyroid fine needle aspiration biopsy (TFNAB) and/or thyroidectomy was performed, pathology reports were examined. The patient group was between 18 and 89 years (48.22 ± 14.07) and the control group was between 18 and 79 years (48.85 ± 14.51). 90% of the patients were female ($n=709$) and 10% were male ($n=79$); 86.9% of the control group were female ($n=192$) and 13.1% ($n=29$). At admission, 74.6% hypothyroidism, 17.3% euthyroidism and 8.1% hyperthyroidism were reported in HT group. In the evaluation of USG, heterogeneous echo was observed almost completely in the HT group, while in the control group 27.1% of the patients had normal echo. In the HT and control groups, approximately half of the patients had nodules at any time during follow-up. The most common cytology results of TFNAB were benign cytology in both groups, and the most common malignant result was papillary cancer (% 3.34-3%). When the results of thyroidectomy were evaluated, it was found that papillary cancer was the most frequent and no significant difference was found between the two groups. The only significant difference among the accompanying diseases was found in Diabetes Mellitus ($P=0.001$). There was no statistically significant increase in any of the malignancies (colon, ac, breast, and ovarian).

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P1221

Severe hypothyroidism, a rare cause of pancytopenia: a case report

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Introduction
Untreated hypothyroidism may lead to decompensation of a patient's homeostasis. While the association between hypothyroidism and anemia has been noted previously, there are very few, cases of white cell lines and platelet counts being affected by hypothyroidism alone. To demonstrate a rare but significant manifestation of hypothyroidism, we present a unique and interesting case of pancytopenia secondary to severe hypothyroidism.
Case report
A70-year-old women, with a past history of diabetes and hypertention for 10 years receiving respectively losartan 50 mg and premixed insulin, patient was admitted for a glycemic imbalance with an HBA1c of 16%, we note a, chronic constipation, progressive weight gain, cold intolerance and drowsiness, there were no signs of adrenal insufficiency. Temperature was 37°C, blood pressure 120/70 mmHg, heart rate 60 beats per minute, with facial myxoedema and normal heart sounds. There was no hepatosplenomegaly. The patient's TSH was 92 mIU/l (0.27–4.2), with total T4 of 1.3 pmol/l (12–22). Antithyroid peroxidase antibodies were not detectable. White cell count was 398 000/ml, hemoglobin 11 g/dl, platelet count 98,000/ml, and mean corpuscular volume 82 fL/cell. Blood smear demonstrated absolute neutropenia, thrombocytopenia and normocytic anemia. The cervical ultrasound finds a thyroid gland of heterogeneous hypoechoic echostructure traversed by hyperechoic trabeculae, transthoracic ultrasonography found a left ventricular hypertrophy, ejection fraction preserved at 60% and a dry pericardium. a low dose of levothyrox was started 12.5 µg/day with an increase of 12.5 µg/15J according to clinical and electrocardiographic tolerance, hydrocortisone substitution was started before levothyrox substitution. 4 weeks later, repeated blood counts citrate tube with blood smear and reticulocyte showed resolution of pancytopenia.
Conclusion
We describe a rare complication of severe hypothyroidism, pancytopenia, and its complete reversal after 1 month of thyroid hormone replacement. Mechanisms of this process remain unclear. Interestingly, the lack of detectable antithyroid peroxidase antibodies, like in our case, makes a hematopoietic antigen-antibody reaction a less likely etiology. In cases of unexplained pancytopenia, hypothyroidism should be considered in the differential diagnosis. Further basic studies are needed to determine this underlying disease mechanism.

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P1222

Screening of transient pulmonary hypertension in patients with Graves' disease

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Introduction
Hyperthyroidism produce changes in cardiac contractility, blood pressure, and systemic or pulmonary vascular resistance. In almost all cases these cardiovascular changes are reversible when the underlying thyroid disorder is recognised and treated. Pulmonary hypertension (PAH) has been associated with hyroid dysfunction, but primaraly with hyperthyroidism. The vast majoity of patients with this form of PAH are usually older with toxic multinoduar goitre. The aim of this study was to determine the clinical correlates of PAH in patients with Graves' disease (GD).
Methods
Our study is prospective and concerning patients with GD referred for echography before using any treatment. PAH hasbeen diagnosis when pulmonary artery systolic pressure was elevated.
Results
Our study concerned 36 patients. It is 22 women and 14 men. The average age is 35. Among 36 consecutive patients with GD referred for echography, 7 patients (19,44%) had PAH measered by Doppler echocardiography (pulmonary artery systolic pressure >35 mmHg). The search for anti-phospholipid antibodies was negative. The patients with PAH had significantly higher pulmonary vascular resistance (PVR), cardiac output, and TSH receptor anti-body (TRAb) compared to those without. Pulmonary artery systolic pressure may had a good correlation with TRAb, but was not related to free T4. All these patients have a reversible pulmonary hypertension after treatment.
Discussion
In addition to the effect of thyroid hormone on the cardiovascular system, auto-immune mediated pulmonary vascular remodelling may play a role in Graves's disease-linked elevated pulmonary artery systolic pressure. An auto-immune processus inducing endothelial damage with GD may play a key role. Future studies should focus on discovering the immunogenetic overlap.
Conclusion
Study highlights the importance of considering hyperthyroidism as an origin of idiopathic PAH, and demonstrates the potential reversibility of its complications. At present, thyroid function tests should be considered in the invertigation of all patients.

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P1223

Unusual evolution of a papillary thyroid carcinoma in a hyperthyroid young woman

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Introduction
Papillary thyroid carcinoma is well known as a differentiated thyroid carcinoma with an established treatment protocol and high survival rates. Poorly differentiated thyroid carcinoma, or anaplastic, is highly aggressive, manifesting with local invasion, recurrence, and distant metastasis; it is well known that these two entities may be connected as a process of dedifferentiation, most commonly met in elderly people with a long term standing untreated well differentiated thyroid carcinoma.
Case report
We present the case of a 48 years old female, Caucasian, from an area of known iodine deficiency, non-smoker, with professional exposure to toxic substances, who was diagnosed in 2013 with toxic goiter, for which she was treated with anti-thyroid drugs. In 2016 she underwent left lobectomy, but the presence of adenopathies imposed the need of surgical reintervention a few months later – total thyroidectomy with lymphadenectomy. The histopathological diagnosis was of papillary thyroid carcinoma with lymph nodes metastases T3N1BMx. Total body RAI showed no signs of local or distant metastasis; so, radioiodine therapy (250 mCi) and suppressive levothyroxine treatment was considered fit. The patient was lost to follow-up until 2018 when she addressed to the surgical department for bilateral cervicotomy and yet again the histopatological diagnosis was of papillary thyroid carcinoma with no tumoral infiltration. Afterwards, the therapeutical approach was radioiodine therapy (400 mCi) and suppressive levothyroxine treatment. A few months later, the patient developed paracicatricial cellulitis with fistula; laboratory testing revealed mild inflammatory changes and CT scan showed fluid accumulation in the left postoperative thyroid bed and multiple necrotic adenopathies as large as 1.8/1.5 cm. Once again, surgical reintervention was needed to remove the cervical necrotic tissue and lymphadenectomy, but this time the histopathological examination stated a low differentiated thyroid carcinoma, this diagnose imposing tyrosine kinase inhibitors (TKI) as the solely therapeutic option.
Discussions
The evolution of this patient's thyroid malignancy proved to be completely unpredictable, considering that the dedifferentiated process of the papillary thyroid carcinoma is improbable to occur in young patients and especially in a such short period of time – less than 8 months between the two different histopathological diagnosis. The biological or molecular trigger for this kind of 'blitz' dedifferentiation remains a question mark, therefore genetic testing might be helpful in better understanding of pathophysiology and evolution of low differentiated thyroid carcinoma.
Keywords: papillary thyroid carcinoma, dedifferentiated thyroid carcinoma
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P1224

Skin fistula after sorafenib use in differentiated thyroid cancer

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Introduction
Papillary thyroid cancer (PTC) has an excellent prognosis in most cases with a 10-year survival rate of more than 95% but decreases drastically in cases of PTC iodine-refractory, in recurrent and/or metastatic disease. Tyrosine kinase inhibitors, such as lenvatinib or sorafenib, have been approved in such cases and in some cases are able to stabilize the disease and prolong survival. However, serious side effects have been reported such as fistula formation, bleeding or ulcers.
Case report
A 69-year-old woman underwent a total thyroidectomy with left cervical lymphadenectomy in which pathological findings revealed an oncocytic papillary thyroid carcinoma with extensive extrathyroidal invasion. Radioactive iodine was administered as incomplete thyroid resection was still observed in the imaging scans. Further radioactive iodine doses (150 mCu altogether) and radiotherapy were ineffective. Sorafenib was started as a tyrosine kinase inhibitor. Despite a fast decrease in thyroglobulin levels and slight clinical improvement, after 16 months attended to our hospital setting with a painful growing mass with cutaneous externalization in the anterior cervical area and a Thyroglobulin of 6997 ng/ml. In the cervical scanner, a tumor recurrence with a large tumor extending to the esophagus and cutaneous plane was observed (see images). The patient underwent a new surgery to remove the tumor mass and close the skin fistula. Unfortunately. the patient died before starting a lenvatinib second line-treatment.
Discussion
Tyrosine kinase inhibitors may rarely produce fistulas and ulcers at the skin level as a side effect. Risk factors related to this adverse event are previous radiotherapy or surgery in tumors invading vital structures of the neck. In these patients, anti-angiogenic tyrosine kinase inhibitors should be used with caution and physicians be aware of possible symptoms or complications.
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P1225

Clinical picture and etiology of severe hypothyroidism in a tertiary hospital setting: Implications for clinical practice

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Introduction
Myxedema coma is a rare life-threatening clinical condition in patients with longstanding severe untreated hypothyroidism, in whom adaptive mechanisms fail to maintain homeostasis. Most patients, however, are not comatose, and, although strict criteria have been proposed, it is often difficult to differentiate it from very severe hypothyroidism, lacking only a precipitating event.
Material and methods
We present the clinical picture of 70 consecutive patients with very severe hypothyroidism seen from 2004 to 2018 at our institution in a retrospective study. Personal history, previous treatment, etiology, clinical symptoms and analytical data variables were recorded. Data were analyzed with the Statistical Package for Social Science (SPSS), version 20.0 (SPSS Inc., Chicago, IL). The results are expressed as mean $\pm$ standard deviation (SD) and as percentages of individuals. The Chi-squared test was used to detect differences between categorical variables, and the normal distribution of continuous variables was tested by the Kolmogorov-Smirnov test. The study was approved by the Ethics Committee.
Results
Seventy consecutive patients (49 females (70%) and 21 males (30%)) were admitted in our hospital, with ages between 21 and 92 years (mean: 52.8 yeas) without significant differences between both genders. Their mean weight was 71.75 kg and BMI 27.87 kg/m^2. Regarding pre-treatment TSH levels, the mean value was 104.1 mUI/l ($\pm$ 34.6), with a range from the minimum of 52.63 mUI/l, to a maximum of 239.53 mUI/l. 78.6% were not previously on replacement therapy. The most frequent etiology was autoimmune disease (64.3%), followed by radioactive iodine treatment (12.8%), amiodarone (11.4%), surgery (5.7%), methimazole (2.8%), radiotherapy (1.4%) and alemtuzumab (1.4%). The most frequent symptoms were asthenia (92.8%) and cold intolerance (78.5%). Weight gain (71.4%), daytime drowsiness (64.2%), constipation (57%), facial edema (42.8%), snoring (22.8%), difficulty to focus (21.4%) and depressive symptoms (17.1%). Cholesterol (273.5$\pm$93 mg/dl), c-HDL (65.7$\pm$29.7 mg/dl), c-LDL (166.8$\pm$60.3 mg/dl), creatinine (1.14$\pm$0.4 mg/dl) and CPK (805.7$\pm$119.2 U/l) were all above normal limits.
Conclusion
Severe hypothyroidism can present with classic symptoms of fatigue, weight gain, cold intolerance and constipation in addition to biochemical alterations and should be treated aggressively due to symptoms that lead to a severe impaired quality of life, an increased risk of premature atherosclerotic vascular disease and the risk of development of a myxedema coma in case a precipitating event occurs.
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P1226

Thyroglobulin in the washout fluid from lymph node fine-needle aspiration and Ultrasound features

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Background
Measurement of thyroglobulin (Tg) in the washout fluid of fine-needle aspirates (FNA-Tg) is useful for diagnosis of Cevical lymph node (CLN) metastasis in papillary thyroid carcinoma (PTC).
Objective
The aim of this study was to evaluate the relationship between FNA-Tg levels and Sonographic findings in CLN in patients with PTC.
Methods
Since January 2017 until December 2018, an ultrasound-guided fine-needle aspiration was done in 34 patients with suspicious CLNs to obtain material for cytology and FNA-Tg.
Results
Data from 34 subjects with suspicious CLN were evaluated. 20 had a cytological diagnosis compatible with PTC lymph node metastases and the median value of FNA-Tg was 2801 µg/L (204–20600). While the other 14, had Tg-PAAF levels of 0.04 µg/L (0.04–0.04) and the cytology results were compatible with lymphoid hyperplasia in 13 patients and 1 compatible with lymph node metastasis of undifferentiated thyroid carcinoma. In the group with Tg-FNA $>$ 1 µg/L the short axis of the adenopathy was larger (0.80 cm vs 0.46 cm, $P<0.05$), with a higher frequency of: microcalcifications (50% vs 7%, $P<0.05$), cystic changes (60% vs 7%, $P<0.05$) and presence of more than one suspicious Sonographic findings (100% vs 10%, $P<0.05$).
Conclusion
FNA-Tg measurement is a simple and effective technique, as a complement to cytology and thyroid ultrasound in the diagnosis of lymph node metastases in the patient with PTC.

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P1227

Beneficial and fast impact of intravenous levothyroxine therapy on the lipid profile in severe hypothyroid patients

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Introduction
Abnormalities of lipid metabolism and arterial hypertension occur with increased frequency in hypothyroidism and are associated with a higher risk of premature atherosclerotic vascular disease. Therefore, a vigorous lipid lowering treatment seems mandatory, including quickly restoration of thyroid function, to reduce vascular risk. We evaluate benefits on lipid profile after intravenous thyroxine treatment in severe hypothyroid patients at three and thirty days.
Material and methods
Our retrospective study includes 70 consecutive severe hypothyroid patients (mean TSH of 104.1 mUI/L ($\pm$34.6)) treated with intravenous levothyroxine from 2004 to 2018 at our institution with a mean dose of 433.3 micrograms in two days and afterwards treated orally with a standard replacement dose. Total cholesterol, LDL-c, HDL-c, triglycerides, creatinine and CPK were measured on days 2–3 and 30 after treatment. No extra lipid lowering agents were used during the study. Data were analyzed with the Statistical Package for Social Science (SPSS), version 20.0 (SPSS Inc., Chicago, IL).
Results

	Mean (+SD) at admission	Mean (+SD) at 2°-3° day	Mean (+SD) at 30 days	*P*
Total Cholesterol (mg/dl)	273.5 (+93.1)	231.13 (+86.1)	175.6 (+42.2)	<0.05
HDL-c (mg/dl)	65.7 (+29.7)	57.4 (+21.1)	50.78 (+14.1)	<0.05
LDL-c (mg/dl)	166.8 (+60.3)	143.6 (+57.8)	104.5 (+36.1)	<0.05
Triglycerides (mg/dl)	151.24 (+28.2)	130.2 (+31.9)	106.3 (+50.5)	<0.05
Creatinine (mg/dl)	1.14 (+0.4)	1.1 (+0.3)	1.0 (+0.4)	<0.05
CPK (U/L)	805.7 (+119.2)	453.7 (+59.6)	-	<0.05

Conclusions
Lipid profile in severe hypothyroid patients shows a fast response in 48 hours to intravenous levothyroxine with marked improvement in all parameters.

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P1228

Radioactive Iodine (RAI) Treatment for Benign Thyroid Disease: A UK District General Hospital Perspective

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Aim
To determine patient outcomes following radioactive iodine (I^{131}) therapy in a UK district general hospital for the treatment of benign thyroid disease.
Methods
A record of all patients at University Hospital Hairmyres (Scotland, UK) undergoing radioactive iodine therapy for benign thyroid disease was kept. Patients were identified using a unique community health index (CHI) number. A retrospective case note review was then carried out for these patients. Patients treated between 2012 and 2016 were included. This ensured a minimum 2 year post radioactive iodine follow-up for all patients included in the review (maximum 6 years follow-up). Retrospective review was undertaken as per Royal College of Physicians (UK) guidelines. Age, gender, indication for RAI therapy, prescribed dosage of RAI, outcome of treatment, post RAI hypothyroidism and the incidence of worsened thyroid eye disease were recorded. GP prescribing records and bloods were examined to identify any further cases of hypothyroidism not immediately identified on case note review.
Results
A total of 37 patients were identified. 32/37 were female. 5/37 were male. Age at time of treatment ranged from 26 to 79 years with a mean age of 55.4 years. 24/37 were given RAI due to Grave's Disease refractory to medical management. 13/37 were treated with RAI for toxic multinodular goitre (TMG). Prescribed radioactive iodine dose ranged from 200 to 600 MBq. Dosage was 400 MBq in 32/37 patients, while 4/37 patients were prescribed 600 MBq. One patient was prescribed 200 MBq of RAI. 35/37 patients were successfully treated following first RAI treatment. 2/37 patients – both with a diagnosis of Grave's Disease - required further treatment for hyperthyroidism following RAI therapy. 26/37 were rendered hypothyroid following RAI. 11/37 were euthyroid at follow-up (minimum 2 years). 4/37 patients had a recorded flair of thyroid eye disease.
Conclusion
RAI is a safe and effective treatment for refractory hyperthyroidism not managed with medical therapy. The majority of patients in our cohort 35/37 were successfully treated with one dose of RAI. 400 MBq was an effective dose for the majority of patients. Hypothyroidism is a common outcome following RAI therapy and patients should be counselled to this effect.

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P1229

Influence of cigarette smoking on the efficacy of intravenous levothyroxine replacement in severe hypothyroidism: a retrospective case control study

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Introduction
Many studies have shown that cigarette smoking exerts multiple effects on the thyroid gland. Smoking seems to induce changes in thyroid function tests, like a left-shift in serum TSH level that is more apparent in iodine-deficient subjects and increase in thyroid hormones. We describe the effect of an intensive thyroxine intravenous treatment in severe hypothyroid patients and the results depending on their smoking status.
Material and methods
Our retrospective study includes 70 consecutive severe hypothyroid patients (mean TSH of 104.1 mUI/L ($\pm$34.6)) treated from 2004 to 2018 at our institution

with intravenous levothyroxine with a mean dose of 433.3 micrograms in two days and then treated orally with a standard replacement dose. We describe their evolution at 1 and 4 weeks comparing TSH, free T4 and free T3 levels and days it took hormonal levels to normalize. Data were analyzed with the Statistical Package for Social Science (SPSS), version 20.0 (SPSS Inc., Chicago, IL).
Results
TSH levels were higher among non-smokers but its response to intravenous levothyroxine was faster and it took fewer days to normalize after treatment due to different free hormone levels despite a smaller oral replacement dose.
Smokers vs Non smokers:
Age 49.1 (+7.6) 54.6 (+8.3), *P* 0.04; Weight 72.9 (+11.8) 68.9 (+12.4), *P* 0.002; pre-treatment TSH 95.2 (+14.6) 110.01 (+21.3), *P* 0.04; TSH 2–3 days post-treatment 85.1 (+8.1) 61.3 (+9.7), *P* 0.001; TSH 10–30 days post- treatment 59.7 (+15.3) 20.2 (+8.4), *P* 0.001; TSH > 30 days post-treatment 11.6 (+4.6) 4.4 (+3.2), *P* 0.001; Pre-treatment T4L 0.3 (+0.1) 0.42 (+0.3), *P* > 0.05; T4L 2–3 days post-treatment 0.4 (+0.1) 0.84 (+0.2), *P* > 0.05; T4L 3–10 days post-treatment 0.6 (+0.2) 1.0 (+0.3), *P* 0.003; T4L 10–30 days post-treatment 1.0 (+ 0.3) 1.0 (+0.4), *P* 0.001; T4L >30 days post-treatment 1.1 (+0.2) 1.25 (+0.3) *P* 0.001; Pre-treatment T3L 2.6 (+0.3) 2.0 (+0.6), *P* 0.02; T3L 2–3 days post-treatment 2.9 (+0.4) 2.5 (+0.2), *P* 0.02; T3L 3–10 days post-treatment 2.9 (+0,6) 2.6 (+0.7), *P* 0.02; T3L 10–30 days post-treatment 2.8 (+0.4) 2.8 (+0.5), *P* 0.001; T3L >30 days post-treatment 2.7 (+0.6) 2.3 (+0.3), *P* 0.02; Oral T4 doses on discharge 130.7 (+23.2) 114.6 (+21.5), *P* 0.001; Days to normalize free T4 8.3 (+1.2) 7.6 (+1.3), *P* > 0.05; Days to normalize free T3 7.4 (+0.6) 9.3 (+0.7), *P* 0.04; Days to normalize TSH 44.7 (+7.8) 28.5 (+5.4), *P* 0.001.
Conclusions
Response to intravenous levothyroxine treatment is different depending on the tobacco habit of patients, with a left-shift on TSH levels probably due to altered thyroid hormone metabolism.

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P1230

Delayed Autoimmune Thyroid Disease after Alemtuzumab Therapy: Hypothyroidism with TPO and TRAK Antibodies

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Alemtuzumab is an approved und well known Medication for the treatment of multiple sclerosis and it is a humanized anti-CD52 monoclonal antibody. Autoimmune diseases are the most common side effect of Alemtuzumab treatment. In our Case is after 18 Months of Alemtuzumab therapy a thyroid autoimmune disease developed. Patient with multiple sclerosis during the normal Follow up appear increased thyroid antibodies TPO 101 KU/L (normal <34) and TRAK 38.2 IU/L (normal <1.75). The Patient is clinically symptom free and the thyroid function shows a heavy hypothyroidism with TSH 48.9 µIU/ml (0.27–4.2), FT4 5.52 ng/l (9.3–17) and FT3 1.58 pg/ml (2.0–4.4). Thyroid sonography showed a normal Thyroid. After therapy with Levothyroxin 75 µg was a euthyroidism achieved. The antibodies ware declining with TPO normal und TRAK 12.2 after 6 Months. Patient is unter regularly follow up. Contrary to published literature, we recorded a delayed autoimmune thyroid disease with all thyroid antibodies increased and a clinical hypothyroidism. Furthermore has be shown that Alemtuzumab caused an immune reaction but also modify the function of the antibodies and that is why we have hypothyroidism with TRAK antibodies. We suggest a long follow up for patients with Alemtuzumab therapy for the delayed side effects. The presence of Antibodies does not insure the same function of the antibodies which should be controlled.

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P1231

Spontaneous thyroid hematoma causing airway compression: a case report

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Introduction
Spontaneous thyroid hematoma is a rare entity that can be favored by anticoagulation therapy. Any neck swelling can be life-threatening by compression of the upper aerodigestive tract and adjacent vascular axes.
Case report
We report the case of an 80-year-old patient with a previously existing goiter, started on vitamin K antagonists for atrial fibrillation, who presented to the emergency room for anterior neck mass that appeared 2 days before admission and rapidly expanding causing airway compromise. The presence of extensive bruising in both arms was suggestive of poisoning by vitamine K antagonists, the INR was at 7 with poorly tolerated anemia requiring blood transfusion. T4 at 40 pmol and TSH inhibited at 0.02 mIU/l with a positive CRP at 166 mg/l. CT showed a large nodular goiter associated with extensive diffuse infiltration of the thyroid gland with collections related to intrathyroid bleeding. The evolution was good under corticoid and antibiotic treatment with regression of the compressive signs. A thyroidectomy was performed one month later.
Discussion
Recent data from the literature report less than 50 cases of spontaneous cervical hematoma, almost half of which are iatrogenic (after anticoagulant therapy) and the thyroid origin of these hematomas is extremely rare. Pre-existing thyroid abnormalities, such as the existence of thyroid nodules may increase the risk of bleeding because of increased and altered vascularity. The treatment is based primarily on maintaining airway patency. Only 1/3 of the cases require surgical evacuation, more than half of the cases having a good response to conservative treatment.
Conclusion
The use of anticoagulant treatments is becoming more common. Bleeding of thyroid origin is rare but could be favored by the pre-existing nodules. This complication of anticoagulants deserves to be known because it can be life-threatening.

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ePoster Presentations

Adrenal and Neuroendocrine Tumours 1

EP1

Pheochromocytoma in the setting of a neurofibromatous type 1

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Introduction
Neurofibromatosis type 1 (NF1) is the most common autosomal dominant disease. The endocrine manifestations of NF1 are represented by pubertal abnormalities and pheochromocytoma. We report a case.
Observation
Mr. G.A, age 28, consulling for a grade 2 HTA evolving for 3 years. The anamnesis notes paroxysmal crises made of Ménard triad. The exam notes a correct blood pressure, 18 coffee latte tasks, lentiginous tasks. Two neurofibromas of 1.5 cm on the dorsal side of the neck. A bottom of the eye realized returned without particularity. The phosphocalcic balance is normal, normetanephrine 9 times normal and metanephrines 2 times normal. The dosage of calcitonin is normal. The imaging shows: At the CT scan: a right adrenal mass of 8 * 7 cm, heterogeneous, taking the contrast of intense way, without ADP satellites. At the MIBG scintigraphy showed a fixation of the mass without further fixation at a distance. Currently the patient is scheduled for right adrenalectomy after medical preparation.
Discussion
The manifestations of NF1 can be particularly serious because of different etiologies, including tumors that can be life-threatening and functional.

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EP2

Congenital adrenal hyperplasia (salt wasting form) with central precocious puberty: A combined therapeutic approach using a nighttime glucocorticoid dose, an aromatase inhibitor and a gonadotropin-releasing hormone analogue

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Congenital adrenal hyperplasia (CAH) describes a group of autosomal recessive disorders where the cortisol biosynthesis is impaired. There are two forms of CAH: the classic form, which includes the salt-wasting and the simple virilizing forms, and the nonclassic form. CAH due to 21-hydroxylase deficiency accounts for 95% of cases. Treatment of the classic form of CAH is targeted at replacing cortisol and aldosterone and effectively controlling excess androgen symptoms by using the lowest possible glucocorticoid dose. We present the case of a 9 and a half-year-old boy, with no other medical history, who has been followed-up in our Department since the age of 2 months for CAH, salt wasting form. In spite of excellent compliance to treatment with hydrocortisone (10–15 mg/m^2/d) and fludrocortisone (0.05–0.1 mg/d) he had always presented with high levels of corticotrophin, 17-hydroxyprogesterone and androstenedione with normal dehydroepiandrosterone sulfate levels and his bone age is advanced by 3 years since the age of 3. At the age of 8 years and 8 months the diagnostic of central precocious puberty was established (Tanner Stage III, accelerated growth velocity since 7 and a half years, high values of LH and testosterone with positive Triptorelin test confirming the diagnostic) and we initiated treatment with Methylprednisolone 1mg/d at bedtime in order to suppress nighttime corticotrophin secretion and with Anastrozole 1 mg/d in order to decrease the subsequent bone age advancement. Two months later we documented a significant decrease in 17-hydroxyprogesterone levels with normalization of androstenedione and testosterone, but with a persistently high LH level and we initiated the treatment of central precocious puberty with gonadotropin-releasing hormone analogue Triptorelin 3.75 mg/month. At the 6 months follow-up we identified a reduction of growth velocity with no clinical progression of puberty, along with a further decrease in 17-hydroxyprogesterone levels with prepubertal values of both LH and testosterone.

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EP3

Depression and anxiety are positively correlated with higher concentrations of cortisol and blood pressure in hypertensive cardiovascular disease patients

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Hypertension or high blood pressure (HBP) has been counted as the chief cause and most significant factor in the development of cardiovascular diseases (CVDs) worldwide. Stress has been defined as an inner process that happens when a person is faced with an ordinant dictation that is perceived to go beyond the resources available to efficaciously respond to it. Cortisol is a hormone released from the zona fasciculata of the adrenal cortex during the times of stress. This biological marker of stress can directly influence the central nervous system, as it affects areas of the brain having responsibility of controlling the blood pressure. Cortisol reactivity, an index of hypothalamic-pituitary-adrenal function, is one of the possible ways through which psychosocial stress may affect the liability of hypertension. The present study was designed to examine stress as a predisposing factor in causing hypertension by determining the level of psychological stress using Depression, Anxiety and Stress Scale (DASS), the level of physiological stress in terms of release of cortisol by using RIA systems and their association with hypertension. Hundred hypertensive CVD patients and hundred age and sex matched healthy subjects between the age of 20 and 60 years were included in the study. Our results revealed that hypertensive CVD patients scored higher on DASS as compared to controls. The majority of hypertensive CVD patients had combined symptoms of depression, anxiety and stress. Similarly, cortisol concentrations were found to be significantly higher in hypertensive CVD patients as compared to healthy subjects in all age groups from 31 to 60 years. There was a strong positive correlation between psychological stress and cortisol in hypertensive CVD patients. Furthermore, there was a positive correlation between depression and anxiety and BP as well as between cortisol and BP, while there was a negative correlation between stress and BP in hypertensive CVD patients in all age groups. The majority of hypertensive CVD patients fell in the age group of 51–60 years. They were males, belonging to the lower-middle class, and were illiterate, overweight, married and non-smokers. They had complaints of headache and sleep apnea with no family history for CVD and were hypertensive from 1 to 10 years. They were treated with a combination of RAASi and non-RAASi. Only 6 patients were taking anti-depressants and other stress medicines. In conclusion, the present study demonstrated that increased psychological stress causes higher secretion of cortisol, which may contribute to the development of hypertension and related CVDs.

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EP4

Metrorrhagia as first manifestation of adrenocortical carcinoma – case report

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Introduction
Adrenocortical carcinoma is a rare tumor with an incidence of 1 per million per year. It occurs in two age groups: in children under 5 years old and in adults from 4th to 6th decade of life. It is potentially curable at an early stage, unfortunatelly, about 70% of these tumors are detected late. Functional carcinomas are present with about 60% with endocrine syndrom: Cushing syndrome (30%); Virilization and premature puberty (22%); Feminization (10%); Primary hyperaldosteronism (2.5%); Combined hormonal excess (35%).

Case report
Postmenopausal, 60 years old woman reported uterine bleeding to a gynaecologist in November 2011. Clinical examination, ECHO and PAPA were non-specific. PH finding after fractionated curettage: Hyperplasia endometrii simplex. Bleeding continued persistently and she was radically gynecologically operated in July 2012. PH finding: Adenomyosis uteri. After surgery: hyperglycaemia, swelling of the legs, gaining in the body weight, redness of the face, hirsutism and non controlled blood pressure occurred. Diagnosed diabetes, highly elevated, non suppressed cortisol in overnight DEX test 1500 nmol/l, LDDST cortisol 1656.0 nmol/l, testosterone 19.2 nmol/l, DHEAS 9.3 mcmol/l, A-dion 18.1 nmol/l, estradiol 2417 pmol/l and Ca19-9 212.3. Gonadotropins and ACTH were suppressed. Aldosteron/ renin and cateholamins were normal. CT scan presented a large, inhomogeneous, low fat content tumor of the left adrenal gland 150×74 mm, which suppressed the left kidney caudally, enlarged retroperitoneal and periaortal lymph nodes up to 24 mm in diameter and secondary deposits in the lungs. She was operated on May 2013, left adrenalectomy, left nephrectomy and splenectomy were done. PH finding: Carcinoma glandulae suprarenalis Weiss scor 6. Early post-operative course was accompanied by numerous severe complications: intra-abdominal bleeding, pulmonary thromboembolism, thrombosis and tumor infiltration of the inferior cava vein and sepsis (Klebsiella). Treatment of complications lasted for 6 months. Patient survived complications. Due to her poor general condition, the Neuroendocrine Tumor Consilium has decided to continue treatment with mitotane at the maximum tolerable dose. In the further course of the disease she was taking mitotan discontinuously, in a reduced dose due to intolerance. She died in July 2017.
Conclusions
i) It is necessary to check the level of estrogen, androgens and gonadotropins in the evaluation of inexplainable vaginal bleeding in postmenopausal age as well as generative age. ii) If hormonal testing was done, our patient would avoid unnecessary gynecological surgery, and the underlying disease would've been diagnosed earlier, when it was potentially curable.

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EP5

Low blood glucose, but why?

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Introduction
Hypoglycaemia in non diabetic patients is a decrease of blood glucose below a threshold of 0.5 g/l, corresponds to a pathological situation, with many etiologies and whose management constitutes a real challenge, both symptomatic and etiological. The purpose of this study is to highlight the profile of these hypoglycaemia and their management.
Patients and method
We have collected cases of hypoglycaemia in non-diabetic subjects encountered in the endocrinology department over the past three years.
Results
We collected eight cases. The average age of these patients was 47.5 years, with a female predominance. The mode of revelation was unconsciousness in four cases, convulsions in one case, and hypoglycemic discomfort in three cases. The etiologies were insulinomas in 6 cases, one in the setting of MEN1 (with hyperparathyroidism and macroprolactinoma). One patient had a mesenchymal tumor of the chest wall secreting IGF2, and a fictitious hypoglycemia in a young depressive patient living in a family-conflict setting. The investigations included hormonemia in 6 cases: average insulinemia was 69 μU/ml (23 times the normal level) and the average peptide C at 1.37 pmol/ml (2.2 times the normal level). The topographic assessment included an octreotide scintigraphy in 7 cases, positive in 4 cases. The treatment was surgical in the case of insulinomas and mesenchymal tumor. The pathological anatomy was conclusive in 3 cases. The evolution was marked by a regression of the hypoglycemias, a decrease of their frequency and their depth. And after 24 hours of monitoring, no hypoglycemia was noted in the factitious intake of insulin.
Discussion
Hypoglycemic discomfort is always a hardship for the patient and a challenge for the practitioner. In the organic hypoglycemia, we can improve the quality of life and avoid complications of the patient by finding an etiology, as it is frequently curable.

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EP6

A case of Cushing syndrome due to primary bilateral macronodular adrenal hyperplasia caused by *ARMC5* mutation and concomitant primary hyperparathyroidism

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Primary bilateral macronodular adrenal hyperplasia (PBMAH) is a rare cause of Cushing syndrome and in 25–55% of cases is caused by mutations in *ARMC5* gene. A 37 y.o. female was referred to our center with a diagnosis of ACTH-independent Cushing syndrome. Laboratory testing confirmed endogenous hypercortisolism (urinary free cortisol 5063.5 nmol/24 h (60–413), midnight salivary cortisol 56.6 nmol/l (0.5–9.4), midnight serum cortisol 1427 nmol/l (46–270). ACTH level was 1 pg/ml (7–66). Adrenal CT scan showed that adrenals were enlarged and their structure was heterogeneous due to numerous nodes ranging in size from 12 to 36 mm; the length of the right adrenal gland was 9.3 cm, the left - 8.9 cm, which was consistent with PBMAH. Bilateral adrenalectomy was performed as the treatment of choice. Morphologic examination confirmed macronodular adrenal hyperplasia. Biochemical testing also revealed increased serum calcium (total calcium 2.54–2.61 (2.15–2.55), ionized 1.24 mmol/l (1.03–1.29) and increase PTH – 70.44 pg/ml (15–65)) enabling to diagnose primary hyperparathyroidism. Parathyroid ultrasound revealed enlarged upper right parathyroid gland 0.8×0.5×0.3 cm. Six months after adrenalectomy hypercalcemia persisted: total serum calcium 2.68–2.78 mmol/l, ionized serum calcium 1.22–1.28 mmol/l. No renal impairment, kidney stones or decreased bone mineral density were detected, thus dynamic control of primary hyperparathyroidism was chosen. The patient's family history was remarkable for the presence of Cushing syndrome and PBMAH in the patient's mother. Due to genetic heterogeneity of PBMAH whole-exome sequencing was performed, which revealed a heterozygous mutation in exon 6 of *ARMC5* gene p.R898W (c.2692C>T) (NM_001105247). The mutation has already been described in patients with PBMAH and Cushing syndrome. Mutations in *ARMC5* have been described in patients with concomitant meningiomas but not with primary hyperparathyroidism. Whether mutations in *ARMC5* gene are associated with parathyroid tumor development is yet to be determined.

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EP7

Adrenal carcinoma presenting as suicidal depression

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Depression can be an early manifestation of Cushing Syndrome (CS) and found to correlate with the severity of the clinical presentation. Rates for major depression vary from 12% to 50–70%. A 37-year-old male was admitted for sad mood, affective lability, suicidal ideation without a plan and micromanian incurability ideation. The medical history of the patient revealed an old anterior-lateral myocardial infarction last year, with percutaneous coronary intervention on diagonal branche D1, hypertension under treatment and type 2 diabetes treated with oral antidiabetic drugs. The relevant clinical signs were overweight, round face and abdominal pain. Laboratory assays revealed hepatic cytolysis (TGP=97 U/l, TGO=61 U/l), cholestasis, inflammatory syndrome, hyperglycemia, A1c of 7.8%, hypopotasemia (K=2.37 mmol/l), with suspicion of CS. Hormonal investigations indicated Cushing-independent-ACTH-syndrome: basal (BC) 87.8 microg/dl, nocturnal cortisol (85.8 microg/dl), free urinary cortisol (1912 microg/24 h) were elevated, low ACTH level (3.15 pg/ml), no suppression at low inhibition test, DHEAS of 5.23 microg/ml, no suppression of the BC at the high dexametasone suppression test. The abdominal ecography showed a left adrenal hypoechoic, homogenous, well diffened tumor of 17/10 cm, retro-peritoneal adenopathys, multiple hepatic nodular areas, dilatation of the

intrahepatic bill ducts with suspicion of adrenocortical carcinoma with liver metastasis. The thoracic-abdominal computer tomography revealed pulmonary and hepatic metastasis, left renal thrombosis, with extension in the inferior cava vein and the left invasive adrenal tumor. The patient developed suicidal ideation with a plan, requiring urgent antidepressive treatment with serotonin uptake inhibitors, benzodiazepines and hypnotic inducers, which were ineffective. He had to do a biopsy for histopathologic exam, but the general condition of the patient rapidly degraded and contrary to medical efforts the prognosis is very poor; palleativ oncological treatment is expected. Major depression is the most common psychiatric disorder seen in CS, and clinicians should remember that it is necessary to screen a patient with depression and symptoms of CS also for adrenocortical carcinoma.

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EP8

Characteristics of factors affecting the survival of patients with adrenal cortical carcinoma treated with mitotane

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Introduction
Adrenal cortical carcinoma (ACC) is a rare malignant neoplasm of epithelial origin, derived from the adrenal cortex, with a high tendency to local invasion and distant metastases.
Aim
The aim was to assess the effect of serum mitotane concentration during mitotane therapy and identify prognostic factors on the survival of ACC patients.
Material and methods
It was a multifactorial analysis of patients from a single endocrinology center. We retrospectively reviewed data on ACC patients (*N* 56) treated with mitotane between 2002 and 2018. Follow up of included patients was conducted in specific time intervals - after the initation of mitotane therapy. Patients evaluation was based on the comparison of subsequent CT and MR results in the formulation of RECIST. We assessed the progression-free survival time as well as the influence of progression factors. We also evaluated the effect of the therapeutical mitotate concentration on the probability of survival and progression-free survival. We considered the following factors: sex, age, tumor size, tumor secretory activity, tumor resection, reoperation, chemotherapy, radiotherapy and therapeutic concentration of mitotane.
Conclusion
The most important factor affecting progression-free survival is the attainment of the therapeutical concentrations of mitotane - a 3-fold progression in patients who did not have therapeutic control was observed. Among factors improving the prognosis, statistically complete resection (R0) is also present. There was no statistically significant effect of sex and tumor sive as well as age of the patient at the time of diagnosis.

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EP9

Singultus persistens as a presentation of addisonian crisis

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Introduction
It is presumed that hiccups are a vestigial reflex in mammals. They are rather common in healthy subjects. Persistent hiccups (lasting >48 h) are a serious clinical sign, and documented in a number of debilitating conditions. According to the available literature persistent hiccups in Addisonian crisis have been previously documented in only two patients.
Case report
In July 2018, a 39 year old man checked into the ER complaining of nausea, vomiting, severe fatigue and persistent hiccups that started 3 days before. Detailed history revealed that the tanning of his skin started two years ago. Fatigue started a year ago, and was worsening since – for the last 3 weeks he struggled to get out of his bed and walk. Other than a penicillin allergy, he denied any other health issues. Basic metabolic panel showed severe hyponatriemia (115 mmol/l) and hyperkaliemia (5.9 mmol/l). Head CT was nominal. He was admitted to our Clinic with a diagnosis of Addisonian crisis and given hydrocortisone intravenously. Six hours after the first dose, nausea and hiccups resolved. Upon admission, serum cortisol was 54 nmol/l and ACTH >440.4 pmol/l. Thorough analysis did not reveal any other endocrinopathies. As he was getting better he was gradually transitioned from IV to oral hydrocortisone and fludrocortisone therapy. His electrolyte levels normalised and fatigue waned. He was released on hydrocortisone and fludrocortisone therapy and was educated on proper therapy modifications in acute stress situations. After 6 months he was complaint-free with quality of life approaching the one before first symptoms.
Conclusion
The rare underlying condition behind persistent hiccups was Addison's disease with, for now, a poorly understood cause-effect relationship.

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EP10

Acquired intermittent long QT syndrome might be challenging in substitution dosing in adult patient with Addison disease: case report after 3 years follow up

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Introduction
Acquired modifible long QT syndrome (LQTS) might be caused by hypocortisolism but also drug-induced. Unique genetic association between them is the background of both. The aim of this case report is to present the patient with Addison disease and LQTS not responding on increased dosage of hydrocortison susbstitution therapy.
Case report
We report a female patient, 65 years old (1950y.). At the age of 34y. (1984y.) Morbus Addisoni was diagnosed and substituted with hydrocortison 20 mg daily. In her 57th y. (2007y.) after interhemilameinectomy chronic pain remained. Patient was treated with polypharmacy: lorazepam 5 mg/day, sulpirid 100 mg/day, paroksetin 10 mg/day and karbamazepim 800 mg/day. Two years later patient developed attack of faintness with headache, fatigue and hypotension (100/70 mmHg). Pottassium level was 4.97 mmol/l, sodium 141 mmol/l and ECG was normal. Dosage of hydrocortison was increased on 25 mg/day. Year later syncope followed with vomiting, retrosternal and left arm pain happened, and next years three times repeated. Head CT was normal. On 24 h Holter ECG maximal QTc of 452 ms was noticed. In July 2015 she developed lost of consciousness with confirmed third-degree AV block with pauses of 10 sec. After therapy with atropin and metilprednisolon 60 mg heart rate increased on 55/min, QT/QTc was 592/581 ms with occasional ventricular premature complexes. On coronarography significant lesions were not detected. VVIR (Ventricular pace, ventricular sense, ventricular inhibit- rate responsive single-chamber ventricular pacing) pacemaker was implanted. Our patient was still on medications previously incriminated and pacemaker just periodically emits electric impulses that stimulate heart to beat at a normal rate. In 2016. incriminated pain killers were excluded andf since that time there was no need for pace maker activation.
Conclusion
Holter monitoring ECG should be performed longer than one day if it is not conclusive, actually so long untill establishing the connection between symptoms (e.g. syncopa) and ECG abnormalities. By excluding the incriminated drugs (pain killers) we have conformed the underlying pathophysiological mechanism that lead to LQRS development.

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EP11

Adrenal hematoma: two cases report

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Introduction
Adrenal hematomas are a relatively rare clinical condition and its prevalence has been reported to be about 1%. Although various causes have been proposed, the ethology and pathophysiology are still not fully understood, and the symptoms range is very variable, from asymptomatic situations to haemorrhagic shock. Imaging is a challenging method to establish the diagnosis of adrenal hematomas, and in most cases, it is only possible after surgery. Surgery is routinely recommended if there is a suspicion of malignancy.
Case Report
We present two cases of adrenal hematomas with diagnosis after surgical intervention and histopathological examination. Male, 81 years old, referred to outpatient clinic by incidentaloma on right adrenal gland, heterogeneous, hypovascular, with 8.1 cm, in an imaging study by renal lithiasis. Personal history of controlled hypertension, atrial fibrillation and dyslipidaemia. Medicated with furosemide 40 mg id, candersatan 10 mg id, dabigatran 110 mg 2 id and simvastatin 20 mg id. No family history. Analytical evaluation without alterations suggesting non-functioning nodule and CT showing: 'expansive formation in the right adrenal with 11.2 cm that could be a benign lesion but cannot exclude carcinoma or pheochromocytoma'. Performed a right adrenalectomy, without immediate complications. Pathological anatomy with nodular and expansive lesion of the right adrenal, organized into a hematoma. A 63-year-old woman, referred to outpatient clinic for a nodule on left adrenal, discovered during the study of hypertensive spikes. Personal history of hypertension, dyslipidaemia and depressive syndrome. Medicated with carvedilol 6.25 mg 2 id, atorvastatin 40 mg id and quetiapine 20 mg id. No family history. Analytical evaluation compatible with non-functioning nodule and CT: 'At the level of the left adrenal, there are two regular nodules with well-defined borders, one homogenous and hypodense suggestive of adenoma, another spontaneously regular heterogeneous measuring 4.2 $\times$ 2.3 cm, washout 30%, which may correspond to an expansive process (…)'. Performed left adrenalectomy by laparoscopy without immediate complications. Pathological anatomy compatible with left adrenal hematoma.
Conclusions
Adrenal hematomas are usually caused by trauma, surgery, anti-coagulant therapy, haemorrhagic diathesis, septicaemia, adrenal neoformation or systemic disease. However, due to the highly vascularized and vulnerable nature of the adrenal gland, it isn't always possible to identify a risk factor. Incidentalomas $\geq$4 cm and/or growth $\geq$ 20% in 6/12 months, with uncertainty in the diagnosis are often surgical indication. There are no established follow-up protocols and is unknown the risk of postoperative recurrence in the contralateral gland.

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EP12

Lost to follow-up in classic congenital adrenal hyperplasia: a case report

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Introduction
Classic congenital adrenal hyperplasias (CAH) are mostly diagnosed in the first months/years of life and require a lifetime follow-up.
Case report
A 33-year-old Caucasian man was admitted twice in the previous year to the emergency department; the first episode due to an acute tonsillitis, the second episode due to a lower respiratory tract infection, both associated with hyponatremia (125 mmol/l). Common causes of hyponatremia were excluded. He was then observed at the endocrine outpatient department. He mentioned an admission at the hospital at the age of 1 after which he initiated corticotherapy, suspended at the age of 10 (lost to follow-up). There is a history of conjugal infertility. Physical examination revealed marked cutaneous pigmentation and low height (-2 S.D.). Baseline endocrine evaluation revealed a morning cortisol of 2 µg/dl with an ACTH of 2643 pg/ml, elevated testosterone 1030 ng/dl (RR 240–830) with suppressed FSH and LH, elevated progesterone 4.63 ng/ml (RR 0.20–1.4), estradiol (E2) 65.2 pg/ml (RR 16–60), 17-OHP 88.40 g/ml (RR $<$ 2.2 ng/ml), 11-deoxycortisol 19.11 ng/ml (RR $<$ 7.2), Δ4-androstenedione $>$ 10 ng/ml (RR 0.6–3.7) and PRL 98.4 ng/ml RR (4–15), normal aldosterone 3.7 ng/dl (RR 1.76–23.3) with elevated renin 728 µUI/ml (RR 4.4–46), S-DHEA 315.8 µg/dl(RR 65–334), TSH 3.15 (RR 0.30–4.20) with normal total T4 and fT4, but elevated total T3 2.31 ng/ml (RR 0.83–2.0) and fT3 5.00 pg/ml (RR 2.0–4.4). Adrenal CT scan showed bilateral adrenal hyperplasia. Testicular ultrasound revealed normal sized testicles presenting bilateral masses on both testes suggestive of nodular hyperplasia of adrenal rest tissues. Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency with adrenal insufficiency was admitted and he initiated therapy with hydrocortisone and fludrocortisone. Endocrine evaluation two months after initiation of therapy revealed a marked reduction of ACTH, progesterone, 17-OHP, 11-deoxycortisol, Δ4-androstenedione and renin. Additionally,testosterone, E2, PRL and thyroid function became normal. Nonetheless he initially referred being asymptomatic, he recognises an enormous improvement in his QoL upon treatment. The genetic study is ongoing.
Discussion
Despite therapy absence from the 10th until the 33rd year of age the patient did not have any major intercurrences. The hyponatremia, that was present in both admissions at the emergency department, is explained by the patient's adrenal insufficiency. The elevated testosterone with suppressed LH and FSH is possibly conditioning the conjugal infertility. As described in literature, this case also suggests that E2 stimulates basal and TRH-elicited both TSH and PRL.

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EP13

Adrenocortical carcinoma - single center experience

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Adrenocortical carcinoma is an aggressive tumor of endocrine system with an annual incidence of 1–2 cases per million. The most significant prognostic factors are tumor size, disease stage at the time of putting the diagnosis and treatment method. Advanced age of the patient, and hormonal activity of the cancer are also related to poor prognosis.
Materials and methods
In our study we collected data of 12 patients who were treated in Endocrinology Clinic of Medical University of Lublin between 2007 and 2017. The following data were analyzed: patient's age at the moment of putting the diagnosis, tumor size, disease stage, surgery method and its completeness and post-operative antineoplastic chemotherapy.
Results
In our group of patients, the majority of patients (66.6%, $n=8$) were women and men accounted for 33.3% of patients ($n=4$). In 58% of cases, tumor mass was located at the left side of the body, and in the remaining 42% of cases - at the right side. In 25% of patients the tumor was hormonally active (Cushing's syndrome). The survival rate was strictly correlated with the tumor stage at the time of establishing the diagnosis. In all patients adjuvant treatment with mitotane was carried out with hydrocortisone treatment introduced simultaneously. Two patients received adjuvant systemic chemotherapy according to EDP regimen (etoposide, doxorubi-sin, and cisplatin).
Conclusions
Adrenocortical carcinoma is an aggressive and very rare tumor. Therefore, the preoperative evaluation and post-surgery treatment and follow-up should be performed in ex-perienced endocrinology clinics in order to improve patients' prognosis.

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EP14

The diagnosis of Cushing's syndrome in pulmonary adenocarcinoma associated with an unilateral adrenal mass - case report

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Cushing's syndrome is a collection of signs and symptoms due to prolonged exposure to cortisol. It can be difficult to diagnose, particularly endogenous

Cushing's syndrome, because other conditions share the same signs and symptoms. Diagnosing Cushing's syndrome can be a long and extensive process, it's treatment may be also an important challenge. We present the case of a 49-year-old man, with a history of asthma and pulmonary cribriform adenocarcinoma (radio and chemo-treated), referred to gastroenterology department with liver cirrhosis observation. Clinically he presented increase in abdomen volume, purple stretch marks, proximal myopathy, physical and mental asthenia, dorsal spine pain; in association with the pulmonary neoplastic pathology, was rised the suspicion of a paraneoplastic Cushing syndrome. The hormonal panel indicated supressed ACTH <5 pg/ml, cortisol after 1 mg dexamethasone suppression test >24.1 ug/dl, rised free urinary cortisol (450 ug/24H) and the thoraco-abdominal CT revealed the presence of an right adrenal mass (27/31/3605 mm), with an washout suggestive for adenoma. Investigations also revealed an hypercoagulability status, modified basal glucose and severe osteoporosis with impeared spinal settlements. Because surgical treatment cannot be performed (obstructive ventilatory dysfunction associated with important heart failure and long evolution asthma), symptomatic medication, antiresorbtive treatment and steroidogenesis inhibitors, represented the only therapy. The particulary of the case consist in pulmonary cribriform adenocarcinoma in association with adrenal mass, differential diagnosis making it hard between paraneoplastic Cushing syndrome, paraneoplastic ascites and adrenal adenoma.

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EP15

Progress in the treatment of unresectable metastatic ileum-cecal NET - Peptide receptor radionuclide therapy (PRRT)

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Neuroendocrine tumors (NETs) represent the second most common malignancy of the small bowel (SB) and despite their indolent nature, NET liver metastasis (NETLMs) will develop in 50 to 60% of patients. Although there have been recent advances in the therapeutic armamentarium in patients with advanced NETs, surgical resection remains the only potentially curative intervention for patients with NETLMs. However, patients whose liver has been significantly invaded by the tumour (more than 50–70%) are very likely to have compromised liver remnant and suffer from postoperative liver failure, which makes them very poor candidates for operation. On the other hand, peptide receptor radionuclide therapy (PRRT) with 177 Lutetium-DOTATATE has gained substantial popularity and is typically employed in the management of grade I and grade II metastatic NETs. Hereby, we describe the case of a 69-year old woman diagnosed in March 2013 with ileum-cecal NET G2 (Ki67 = 5%), presenting at the Clinic of Endocrinology, UMP Iuliu-Hatieganu, Cluj-Napoca in 2016 with the clinical picture of liver metastasis and carcinoid syndrome, and later also of carcinoid heart disease. Her liver metastases were unresectable and there was no response in terms of clinical manifestations, NETs markers and tumor progression with high doses of somatostatin analogs (SSAs) therapy. Hence, a ^{68}Ga DOTANOC PET/CT was employed at Viena (AKH) in April 2017, which revelead the SSTR expression at the ileocecal valve, in the liver and in the bone as well. The patient underwent 4 cycles of PRRT with Lutetium 177- labeled DOTATATE in the same center. A significant clinical improvement as regard to the carcinoid syndrome was noted. Additionally, the response evaluation performed with ^{68}Ga-Dotanoc PET/CT in December 2017 revealed an improvement as well, with a reduction in the liver metastasis and a slightly lower tracer uptake on the mentioned areas (ileocecal valve, liver, bone). Therfore, PRRT may represent a promising therapeutical option in the care of patients with unresectable metastatic ileum-cecal NET, which can lengthen the time-to-progression and the time to health-related QoL deterioration, as well as increase survival probability.

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EP16

Multiple endocrine neoplasia typu 2B – case report

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Introduction
Multiple endocrine neoplasia type 2 (MEN2) is an autosomal dominant disorder with an estimated prevalence of 1 per 30,000 in the general population. MEN2 is subclassified into two distinct syndromes: types 2A (MEN2A) and 2B (MEN2B). MEN2A and 2B are inherited in an autosomal dominant pattern with very high penetrance. In both syndromes, there is an occurrence of multicentric tumour formation in all organs where the *RET* proto-oncogene is expressed.
Case
We present a 34 years old patient with MEN2B. He is after total thyroidectomy for medullary thyroid cancer (T1bmN1aM0) in 2013. After operation, there was normalisation of calcitonin levels with negative finding on ultrasound of the neck. That's why he was not indicated for neck lymph node dissection. External beam radiotherapy (60Gy) was provided. According to genetic examination he is a carrier of a germ point heterozygous mutation in the 11th exon of the RET proto-oncogene. During our surveillance there were borderline calcitonin levels with increase after stimulation. 18F-FDG PET/CT was indicated with the finding of FDG accumulation on both adrenal glands. Surprisingly results of metanephrine and normetanephrine were negative at first time (MNP 0.282 nmol/l, normal values 0.06–0.31, NMNP 0.568 nmol/l, normal values 0.1–0.61). At the second time our suspicion was laboratory confirmed (MNP 1.566 nmol/l, NMNP 1.147 nmol/l). After alpha blockade treatment bilateral adrenalectomy was done and diagnosis of bilateral pheochromocytoma was confirmed. After operation glucocorticoid substitution was provided.
Conclusion
Patients with medullary thyroid cancer should have a genetic examination and should be evaluated for possible pheochromocytoma and primary hyperparathyroidism. In our case, at first time, we had false negative laboratory results. Laboratory tests, to exclude pheochromocytoma, should be repeated if there is clinical suspicion.

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EP17

A rare case of ectopic ACTH syndrome due to recurrence of olfactory neuroblastoma

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We hereby report a rare case of ectopic adrenocorticotropic hormone (ACTH) syndrome due to recurrence of olfactory neuroblastoma which has few published reports. The female patient had surgery of olfactory neuroblastoma at 31 years old without the symptom of Cushing's syndrome. Hypercortisolemia during treatment for recurrence of olfactory neuroblastoma were observed at 40 years old. The clinical findings were as followed; full moon face, central obesity, buffalo hump, and impaired glucose tolerance. Tumors of size 40–50 mm considered to be metastases from olfactory neuroblastoma were confirmed by lateral cervical Computed Tomography (CT). ACTH staining was positive in biopsy specimen and that the patient was diagnosed as ectopic ACTH syndrome from metastatic olfactory neuroblastoma. ACTH was not detected in the specimen of craniotomy at 31 years old. Therefore, it was considered that the ACTH producing tumor was manifested at the time of this recurrence at 40 years old. In order to suppress cortisol production, methyrapone started and the blood cortisol level decreased. Furthermore, resection of a bilateral cervix tumor, that is supposed to be an ACTH production site, decreased serum level of ACTH and cortisol level and the dose of methyrapone. Ectopic ACTH producing tumors present featured clinical findings of Cushing's syndrome. The common origins of tumors are small cell lung tumors, carcinoids and pancreatic neuroendocrine tumors. Few cases of ACTH producing olfactory neuroblastoma were reported in database. Moreover Cushing's syndrome is basically considered to have a good prognosis, but it can cause various complications such as infection, hypertension, diabetes, dyslipidemia and cardiovascular disease. Therefore, it is important to intervene at an early stage to prevent complications.

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EP18

Characteristics, management and outcome of patients with adrenocortical carcinoma in a tertiary hospital: a retrospective study

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Adrenocortical carcinoma (ACC) is a rare, aggressive tumor with poor prognosis, affecting 0.5–2 cases/10^6population/year.
Objective
To analyse retrospectively characteristics, management and outcome of ACC patients, followed in our center between 2010–2018.
Material and methods
The medical records related to diagnosis, treatment and follow-up of nine patients of 59.2 ± 13.8 years with histological diagnosis of ACC (Weiss score >3) were considered.
Results
At diagnosis, 4 patients suffered from muscle weakness and hypokalemia, 1 from abdominal pain, 1 from hirsutism and menstrual disturbances, 1 had severe hypertension and 2 were asymptomatic. Eight patients were functioning: 6 with hypercortisolism alone or in combination with either hyperandrogenism or hyperaldosteronism, 1 with isolated hyperaldosteronism and 1 with isolated hyperandrogenism. Mean adrenal tumor size was 7.96 ± 4.43, Weiss score 5.7 ± 1.9, Ki67 $16.9 \pm 7.04\%$ and mitotic count 18.4 ± 14.5/50 HPFs. According to ENSAT staging: 2 patients were in stage IV, 5 in stage III, and 2 in stage II. Median follow-up was 27months. All patients underwent surgery: 5 had a complete resection and 3 patients underwent re-resection after recurrence. Mitotane was administrated in 8 out of 9 patients either as adjuvant (4) or as palliative (4) treatment. Simultaneous chemotherapy (EDP) was administrated in 1 patient. Median treatment duration was 20 months. Three patients (stage III or IV, Weiss score 8 ± 1, Ki67 25 ± 5, mitotic count 35 ± 8.6 with treatment duration of 14.3 ± 18.7 months) had progressive disease (PD); 2 (stage III or IV, Weiss score 4, Ki67 12.5 ± 3.5, mitotic count 5.5 ± 2.1 with treatment duration of 54.5 ± 57.2 months) had complete response (CR); and 3 who received adjuvant treatment (stage II or III, Weiss score 4.6 ± 0.57, Ki67 14 ± 3.6, mitotic count 15.5 ± 8.6 with treatment duration of 37 ± 35.8 months) were with not evidence of disease. Patients with PD had higher Weiss score, Ki67 and mitotic count than those with no evidence of disease or with CR ($P < 0.05$ in all comparisons). Therapeutic mitotane levels were achieved in 67% of patients with a daily dose of 5 ± 1.4 gr within 6 months. Adrenal insufficiency occurred in all patients, hypothyroidism in 75% of patients. Serious adverse events (grade 3 and 4) occurred in 62% of patients. Two out of 3 patients who died discontinued treatment in <6 months because of serious adverse events.
Conclusions
In our center most ACC were functioning and diagnosed in advanced stages. Histological indices seem to be prognostics factors for the patients' outcome. Mitotane was a beneficial treatment.

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EP19

ACTH-Producing neuroendocrine cancer of the thymus with pancreatic metastasis, presenting with flush

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Context
ACTH-producing neuroendocrine cancer (NEC) of the thymus is rare. Lymph nodes and bone are most common metastatic sites. ACTH-secreting thymic NEC with pancreatic metastasis was only reported in one case. Most cases presented with florid Cushing syndrome (CS). Our case had thymic NEC with pancreatic metastasis, presenting with intermittent flush instead of typical CS. We demonstrate the comprehensive information of somatostatin receptors (SSTR), three different kinds of positron emission tomography (PET) scans, and the complete treatment course of this rare cancer.
Case description
A 58-year-old female patient presented with intermittent flush associated with sweating and weight loss. The following exams showed mediastinum widening and elevated tumor markers. Further image survey revealed tumors in the mediastinum, pancreas and bones. Ultrasound-guided biopsy of the mediastinum tumor was performed. Pathology with immunohistochemical (IHC) staining resulted in a thymic NEC. SSTR2 and SSTR5 were negative in IHC stain. The mediastinal tumor showed intense fludeoxyglucose, mild 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine, and mild ^{68}Ga-DOTA-tyr3-Octreotide avidity on PET scans. IHC staining of ACTH was positive. Serum and urine cortisol levels elevated, but the patient did not have apparent Cushing appearance. The patient received mediastinum tumor resection followed by radiation therapy, alcohol injection to the pancreatic metastasis lesion, and systemic anti-cancer medications including sandostatin, pasireotide and everolimus. After the initial tumor resection, symptom of flush improved significantly. The 24-hour urine free cortisol (UFC), serum cortisol and ACTH also decreased obviously. However, thymic and pancreatic tumors enlarged gradually under the following systemic treatment. Fluconazole was prescribed for the hypercortisolism. Bilateral adrenalectomy was also suggested but the patient refused. She died from infection 16 months after the diagnosis of NEC.
Conclusions
Pancreatic metastasis and ACTH-secretion should be warrant in cases of thymic NEC even without apparent CS. Intermittent flush could be the initial presentation of patients with ACTH-secreting NEC. Multi-faceted treatments are necessary. SSTR staining and ^{68}Ga-DOTATOC PET scan may be reference for treatment choice.

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EP20

Adrenocortical carcinoma: epidemiological, clinical and paraclinical profile: about 4 cases

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Introduction
The adrenocortical carcinoma (ACC) is a primary malignant tumor developed in depends of the adrenal cortex, defined by a Weiss score ≥ 3. Despite the therapeutic progress, its prognosis is still severe.
Patients and methods
This retrospective descriptive study evaluated 4 patients with adrenal corticosteroid followed in the endocrinology department of Sfax - Tunisia between 2010 and 2018.
Results
There were 3 women and 1 man. The mean age at diagnosis was 48.7 ± 13.5 years (34, 57, 63 and 41 years). The circumstances of discovery were, respectively: an adrenal incidentaloma, lumbar pain with cachexia, Cushing's syndrome, and signs of hyperestrogenism in men. Clinical examination revealed respectively: asympotomatic, hirsutism, cushing syndrome and gynecomastia with decreased libido in men. The mean tumor size estimated by CT was: 13.5 ± 5.7 cm. The evaluation of the extent of loco-regional recurrence and distant metastasis was positive in two cases with presence of liver and kidney metastases in one case, pulmonary liver metastases in an another case. All these patients were operated. The anatomopathological examination confirmed the diagnosis of adrenocortical carcinoma with a Weiss score ≥ 3 (from 3 to 9). In two cases, the tumor was classified stage II, for the rest it was classified stage III according to the classification of the ENSAT. In the postoperative period, one woman received a chemotherapy treatment and is currently on Lysodren. The clinical and biological evolution is good for two cases, stable for one case, dark for another case with appearance of secondary locations and peritoneal carcinomatosis.
Conclusion
The ACC is a rare agressive tumor with poor prognosis Therefore, every adrenal mass should be explored to not under estimate this fatal diagnosis. The standard treatment is surgery associated with Lysodren, to improve and increase survival.

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EP21

Primary hyperaldosteron detecting among the patients with essential hypertension

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Objective
Diagnosis of primary hyperaldosteron in patients with malignant arterial hypertension.
Materials and methods
The study included 125 patients with hypertension (68 men, 57 women, ages 16–74). All patients underwent biochemical hormonal analyzes of blood and ECG, MSCT. All patients tested ARS, out of 125 in 18 patients with ARS $>$ 30. Patients with primary hyper aldosteronism 18 of them women 7, men 11, patients age 34 ± 8.8 years, hypertension for 3.9 years (1–23), SBP-189.5 ± 22.3 mm.rt.st. DBP-118.5 ± 19.1 mm.rt.st, in all these patients, ARS averaged 74.6 (31.16–330.6), from the biochemical indicators of blood potassium 3.75 ± 0.33, creatine blood-92.8 ± 10.3 (mmol/l). In our sample of patients with hypertension, the prevalence of PGA was found to be 14.4%. Of 18 patients, 60% were diagnosed with left ventricular hypertrophy on ECG and 5 patients with Q-T lengthening at leads V1 and V2. Also in 5 patients, the level of potassium concentration in the blood plasma was <3.6 mmol/l. Regression analysis showed a linear dependence of the increase in SBP from the level of aldosterone, so when the level of aldosterone in the blood increases by 10 pg/ml, SBP increases 2.37 mm Hg. Pearson's correlation analysis revealed a strong statistical significance of SBP from aldosterone level: $r = 0.5211$ ($P < 0.05$).
Conclusion
1. When determining potassium in the blood showed that of 18 patients in 5 with hypokalemia, hyperaldosteronism was detected, in 13 patients with normalization there was hyperaldosteronism. A reliable method of diagnosing PHA is the determination of APC.
2. Regression analysis showed a linear dependence of the increase in SBP from the level of aldosterone, so when the level of aldosterone in the blood increases by 10 pg/ml SBP, 2.37 mm Hg raises.

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EP22

The rare outcome of pituitary adenoma treatment

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Abstract
A 41-year-old woman admitted Ginekological Clinic to surgical intervention due to ovarial enlargement. It was suspected diagnoses of Acromegalia according to the clinical manifestations: amenorrhea, headache, dizziness, enlarged phalangeal digits. nose. The patient underwent laboratory and instrumental investigations. MRI showed the pituitary adenoma ($1.4 \times 1.0 \times 1.0$ cm), GH, Prolactin and TSH were sharply increased, Ultrasound revealed remarkably enlarged ovaries (Right-53.4 cm^3, left 50.3 cm^3). The patient was diagnosed with: Acromegaly and Hyperprolactinemia. It was decided to start treatment with a one-month Radiotherapy, which was followed by Bromocriptine. and Levothyroxine. Furthermore, the patient had autoimmune thyroiditis, primary Hypothyroidism with multinodular goiter and Insulin resistance, which is why Metformin and Levothyroxine were also prescribed. During the 12 yaers dose of Bromocriptine has been reduced and at last, removed six months ago. The sizes of ovaries have remarkably reduced–right one from 53.4 cm^3 to 7.2 cm^3 and left one from 50.3 to 8.5 cm^3. MRI imaging shows only residual disorders in Sella Turcica. There is no increase in pituitary Hormones.
Conclusion
This is rare outcome of Pituitary adenoma treatment The patient is under observation, This case outlines, that in some patients radiotherapy + conservative treatment can be as effective as Surgery.

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EP23

Case report: patient presenting with tumor on the left adrenal gland

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The aim
To study the peculiarities of the clinical manifestations of hypercortisolism in the case of a mass formation in the adrenal gland.
Materials and methods
Children's Endocrinology of the Republican Specialized Scientific and Practical Medical Center of Endocrinology was hospitalized a boy 5 years old with a diagnosis of extensive tumor of the left adrenal gland.
Results
At the time of the examination, the patient complained with overweight, increased appetite, lethargy, increased blood pressure, and recurrent headaches. Sick for 1.5 years, the age of onset of obesity is 3.5 years. Physical activity is low. Parents are relatives. The onset of the disease they associate with the time of the injury of the arm, after which it became inactive. Complaints of headaches began, blood pressure increased to 130–140/80–90 mmHg; ultrasound revealed a lesion of the left adrenal gland.The general condition of moderate severity, lethargy, speech is fuzzy. The skin is dry, pale. Red-ruddy face, eyelids and bodies, hyperkeratosis on the elbows, knees, round face, fatigue and poor concentration. Excessive deposition of subcutaneous fat in the abdomen and chest with relatively thin limbs. Fat pads over the clavicles and in the area of the VII cervical vertebra (climacteric hump). According to the results of bone radiography, the child is 3–3.5 years old, with a chronological age of 4 years and 9 months. According to the biochemical blood test: ACTH-5.5 ng/ml: Cortisol - 153.0 nmol/l: Cortisol - 149.0 nmol/l (12:00 p.m), cortisol 225.7 nmol/l (6:00 p.m). Recommended: tab. Ketokonazole 200 mg 1 time per day before surgery; Tab. ACE inhibitor 5 mg 2.5 mg 2 times a day; Control blood pressure monitoring every 3 hours.
Conclusion
The given example of this clinical case showed the features of the course of ACTH independent Cushing's syndrome, corticosteroma. It was recommend consulting an oncologist with the aim of solving the surgical treatment of adrenal tumor surgery. Cushing's disease is a rarity that can be difficult to diagnose due to the significant number of varied pathologies indicated by its signs and symptoms.

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Calcium and Bone

EP24

A case of benign hypocalciuric hypercalcemia in a HLA B 27 positive ankylosing spondylitis patient

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Abstract
Familial benign hypocalciuric hypercalcemia (FHH) is a rare AD disorder exhibiting benign hypercalcemia, inappropriately normal PTH levels and relative hypocalciuria, thus reflecting partial resistance to the normal effects of extracellular calcium on parathyroid glands and kidneys. We report a 74-year-old women, with no fracture history, with bisphosphonate osteoporosis treatment (2011-present), with HLA B 27 positive ankylosing spondylitis. The clinical exam revealed chronic joint pain, inflammatory lumbar pain, low spinal mobility, dorsal kyphosis and positive sacroiliac joint maneuvers. Calcemia levels were between 10.2-11.2 mg/dl, with normal PTH level after compensating the vitamin D deficiency. Urinary calcium/creatinine ratio was 0.0016 mg/dl and 24 h urinary calcium was 0.93 mg/kg per day. Parathyroid ultrasound was normal. Densitometry showed a good response to bisphosphonates with most recent lumbar BMD $= 0.701$ g/cm^2, a T-score $= -2.4$ S.D. and left total hip BMD $=$ 1.189 g/cm^2, a T-score $= -0.3$ S.D. Her son is also presenting with asymptomatic hypercalcemia and a positive HLA B27, without evidence of spondilytis. We are discussing the association of two genetic illnesses, with an active form of ankylosing spondilytis diagnosed at a female patient and at an older age than usual.

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EP25

Treatment sequence after teriparatide

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Introduction
Teriparatide is prescribed for severe osteoporosis based on national protocols. The osteoanabolic drug is followed by an anti-resorbtive medication.
Aim
We analyze the treatment sequence options after Teriparatide in patients who finished the 2-year protocol or were early droppers.
Material and method
This is a real life study based on Romanian protocol of Teriparatide for severe primary or/and glucocorticoid osteoporosis (subcutaneous 20 μg/day, for 2 years, once in a lifetime). The inclusion and exclusion criteria are the specific features for free reimbursement of the drug in the country in addition to general approach of the medication. SPSS was used for statistical analyze (the cut-off of significance is $P < 0.05$).
Results
28 patients (female/male ratio is 27/1) of 66 years (median, ranges between 47 and 83 years) were offered Teriparatide. First time users of specific anti-osteoporotic drugs are one of ten. 16 subjects finished the 24 months protocol, while 12 persons were early droppers (before 2 years). No statistical significance was found between Bone Mineral Density at central DXA, neither age, number of fractures, of time of prior exposure to specific anti-osteoporotic medication before osteoanabolic medication between two groups. 84% of all subjects continued with bisphosphonates, and 80% of all were offered non-oral drugs. The drug sequence following Teriparatide was: 28% zolendronate, 4% risendronate, 16% alendronate, 36% ibandronate (regardless the route of administration), and 16% denosumab.
Discussion
As limits of the study we mention the size of the cohort and the need for longitudinal data.
Conclusion
Based on our observations, the treatment sequence following Teriparatide includes mostly bisphoshonates and injectable medication.

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EP26

Measurement of daily calcium intake by students of 2nd year education of master degree of the tashkent pediatric medical institute

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Calcium is an important part of bone tissue. Appropriate calcium intake is necessary for maintenance of healthy bones. In accordance with international recommendations, people at age from 19 to 50 have to consume 1000 mg of calcium daily. For the measurement of the level of the calcium intake we develop worksheet, which contains denomination of different foods and products, with their calcium content (mg), which usually are consumed. Purpose: Measurement of calcium intake by students of 2nd year education of master degree of the Tashkent Pediatric Medical Institute (TPMI). Materials and Methods: We developed worksheet which contains denomination of foods and products with their average portion and the calcium content of portion of each denomination according to data of International Osteoporosis Foundation (IOF). Worksheets are filled by 30 students of 2nd year education of master degree of the TPMI. 8 students was male with the average age 26.8 year and 22 students was female with average age 26.7 year. Results: Statistical analysis of filled worksheets showed that 16 students (53.3%) consume less than 1000 mg of calcium daily. Other 14 students (46.6%) consume more than 1000 mg of calcium daily. Also now known, that average student who are consume less than 1000 mg of calcium eats 3.7 times lesser of milk, 9.5 times lesser of yoghurt, 12.2 times lesser of chees, 6.2 times lesser of kefir, 4.8 times lesser of sour cream and curd, 12.8 times lesser of brinsen chees than average student who consume more than 1000 mg of calcium daily. Conclusion: Measurement of calcium intake by students of 2nd year education of master degree of the TPMI showed that half of students (16 students) consume less than 1000 mg of calcium daily and also eat less milk products than another half (14 students) who consume more than 1000 mg of calcium daily.

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EP27

Hypertension during primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism is associated with an increased prevalence of high blood pressure. The objective of our work was to evaluate the prevalence and blood pressure profile in patients with primary hyperparathyroidism.
Methods
Retrospective study conducted at the Department of Endocrinology Diabetology and Metabolic Diseases of the University Hospital of Casablanca for a period of 4 years (2014–2018) including all patients followed up for primary hyperparathyroidism.
Results
25 patients were followed during this period for hyperparathyroidism. The average age was 56.7 years (34–76) with a clear female predominance (84%). 10 had arterial hypertension a prevalence of 40% with an average duration of evolution of 3.75 years. It pre-existed before the diagnosis of hyperparathyroidism. It was moderate in the majority of cases with an average tension of 14/10 cmHg. One patient was on dual therapy, another did not observe treatment and the rest monotherapy. They were all dyspnea on exercise and two patients had cardiac arrhythmias on the electrocardiogram, cardiac echocardiography showed good left ventricular function, one patient had ischemic cardiomyopathy and another had dilatation of the ascending aorta. No ocular repercussions were observed in our cohort and 50% with a moderate insufficiency with an average GFR of 70 ml/min, one patient had already had a cerebrovascular accident.
Conclusion
During primary hyperparathyroidism, hypertension appears moderate, rare complications and balanced tension monotherapy. Our work emphasizes the interest of systematically screening for blood pressure disorders, especially arterial hypertension, in affected individuals.

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EP28

The impact of gastrointestinal diseases on bone quality: description of two cases

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Introduction
Diseases of the gastrointestinal tract may have on effect on bone quality manifesting either as osteomalacia or as osteoporosis. Gastritis may have an effect on bone as it requires long term treatment with proton pump inhibitors. Gastrointestinal neoplasms may be accompanied by nutrient malabsorption. These diseases may also be related with vitamin D deficiency.
Aim
The aim was to describe two cases of gastrointestinal diseases, namely chronic gastritis and colon cancer who developed osteoporosis.
Cases description
The cases of two patients with gastrointestinal disorders who developed vitamin D deficiency and osteoporosis and osteoporosis, respectively, are described. The first patient, a female aged 84 presented with epigastric pain. Gastroscopy was performed and chronic gastritis was diagnosed. Laboratory investigations

revealed levels of 25(OH)D_3 15 ng/ml. Bone mineral density of the left femur was measured and revealed a T score of −3.9. The second patient, a female aged 85 presented with right flank pain. Laboratory investigations revealed anemia. Gastroscopy was performed and showed gastritis. Radiology of the abdomen revealed a large malignant colon cancer in the area of the sigmoid. Bone mineral density of the left femur showed a T score of −3.1. In the first case gastritis was managed conservatively and vitamin D and antiosteoporotic treatment were administered. In the second case the colon cancer was surgically removed and antiosteoporotic treatment was given.

Conclusions

The cases of two patients with gastrointestinal disorders are described who presented with vitamin D deficiency and osteoporosis. Gastrointestinal disorders may have an effect on bone quality. They may cause malabsorption, due either to nutrition disorders or to loss of appetite and they may require long term treatment with proton pump inhibitors, which causes bone loss. Additionally, treatment for osteoporosis may be a problem, as some of the drugs for osteoporosis may be accompanied by adverse effects from the gastrointestinal tract, in particular, gastritis. In conclusion, patients with gastrointestinal disorders should be evaluated for osteoporosis and vitamin D deficiency.

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EP29

Hypertension, diabetes, cognitive impairment, renal cancer, polymyalgia rheumatica and chronic hemodialysis treatment: so many diseases or just only one?

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Introduction

Hypertension and diabetes are common causes of kidney failure leading to hemodialysis treatment. Conn syndrome in hemodialysis patients is not very common. Because of it we intend to present a man with hypertension since many years, more and more difficult to treat who in age of 48 years presented with type 2 diabetes. Both diabetes and hypertension were bad controlled (HbA1C = 9.6%) and complications in form of retinopathy, coronary disease and atrial fibrillation occurred. Hypertension control was possible only with multi drug therapy (ACE-I, ARB, beta-blocker, a-blocker, clonidine, loop diuretics and spironolactone). In this time the diagnosis of Conn syndrome was done. The patient refused an operation, while conservative therapy was not sufficient to prevent kidney failure. Additional unpleasant consequence of chronic kidney disease was the necessity for discontinuation of spironolactone. There was also nephrotic range of proteinuria observed. The next very big problem was the occurrence of cancer of the left kidney. After nephrectomy, the kidney function deteriorated slow but consequent and dialysis were necessary. After few months we observed polymyalgia rheumatica which was successfully treated with steroid. Despite dialysis therapy, probably as a consequence of hyperaldosteronism the next complication was atherosclerosis with mild cognitive impairment. We observed improvement after beginning of dialysis. Unfortunately, the patient died 12 month from beginning of dialysotherapy because of severe sepsis.

Conclusion

We presented a men with multimorbidity which in a significant part (whole?) is associated with the Conn syndrome.

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EP30

Abnormalities of glucidic metabolism during hyperparathyroidism

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Introduction

Patients with hyperparathyroidism have impaired carbohydrate metabolism characterized by insulin resistance, hyperinsulinemia and glucose intolerance. The objective of our work was to evaluate the prevalence of different carbohydrate metabolism disorders in patients with hyperparathyroidism and the impact of parathyroidectomy in improving glycemic counts.

Methods

Retrospective study conducted at the Department of Endocrinology Diabetology and Metabolic Diseases of the University Hospital of Casablanca for a period of 4 years (2014–2018) including all patients followed up for primary hyperparathyroidism.

Results

25 patients were followed during this period for hyperparathyroidism. The average age was 56.7 years (34–76) with a clear female predominance (84%). The reason for consultation found was hypercalcemia in 84%. The main etiology of hyperparathyroidism was represented by a parathyroid adenoma in 95% of cases. Among these 25 patients, 5 had a disorder of glycoregulation including type 2 diabetes or a prevalence of 20%. Two out of five diabetic patients were operated on, following the removal of the parathyroid adenoma, we noted a significant improvement of the postoperative glycemic figures and also compared to the control group of the 3 non-operated diabetic patients.

Conclusion

During hyperparathyroidism, carbohydrate homeostasis may break down, leading to abnormal carbohydrate metabolism, the main finding of which in our work was type 2 diabetes. Our work highlights the importance of systematically detecting glycoregulation disorders, particularly diabetes in affected patients.

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Diabetes, Obesity and Metabolism

EP31

Interrelation between obesity, metabolic syndrome and molecular-genetic mechanisms of their formation

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Introduction

Metabolic syndrome (MS) is a disease that develops in obesity in adult patients with the development of numerous metabolic and vascular disorders. In patients with MS, the risk of developing cardiovascular diseases is increased compared to the general population by 1.78 times as a whole and 2.25 times in women. Currently, the number of overweight children and the development of metabolic complications such as fatty liver, hypertension, and type 2 diabetes are increasing. The role of genetic factors in the development of obesity and metabolic syndrome is not excluded.

Aim

The aim was to study genetic markers and chromosomal regions directly or indirectly associated with the obesity phenotype.

Results

Fifty syndromic and 8 monogenic forms of obesity are identified. Complete inactivation of 5 genes - LEP, LEPR, POMC, PCSK1 and MC4R is accompanied by severe hyperphagia and early onset of marked obesity in humans. The share of such hereditary options accounts for no more than 5% of all cases of obesity. The world literature describes 14 cases of complete deficiency of LEP, LEPR - 13, POMC - 7, PCSK1–3 and MC4R - 20 people. The deficiency of BDNF and its high-affinity receptor NTRK2 (TrKb), as well as SIM1, is associated with severe hyperphagic obesity in mice, and the partial defect also causes them to be hyperphagy and obesity. Leptin deficiency (LEP) - has autosomal recessive inheritance. Leptin receptor deficiency (LEPR) - also has autosomal recessive inheritance, similar to the leptin deficiency clinic. However, with a LEPR defect, signs are less pronounced than with LEP, and hypothyroidism is rare. Mutation of the proopiomelanocortin (POMC) gene is an autosomal recessive disorder accompanied by a defect in the anorexigenic action of melanocortin. Mutation of prohormone convertase 1 (PCSK1) is inherited autosomal recessively. The enzyme convertase prohormone 1 (KP 1) cleaves prohormone. A mutation of the 4 R - melanocortin receptor gene (MC4R) is transmitted autosomally dominantly. Melanocortins, as conductors of leptin signals, act through binding to the MC4 receptors. Mutations in the MC4 P gene also cause obesity. >3 mutations in the LEP gene and a series of mutations in the LERP gene that cause severe obesity in homozygotes have been identified. Partial failure of BDNF, NTRK2, SIM1 is accompanied by severe obesity with hyperphagia.

Conclusion

Identification of a large number of genes associated with obesity and the development of MS indicates the polygenicity of these conditions, the relevance of genetic expertise for diagnosis and therapy.

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EP32

Personality traits in the morbidly obese patients awaiting bariactric surgery and in the group of patients who have undergone surgery

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Objectives
To evaluate the psychosocial aspects in a group of patients in follow-up in specific consultation of bariatric surgery prior to the intervention and in a group of patients intervened.
Methods
Cross-sectional study of patients in follow-up in the specific morbid obesity consultation of the University Hospital Puerta del Mar (Cádiz) not intervened and a group intervened and in a group intervened, at 6–12 months of follow-up.
Results
1. Group not intervened: 110 patients were analyzed, of which 68.2% are women, with an average age of 44.63 years. Regarding the level of studies, 30.2% had only primary studies and 47.7% had primary and secondary studies. 32.7% were unemployed and 8.4% were disabled.
2. Group intervened: 88 patients were analyzed, of which 70.5% ($N=62$) are women, with an average age of $45.01+/-8.55$ years. The BMI before the intervention was $47.29+/-5.54$ kg/m^2 being $34.52+/-6.48$ kg/m^2 at present. Regarding the level of studies, 30.2% had only primary studies. 26.7% were unemployed and 15% disabled. The majority (90.7%) has good family support.
Conclusions
The profile of patients in two groups usually presents a basic level of studies - primary and secondary-, relatively frequent in the case of unemployment or early retirement.

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EP33

The effects of metabolic dysfunction (obesity diabetes type II) on the cervical epithelium cytology from Pap test survey

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Abstract
The effects of diabetes type II and obesity on the cervical epithelium reaction were studied on the Georgian population based of Pap-test survey. Goal is to examine the association between obesity, metabolic disorders (diabetes, thyroid dysfunction) and cervical Pap test results. Study group includes 56 patients. According to the Georgian Low, written informed consent was required. From the study population, we used data zf all 56 women aged 23–52 years. The socio - demographic status, level of education (non-high school graduate/ high school graduate), marital status were included. Body mass index was calculated in kg/m^2 and divided as obese (BMI $>$ 30 kg/m^2) or not obese (BMI $\leq$30 kg/m^2) persons. Summarizing results were shown that:
1. obesity is strongly associated with a low grade squamous abnormalities and undetermined significance (ASCUS) (2007 Bethesda system).
2. Hypertension, diabetes, thyroid dysfunctions provoke abnormal Pap. Smears - had history of STDs (Trichomonas vaginalis and genital HSV infection).
3. 22% of the morbid obese women, had a history of primary infertility and significant differences in Pap test results, than women without these associations. In conclusion, our study demonstrates an increased prevalence of abnormal Pap test (LSIL), high-risk of infertility and opportunistic endometrial infection compared with nonobese women.

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EP34

Prevalence of high blood pressure in a group of Tunisian obese

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The progression of obesity around the world is largely responsible for the high blood pressure (HBP) most commonly associated with this condition. This morbid association leads to an increase in morbid cardiovascular mortality. The aim of our work was to study the prevalence of hypertension in a group of Tunisian obese people. This is a descriptive cross-sectional study conducted at the Obesity Unit of the Tunis Institute of Nutrition about 100 obese patients who visited between January and March 2018. Medical history taking and a complete clinical examination have been realized for all these patients. The average age was 45.08 ± 13.93 years with a clear female predominance of 88%. The average body mass index was 38.95 ± 5.72 kg/m^2. It was class 3 obesity in 44% of cases. Our patients were smokers in 13% of cases and sedentary in 60%. Mean systolic and diastolic arterial pressures were 12.05 ± 1.75 cmHg and 7.40 ± 0.96 cmHg, respectively. The prevalence of HBP was 34%. They were on monotherapy in 33.3%, dual therapy in 56.7% and tritherapy in 10% of cases. We also found high blood pressure figures in unknown hypertensive patients in 10% of cases. The prevalence of HBP in obese patients is increasing exponentially as the prevalence of obesity and cardiovascular disease has increased. Weight reduction and initiation of antihypertensive treatment are the key elements of its management.

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EP35

Efficacy of combination of ezetimibe and rosuvastatin in patients with dyslipidemia in type 2 diabetes mellitus

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Aim
The increase in the prevalence of type 2 diabetes is a major public health problem worldwide. In patients with diabetes, the risk of developing CVD is greatest. Atherosclerotic diseases are the main cause of death in type 2 diabetes. Thus, ischemic heart disease, as a macrovascular complication of diabetes is the main cause of death in patients with diabetes, with 90% of patients suffering from type 2 diabetes. A modern strategy for treating patients with diabetes involves the early administration of lipid-lowering drugs. The first choice is statins. Many patients with type 2 diabetes currently receiving statins, the achievement rate of the target low density lipoproteins (LDL)level remains low with statin monotherapy. Thus the addition of ezetimib to the statins and study the efficacy of lipid- lowering effects in comparison with monotherapy is the main aim of the study.
Methods
The study included 82 patients with Diabetes Mellitus with level of lipoproteins of low dencity more than 7.0 mmol/l under treatment with rosuvastatin 5 mg (Rozulip). The patients were randomly divided into two groups. Allocated to a group that received add-on therapy with ezetimibe at 10 mg/day-Rozulip plus 5/10 (combination group, $n=42$) or an increase of the rosuvastatin dose to 10 mg/day (dose escalation group, $n=40$) and after 10 weeks they were compared.
Results
In the group under treatment with Rozulip plus (R + E) the percent change of LDL was -35% and -12% under Rozulip treatment. In both groups, there was a significant decrease in the levels of LDL, but the greater percent changes were in the combination group.
Conclusions
Combination of rosuvastatin and ezetimibe achieved improvement of lipid levels in type 2 Diabetes Mellitus patients rather than monotherapy with rosuvastatin. According to results suggesting that this combination could suppress the progression of atherosclerosis.

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EP36

Diabetic ketoacidosis

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Diabetic ketoacidosis is a well- known and a major acute complication of diabetes, mainly of the patients with type 1 diabetes. It is not uncommon in patients with type 2 diabetes. This situation is characterised by the presence of serum ketones greater than 5 mEq/l and ketonuria, a blood glucose level greater than 250 mg/dl, a blood PH less than 7.3 and a serum bicarbonate level of less than 18 mEq/l. There are different factors that cause ketoacidosis. DKA can be the

initial presentation of diabetes mellitus. But there are other precipitating factors like infections which are one of the most common causes, acute myocardial infarction, cerebrovascular event or postoperative stress. Noncompliance of the patient is a major cause of DKA. The patients with DKA are dehydrated, they have a characteristic smell of acetone on the breath and a Kussmaul respiration. DKA Other symptoms are thirst, polyuria, nausea, vomiting, abdominal pain. Our prospective study includes 50 patients admitted in Emergency and Endocrinology, Diabetology and Metabolic Disorders in 'Mother Teresa' Hospital in Tirana during the last year with the diagnosis of diabetic ketosis or ketoacidosis. Out of 50 patients, 30 of them were with type 1 of diabetes and the others with type 2. 18 of them had DKA as the initial presentation of diabetes, 10 of them suffered from different infections like urinary tract infections or pneumonia. On the other hand, noncompliance to the treatment is still a major cause of DKA, in our study it is present in 12 patients. Nausea and vomiting were the most common symptoms (in 70% of patients). Mean fluid requirement for clearance of urinary ketones was 10 litres and mean insulin dosage was 130 units. One of the patients who came with blood PH = 7, serum bicarbonates = 7 mEq/l was rehydrated with 10.5 litres of liquids (NaCl or Glucose) and treated with 146 UI Insuline for 36 hours till the clearance of urinary ketones. So diabetic ketoacidosis remains an acute, life threating situation with heterogeneous clinical presentation. It is very important the early diagnosis and treatment to minimise the risk of morbidity and mortality.

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EP37

Abstract Unavailable.

EP38

Lipid profile and cardiovascular risk in psoriatic arthritis

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Introduction
Psoriatic arthritis (PsA) is a chronic systemic autoimmune disorder. Currently, various biologic agents are administered in PsA patients, improving significantly disease manifestations as well as quality of life. Biologic treatment may have an effect on lipid profile and the cardiovascular risk in the disease.
Aim
The aim was to follow-up a group of PsA patients and to evaluate comorbidities, lipid profile and cardiovascular risk and the effect of treatment with biologic agents on these parameters.
Methods
Disease activity was estimated using the DAPSA before and after treatment. Blood total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were measured at baseline and after treatment at 3, 6 and 9 months. The 10-year cardiovascular risk was evaluated using the Heart Score Greece, at baseline and after 3, 6 and 9 months on treatment with biologic agents.
Results
The BMI of the patients was 29.01 ± 0.65 before treatment and 28.63 ± 0.6, 28.37 ± 0.6 and 29.39 ± 0.87 after treatment at 3, 6 and 9 months, respectively. Disease activity decreased very significantly after treatment with biologic agents in PsA patients, the DAPSA score decreasing from 27.56 ± 0.65 (mean $\pm$ SEM) before treatment to 12.56 ± 0.40, 5.76 ± 0.38 and 4.43 ± 0.57 at 3, 6, and 9 months after treatment, respectively ($P < 0.001$, Student's t test). Total cholesterol decreased from 231.56 ± 6.23 mg/dl before treatment to 202.91 ± 3.96 mg/dl, 188.38 ± 4.48 mg/dl and 171.29 ± 6.89 mg/dl after treatment at 3, 6 and 9 months, respectively ($P < 0.001$). HDL cholesterol increased from 50.62 ± 2.07 mg/dl before treatment to 55.26 ± 1.09 mg/dl, 56.03 ± 0.98 mg/dl and 57.57 ± 1.04 mg/dl after treatment, at 3, 6 and 9 months, respectively ($P < 0.001$). LDL cholesterol decreased from 154.47 ± 5.74 mg/dl before treatment to 139.61 ± 4.90 mg/dl, 128.21 ± 5.15 mg/dl and 92.71 ± 5.96 mg/dl after treatment at 3, 6 and 9 months, respectively ($P < 0.001$). Triglycerides were 152.03 ± 9.26 mg/dl before treatment and decreased to 132.32 ± 5.42 mg/dl, 121.05 ± 4.52 mg/dl and 95.65 ± 8.14 mg/dl after treatment at 3, 6 and 9 months, respectively ($P < 0.001$). The Heart Score Greece decreased from $4.35 \pm 0.006\%$ before treatment, to $3.71 \pm 0.005\%$, $3.5 \pm 0.004\%$ and $2.8 \pm 0.005\%$ after treatment, at 3, 6 and 9 months, respectively ($P < 0.001$).
Conclusions
It appears that in PsA disease activity decreases very significantly after treatment with biologic agents, whereas the lipid profile and the heart disease risk is significantly improved.

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EP39

Lipid profile changes during menopausal transition

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The adult female life could be divided into three broad phases: reproductive, perimenopause and postmenopause. The perimenopause starts 2 years before last bleeding and the postmenopause begins 12 months after amenorrhea (Harlow SD y Group 2012). Cardiovascular disease is the main cause of mortality in postmenopausal women and the factors that increase cardiovascular risk are well known but there is no evidence of relationship between menopause and cardiometabolic changes. Some results show metabolic variations during menopause in Chinese women but Spanish data are insufficient to determine an association between metabolic changes and menopausal transition. The main objective of this study was to evaluate the changes at the lipid profile in women that are in transition from perimenopause to postmenopause. This is a retrospective observational study of women who visited the Gynaecologist at Quiron hospital in Madrid from 2007–2018 years to consult about menopause or menopausal symptoms. Women were included if they had at least one analytic report with glucose and lipid profile (total cholesterol [TC], cholesterol-Low Density Lipoprotein [c-LDL], cholesterol-High Density Lipoprotein [c-HDL] and triglycerides [TG]) data. The information was collected anonymized from the hospital database. Women were classified according their last bleeding day on perimenopausal or postmenopausal following the 2011 Stages of Reproductive Aging Workshop. 275 women were included in the study; 242 postmenopausal and 33 perimenopausal. The menopause was natural on 85.95% and the median age of menopause was 50.0 years old (IQR = 5.0) When analysing cardiovascular risk factors, 24.26% were smokers, 4.00% were diabetic, 14.55% had hypertension and 23.27% presented dyslipidaemia. Regarding the treatments 4.73% were receiving an antidiabetic, 20.73% a lipid lowering therapy, 13.82% an antihypertensive and 15.64% an antiosteoporotic drug. At the moment of the analytic report women were 55 ± 13.0 years old; 1,731 (82%) reports were from postmenopausal women and 381 (18%) from perimenopausal with a mean of 7.68 reports/women. When comparing lipid profile, postmenopausal women had a significant lower c-HDL (67 mg/dl vs 62 mg/dl; P-value < 0.001) and a significant higher c-LDL (118.6 mg/dl vs 133.9 mg/dl; p-value < 0.001); TC (204.1 mg/dl vs 215.5 mg/dl, P value < 0.001) and TG (74 mg/dl vs 87 mg/dl; P-value < 0.001). These preliminary results showed that there exists a change on lipid profile during the menopausal transition.

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EP40

Afraid that your prediabetic patients may develop type 2 diabetes with statins? Give red yeast rice + berberin a try!

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Aim
To establish the effect of a supplement containing 250 mg red yeast rice extract, 525 mg berberine and 50 mg coenzyme Q10 on insulin sensitivity in patients with hypercholesterolemia and prediabetes.
Methods
For this open, uncontrolled study, patients of age 30–75 years, with hypercholesterolemia (LDL cholesterol >130 mg/dl and triglycerides <300 mg/dl), and prediabetes without overt cardiovascular disease, untreated in the previous 6 months were recruited. Insulin sensitivity was estimated by the HOMA2 calculator (https://www.dtu.ox.ac.uk/homacalculator/), at baseline and after 2–4 months of supplementation with the referred supplement once daily.
Results
29 patients were recruited, age 57.6±10.9 years, 16 women (55%), No patients were lost to follow-up, but only 26 (90%) of the patients reported adequate compliance (>80%). None of the patients reported adverse effects attributed to the supplement, or had AST, ALT or CK > 3× upper normal limit. None of the patients developed type 2 diabetes, and 4 of them (14%) no longer maintained criteria for prediabetes. The HOMA2 Insulin Resistance Index was significantly reduced and the full results are presented in Table 1.
Conclusions

Table 1

Parameters	Baseline	After supplementation	Change %	*P*- value
HOMA2-IR index	3.72±0.7	2.95±0.6	−22%	< 0.01
Fasting Insulin (mU/l)	13.7±3.6	11.4±3.7	−17%	< 0.01
Fasting glycemia (mg/dL)	112±10	106±7	−5%	NS
HbA1C (%)	5.9±0.3	5.6±0.3	−5%	NS
LDL-cholesterol (mg/dL)	172.2±33.6	133.5±21.9	−21%	< 0.001
Total cholesterol total (mg/dL)	254.4±47.9	215.3±38.6	−15%	0.008
HDL-cholesterol (mg/dL)	39.6±8.1	43.6±9.2	+10%	NS
Triglycerides (mg/dL)	218.8±68.6	191.0±75.3	−13%	NS
AST (U/L)	41.2±10.9	36.8±10.3	−11%	NS
ALT (U/L)	35.8±8.7	33.5±8.9	−6%	NS
GGT (U/L)	65.4±16.2	61.1±15.4	−7%	NS
CK (U/L)	98.1±15.9	98.6±14.4	+0%	NS
Estimated GFR CKD-EPI (ml/min/1.73m^2)	72.5±12.6	74.6±11.6	+3%	NS
BMI (kg/m^2)	28.8±4.8	28.6±4.3	−1%,	NS
SBP (mmHg)	141±10	138±11	−2%	NS
DBP (mmHg)	81±8	80±6	−1%	NS
HR (bpm)	76±7	77±9	+1%	NS

Supplementation with red yeast rice extract, berberine and coenzyme Q10 in patients with hypercholesterolemia and prediabetes significantly reduced their total and LDL-cholesterol, as expected, without tolerance issues. Progression to type 2 diabetes was not observed. The patients were clearly insulin resistant at baseline, with high HOMA2 index, but their insulin resistance was significantly reduced with the supplementation. This effect could be expected to reduce their long term risk of progression to type 2 diabetes.

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EP41

Characterization of essential hypertension vs secondary hypertension in late childhood and adolescence: Experience in an outpatient hypertension clinic

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Aim
Description of the differences between patients diagnosed of essential (EH) vs. secondary (SH) hypertension in our Outpatient Hypertension Clinic.
Methods
Review of the Clinical Records and of the relevant literature. Comparisons were made by non-paired t-test in continuous variables and Fisher's exact test in discrete variables.
Results
From 1994 to 2018, 49 patients < 20 years old were referred to our (mostly adult) Clinic for hypertension workup and treatment; 22 (45%) were diagnosed of SH, (16 primary aldosteronism, 2 glomerulonephritis, 2 arterial renal dysplasia, 1 paraganglioma, 1 aortic coarctation), and 27 (55%) of EH by exclusion.
Gender: 13 female, 9 male (SH); 11 female, 16 male (EH); $P=0.2563$
Age (years): 14.9+3.2 (SH); 16.1+2.5 (EH); $P=0.1471$
BMI (Kg/m^2): 18.9+2.4 (SH); 27.8+8.4 (EH); $P < 0.0001$
SH group: 2 people overweight, none obese; EH group 14 overweight, 8 obese (3 morbidly); $P < 0.0001$ for overweight + obesity, $P=0.0056$ for obesity, $P=0.2423$ for morbid obesity.
Prediabetes: 1 (SH); 6 (EH); Diabetes: None (SH); 1 T1DM +4 T2DM (EH); $P < 0.0001$ for dysglycemia, $P=0.0561$ for DM.
Fasting glucose (mg/dL): 79+8 (SH); 98+15 (EH); $P < 0.0001$
HbA1C (%): 4.9+0.4 (SH); 5.8+0.5 (EH); $P < 0.0001$
$HOMA_2$: 2.5+0.4 (SH); 4.6+1.8 (EH); $P < 0.0001$
eGFR (ml/min/1.73 m^2): 78.6+15.4 (SH); 102.0+31.4 (EH); $P < 0.0025$
Total cholesterol (mg/dL): 168+15 (SH); 216+31 (EH); $P < 0.0001$
HDL-cholesterol (mg/dL): 55+7 (SH); 36+9 (EH); $P < 0.0001$
LDL-cholesterol (mg/dL): 89+9 (SH); 133+21 (EH); $P < 0.0001$
Triglycerides (mg/dL): 118+5 (SH); 234+106 (EH); $P < 0.0001$
AST (IU/L): 23+6 (SH); 38+9 (EH); $P < 0.0001$
ALT(IU/L): 18+5 (SH); 35+8 (EH); $P < 0.0001$
GGT (IU/L): 29+4 (SH); 67+15 (EH); $P < 0.0001$
PCR (mg/L): 0.4+0.1 (SH); 2.8+1.2 (EH); $P < 0.0001$
Target organ damage: 6 low eFGR +3 CVD (SH); 1 low eGFR (EH); P=0.0027 (globally), P=0.0946 (low eGFR).
Conclusions
Near half of the hypertensive patients in this age group had SH, mostly primary aldosteronism, emphasizing that hypertension in this age group requires diagnostic workup. EH in this age group is associated with the 'metabolic syndrome' profile, with overweight and obesity, dysglycemia, dislipidemia, liver enzyme profile suggesting steatosis, and low-grade chronic inflammation. The prevalence of target organ damage was higher in the SH group.

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EP42

High level hypertriglyceridemia fluctuation

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Introduction
Hypertriglyceridemia (hyperTG) may increase the risk of cardiovascular disease and values above 1000 mg/dl are a risk factor for pancreatitis, including non-fasting measurements. The American Heart Association suggested that providers could use nonfasting triglycerides >200 mg/dl to identify hyperTG states. When an elevated result is observed, a fasting triglyceride measure may be reassessed, with exception for extreme levels (for example approximately 1000 mg/dl), when there is no need for repeat of fasting lipids prior to treatment.
Clinical case
Male, 41 years old, heavy smoker, medicated with prednisolone 5 mg/day for eczema, without other known diseases. Recent routine blood tests with hyperTG of 2714 mg/dl (with milky serum), hypercholesterolemia (388 mg/dl), without alteration of the hepatic profile, glycemia of 99 mg/dl and leukocytosis (11930×10^6/L). No family history of hyperTG. Asymptomatic, with no changes to the physical exam, with body mass index of 24.8 kg/m^2. Copious meals and alcohol abuse in the past 2 days, although with fasting of 12 hours previous to testing.

Reevaluation of blood tests 15 days later, after diet, alcohol restriction and maintaining prednisolone, the patient had no hyperTG (69 mg/dl), with hypercholesterolemia (213 mg/dl), hyperlipidemia (154 mg/dl), leukocytosis (15600×10^6/L), neutrophilia (9980×10^6/L), protein electrophoresis, total proteins and albumin without alterations, euthyroidism.

Discussion

Normally the triglyceride (TG) value reach a peak 3 to 6 hours after a high fat meal and declines to baseline after 10 hours of fasting. However, alcohol consumption increases the hepatic synthesis of fatty acids, decreasing their oxidation, leading to the production of TG. Thus, excessive alcohol consumption associated with high fat meals previous to blood tests may explain transient hyperTG in the first analytical evaluation. In addition, a concomitant dose of corticosteroids also increase TG, and the combination with alcohol consumption may have contributed to such a significant increase. In the second evaluation, the patient complied with low fat meals, avoiding alcohol consumption in the previous days, which may have contributed to TG value normalization without medication.

Conclusion

While some components of the lipid profile (total cholesterol and high-density lipoprotein cholesterol) are not affected by food, others, particularly the level of TG, may be. Although the risk for pancreatitis increases significantly with TG levels >1000 mg/dl, the background on which the measurement is done should be assessed, and if needed, TG levels should be reassessed, as shown.

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EP43

A diagnosis challenge: endogenous hyperinsulinism and negative localisation tests: case report

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Introduction

Persistent hyperinsulinemic hypoglycemia may be caused either by a solitary tumor of the pancreas secreting excessive amount of insulin, known as insulinoma or, rarely, by nesidioblastosis. Nesidioblastosis is a rare cause of persistent hyperinsulinemic hypoglycemia in adults.

Methods

We describe the case of a 25-year-old male patient who was referred to our clinic for repeted hypoglycemia episodes.

Results

Our patient described several fasting episodes of hypoglycemia (less than 30 mg/dl) in the past months. Coinciding with these episodes he presented trembling and sweating. He had been diagnosed with epilepsy 2 years earlier and was taking treatment with levetiracetam and valproic acid. He had gained 12 Kilos recently. We performed a 72-hour-fasting test with confirmation of endogenous hypoglycemia after 6 hours of fasting. Suspecting an insulinoma we performed several imaging tests with negative results (somatostin receptors scintigraphy, CT scan, MRI, echoendoscopy and 18F-*DOPA PET*/CT). The patient also underwent 2 intra-arterial selective calcium test procedures observing increased insulinemia levels in superior mesenteric artery and splenic artery. He was in the meantime taking diazoxide for controlling hypoglycemia with improvement in the number and severity of hypoglycemia episodes but with poor gastro-intestinal tolerance of this medication. Finally we performed an exploratory laparotomy with pancreatic palpation and ultrasound and pancreatic biopsy analysis showing pancreatic tissue with mild increase, in size and number, of islets, compatible with islet hyperplasia B. In a second time the patient underwent corporo-caudal pancreatectomy confirming the suspected diagnosis of pancreatogenous hypoglycemia non-insulinoma (nesidioblastosis of the adult). After surgery our patient has not presented new hypoglycemia episodes and has a good glycemic control.

Conclusion

Nesidioblastosis is a very rare disease of difficult diagnosis but it should be considered in all cases of failure to locate an insulinoma, as this may be presented in up to 4% of persistent hyperinsulinemic hypoglycemia.

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EP44

Feasibility and effectiveness of a low carbohydrate diet in a traditionally high carbohydrate intake population

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Background

India ranks among the countries with a relatively high proportion of calories (71%) from carbohydrates (1). Various types of 'low' carbohydrate diets have had intermittent popularity over the past century, most of which also recommend high intake of animal protein. This would not be suitable for a predominantly vegetarian population (32% of Indians are vegetarian compared with $<5\%$ in Western societies) (2).

Aim

We wanted to test the feasibility and effectiveness of lowering carbohydrate intake in a traditionally high carbohydrate intake population.

Methods

142 overweight or obese people (9 with diabetes) were advised on a 50–70 gms/day carbohydrate, high fiber, moderate fat and protein diet with options to suit both vegetarians and non-vegetarians in our clinic.

Results

We present the data for 41 people who followed up with us for at least 1 return visit, with average follow up ranging from 1–6 months. Reducing the carbohydrate intake lead to significant reduction in weight, BMI and waist circumference. The average reduction in BMI was -1.38 (range -7.5 to $+0.6$). The average reduction in waist circumference was -4.8 cms (range -23 cms to $+8$ cms). Of the 9 people who had diabetes, 2 were on SGLT-2 inhibitors and 6 on metformin. The remainder had either prediabetes or normal glucose tolerance and were on no other medications. In 16 people in whom repeat HbA1C measurements were available, HbA1C dropped by 0.59% in 12/16 (range 0.1 to 1.7), did not change in 3 and increased by 1.6% in 1. In 26 people who had a BP reading on at least 2 occasions, the systolic BP dropped by 0–10 mm Hg. There was no difference in diastolic BP. In 6 people who had repeat lipid profile, Cholesterol (total and LDL-c) dropped along with triglycerides and HDL-c increased.

Conclusions

We have shown the feasibility and effectiveness of initiating and maintaining a low carbohydrate diet in a traditional high carbohydrate vegetarian society. Various parameters of visceral obesity and metabolic syndrome improved significantly. We plan to continue to collect data for a longer period of time to demonstrate long term ability to maintain the diet and weight reduction.

1. http://chartsbin.com/view/1160 (accessed on 03/02/2019)
2. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0110586 (accessed on 03/02/2019)

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EP45

Insulin resistance and metabolic disorders in women with morbid obesity

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Introduction

Metabolic abnormalities are usually linked with obesity. However, a proportion of obese individuals might not be at an increased risk of metabolic complications of obesity and therefore their phenotype can be referred to as metabolically healthy obesity. The aim of our study was to evaluate the metabolic status in women with morbid obesity and to determine its association with insulin resistance.

Methods

In a cross sectional study, we enrolled 50 morbidly obese women. All participants had physical examination and metabolic investigations. Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR) = fasting insulin (uU/ml) $\times$ fasting plasma glucose (mmol/l)/22.5.

Results

The average age of participants was 34.2 ± 7.51 years. They had a mean body mass index (BMI) of 44.53 ± 3.97 kg/m^2 (range: 40–55.58) and a waist

circumference (WC) of 123.38 ± 10.89 cm (range: 100–155). Metabolic syndrome was diagnosed in 96% of cases. The average HOMA index was 4 ± 4.15. Insulin resistance was present in 48% of patients. All cases had metabolic syndrome. BMI ($r=0.34$, $P=0.01$), WC ($r=0.41$, 0.003), Fasting blood glucose ($r=0.37$, 0.007), triglycerides ($r=0.37$, 0.008) and uric acid ($r=0.34$, $P=0.01$) were positively correlated with the HOMA index. Diabetes or prediabetes (OR = 4.8, $P=0.01$) and hypoHDLemia (OR = 2.1, $P=0.006$) were significantly associated with insulin resistance. However the presence of high blood pressure, hypertriglyceridemia, hypercholesterolemia and hyperuricemia were not associated with insulin resistance.

Conclusion

Our results demonstrated a high prevalence of metabolic syndrome and insulin resistance in morbidly obese women. Insulin resistance was significantly associated with diabetes or prediabestes and hypoHDLemia. Thus, adequate management of morbid obesity is mandatory to prevent the occurrence of these complications.

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EP46

Prevalence of non alcoholic fatty liver disease in women with morbid obesity

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Introduction

Obesity related disease complications reduce life quality and expectancy and increase health care costs. Non-alcoholic fatty liver disease (NAFLD) is one of the major complications associated with obesity and is considered to be the hepatic manifestation of the metabolic syndrome. Our objective was to determine the prevalence of the NAFLD and to identify its clinical and biological associated factors in women with morbid obesity.

Methods

This was a cross-sectional study involving 50 women with morbid obesity. Patients with a history of chronic alcoholism, known hepatopthy or taking hepatotoxic drugs have been excluded. Metabolic investigations and liver ultrasound were performed in all participants.

Results

The average age of the participants were 34.2 ± 7.51 years with extremes ranging from 18 to 45 years. Metabolic syndrome and NAFLD were diagnosed in 96% and 70% of cases, respectively. HOMA index (4.8 ± 4.7 vs 2.3 ± 1.7, $P=0.02$), basal insulinemia (19.3 ± 19.8 vs 10.1 ± 7.0, $P=0.02$), Gamma-glutamyl-transpeptidases (γ GT) level (27.3 ± 12.9 vs 20.5 ± 4.8, $P=0.01$) and uric acid level (52.81 ± 13.7 vs 45.92 ± 7.4, $P=0.03$) were significantly higher in patients with NAFLD. However, anthropometric parameters, fasting blood glucose, cholesterol, triglycerides, HDLc, LDLc and transaminases levels were comparable between the two groups. Acanthosis nigricans ($P=0.02$), hyperinsulinemia ($P=0.03$), dyslipidemia ($P=0.04$), and hyperuricemia ($P=0.04$) were significantly more frequent in patients with NAFLD.

Conclusion

Our results revealed a high prevalence of NAFLD among women with morbid obesity. It was essentially associated with insulin resistance and hyperinsulinemia. Therefore a systematic biological and radiological screening for NAFLD is indicated in morbidly obese patients.

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EP47

Clinical and metabolic characteristics in a population of obese tunisian women with polykystic ovary syndrome (pkos)

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Introduction

PCOS is common in Tunisia. It is characterized by the high frequency of clinical and metabolic abnormalities associated with cardiovascular risk. The aim of our work was to describe the clinico-metabolic profile of a Tunisian women population with polycystic ovary syndrome.

Methods

This is a prospective study conducted on 53 Tunisian patients with PCOS, referred by their gynecologist to the Obesity Unit of A departement of the National Institute of Nutrition of Tunis, to take charge of their obesity.Clinical and biological data were collected through careful interrogation and clinical examination and referring to medical records.

Results

The average age was 29.6 ± 3.2 years. 9.4% were active smokers. All patients were obese with an average BMI of 33.6 ± 1.2 kh/m^2. Obesity was visceral in 100% of cases with a mean waist circumference of 96.6 ± 4.2 cm. Menstrual disorders were reported by 84.9% of patients. Clinically, 39.6% of patients had acanthosis nigricans, 75.4% had hirsutism. 35.8% were hypertensive. Dyslipidemia and carbohydrate tolerance disorders were found in 28.3% and 43.3%, respectively. Acanthosis nigricans were significantly correlated with BMI ($P=0.001$), as was hirsutism ($P=0.004$), hypertension ($P=0.019$) and carbohydrate tolerance disorders ($P=0.023$).

Conclusion

Our results are concur with those of the literature concerning the frequency of clinico-metabolic abnormalities in patients with PCOS. The detection of metabolic abnormalities and their management will improve the cardiovascular prognosis of these patients.

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EP48

Assessment of body composition (service experience)

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Purpose

The evaluation of body composition using indirect techniques is used to estimate the nutritional status of patients. The objective of our study was to determine the profile of patients' body composition according to the bioelectrical impedance meter and to study its relationship to body mass index and waist circumference.

Patients and methods

Cross-sectional study, conducted over 9 months from March to December 2018, in the endocrinology department of Ibn Rochd University Hospital of Casablanca, in all patients attending the day hospital. The body composition was interpreted by the OMROM BF 508 impedance meter, according to the standards of use based on WHO recommendations. Statistical analysis made by Spss software version 25.0.

Results

Our series included 200 patients, mean age of 50.22 ± 13.02 years with a sex ratio H/F of 0.6, an average waist circumference of 100.7 ± 23 cm and an average BMI of 30.35 ± 7.08 kg/m^2. The prevalence of overweight and obesity was 19% and 53.5%, respectively. The comorbidities found were diabetes (30%), hypertension (20%) and dyslipidemia (10%). Mean visceral fat (13.66 ± 6%) and mean body fat (38.22 ± 10.5%). The fat mass was increased more (37.5%) in the age group (40-59 years), with a predominance of women (47.5%). Body mass index was strongly correlated with body fat ($P<0.0001$, $r=0.71$), visceral fat ($P<0.0001$, $r=0.57$), and waist circumference ($P<0.0001$, $r=0.83$).

Conclusion

Our work has revealed sedentary problems associated with overweight, which constitute a risk factor for health. The evaluation of this composition could be an option for detecting body functions and their disturbances.

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EP49

Side effects of topical corticosteroids in the treatment of psoriasis: a case report

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Using topical corticosteroids, severe adverse reactions occur very rarely, especially - adrenal insufficiency. We describe the case of a patient who presented adrenal insufficiency using topical GCC. 28 y/o female with a history of mild form psoriasis was treated with topical GCC (DERMOVATE) for about 12 years. Thinned skin, translucent vascular-network all over the body (~6 years), weight gain (+10 kg/12 months) and spontaneous haematomas appeared within the time and progressed. The patient was clinically diagnosed with adernal insufficiency syndrome. Topical steroids were discontinued and she received a daily dose of 15 mg to 20 mg hydrocortisone. After three months, a dose of hydrocortisone was reduced. Exogenous glucocorticoids even in topical form have suppressive effects on hypothalamic cortisol releasing hormone and pituitary adrenocorticotropic hormone.

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EP50

Diabetes secondary to pancreatectomy an inevitable complication

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Introduction
Patients undergoing extensive pancreatic resection for benign pancreatic disease are subject to significant metabolic complications and may develop insulin-dependent diabetes that is difficult to balance due to the lack of a counter-regulatory mechanism. Diabetes appears classically after removal of more than 80% of the pancreas, especially with a risk of severe and prolonged hypoglycaemia. We illustrate the problem with the following clinical case.
Observation
Mr. D T, 51 years old, at ATCD of benign pancreatic neoplasia, operated on at home pancreatectomy, the patient developed secondary diabetes with signs of external pancreatic insufficiency with chronic diarrhea and a malabsorption syndrome. Hospitalized at our level for chronic glycemic imbalance marked by an impairment of quality of life following disabling repeated hypoglycaemia. Insulin requirements are low and typically reduced during the night.
Conclusion
Management of insulin-dependent diabetes following pancreatectomy is difficult to balance due to the lack of a counter-regulatory mechanism. Therapeutic patient education is an important weapon in achieving these goals of improving quality of life.

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EP51

Effect of diabetes and high blood pressure association on degenerative complications of diabetes

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High blood pressure is a condition that is frequently associated with diabetes. It aggravates the prognosis of the diabetic by increasing the cardiovascular risk and accelerating the occurrence of degenerative complications. The aim of our work was to study the effect of the association of high blood pressure and diabetes on the degenerative complications of diabetes. This is a descriptive retrospective study conducted at the C department of the National Institute of Nutrition in Tunis about 156 type 2 diabetics hospitalized between January and March 2018. The average age was 54.57 ± 11.17 years old. The sex ratio was 1.02. The prevalence of high blood pressure was 58.3%. Retinopathy was present in 41.02% and was proliferative in 13.5% of cases. Nephropathy and neuropathy were present in 17.3% and 35.9% of cases, respectively. 20.5% of patients had coronary disease. A history of stroke was found in 5.8% of cases. Obliterative arteriopathy of the lower extremities was found in 8.3% of patients. We found a strong correlation between the degenerative complications of diabetes and the presence of hypertension: retinopathy ($P=0.048$), neuropathy ($P=0.012$), nephropathy ($P=0.002$), coronary artery disease ($P=0.001$), stroke ($P=0.011$) and peripheral arterial occlusive disease ($P=0.008$). Our study highlights the negative effect of high blood pressure on degenerative complications of diabetes. Optimal control of blood pressure is essential to limit the progression of these complications.

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EP52

Penitentiary: diabetes and metabolic risk

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Introduction
The prison environment is a space that involves some restrictions. However, diabetic patients require special attention. The aim of this work is to evaluate the impact of this area on the glycemic control and the metabolic profile.
Patients and method
Descriptive cross-sectional study carried out on a day of health campaign in a penitentiary center, in the sector for men, and concerned the 62 known diabetic patients of the institution.
Results
The prevalence of diabetes was 12% and he was diagnosed in penitentiary in 3 cases. The average age was 42.3 years and type 2 diabetes was found in 93.1% of cases. The average duration of diabetes was 6.15 years, 76.4% of patients were on oral treatment. Mean HbA1c was 8.2%. The average blood glucose on examination was 1.92 g/l and waist circumference was pathological in 32% of cases. Hypertension and dyslipidemia were associated in 26% of the cases. Patients complied with the rules of hygiene and diet (physical activity and diet) in 36% of cases.
Discussion
In prison, the health care system deals with a temporarily or chronically vulnerable population. In our study, diabetes was more common than in the general population. The exclusive male sex is a cardiovascular risk factor in its own right. The detention environment presupposes a physical activity that is often limited and an imposed diet. However, the institution tries to encourage a healthy lifestyle. Also, access to care and treatment is available and provided by the penitentiary pharmacy.

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EP53

Immunological interference with hemoglobin A1c assay

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Introduction
The quality of assay methods for HbA1c assessment has importantly improved last decades, however analytical interferences due to variants of hemoglobin remain of matter vigilance. Immunological interferences, although no longer described, may also occur.
Observation
A 84-years-old woman without significant medical history was explored for polyneuropathy. Additional investigation as HbA1c was requested. As no value of HbA1c was obtained when assayed with immunoassay (Roche Tina-quant Hemoglobin A1c Gen.3), the analysis was made with high-performance liquid

chromatography (HPLC) (ADAMS A1c). This later method gave 5.8% of HbA1c. Hemoglobin electrophoresis was normal. Antibody interference was considered. After washing blood cells, HbA1c level was 5.6% using the immunoassay. Both rheumatoid factor and heterophilic antibodies could be involved.

Conclusion

Ultimately, one should bear in mind the possibility of antibody interference with HbA1c assessed using an immunological assay. It must be considered in case of unavailable result or when clinical findings and laboratory results show discrepancies. Washing blood cells would be a handy method to discard antibody interference.

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EP54

Diabetes mellitus revealed by hemichorea: a case report

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Abnormal movements like hemichorea are rarely described as neurological manifestations of hyperglycemia. It is occur in nonketotic hyperglycemia with a pathognomonic radiological findings. We report a case of a 70 years old women with no past medical history who presented to the emergency department with abnormal limb movements. It was repetitive, brief, involuntary movement of the right arm evolving for 5 days. On admission, neurological examination showed right hemichorea. She did not demonstrate any other neurologic deficit, such as hemiparesis or sensory change. Blood glucose level was 3.47 g/l and ketone bodies were not detected in the urine. Full blood count, liver function tests, renal function tests, inflammatory markers, thyroid function tests and electrocardiogram were normal. The CT scan showed unilateral spontaneous hyperdensity of the left lenticular nucleus. The patient was started on insulin. Evolution was marked by the gradual decrease of chorea until complete disappearance after one week. In conclusion Hemichorea is a rare manifestation of nonketotic hyperglycemia. Recognition of this clinicoradiologic syndrome is important because correction of hyperglycemia lead to neurological improvement.

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EP55

Münchhausen syndrome: in the light of 4 observations

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Definition

Fake hypoglycaemia in children and adults is due to self-administration of insulin or insulin secretagogue. They represent one of the best described facets of the Münchhausen syndrome. Here we report four cases of false hypoglycemia following insulin injection.

Material and method

Prospective study that took place over 2 years to collect 4 hospitalized cases for etiological assessment of severe hypoglycaemia up to 0.2 g/l and complicated convulsive state with coma post-criticism in a case- 3 girls and a teenager, whose age was between 13 and 21 years old. 2 patients are not diabetic while the remaining two are well-followed type 1 diabetics. A hormonal, immunological, morphological assessment was carried out having excluded in the 4 cases the presence of an organic etiology with even the discovery in intra-hospital of a factitious catch of insulin. Psychiatric help was proposed revealing the presence of depression, family conflict, death of a relative, attempted rape.

Discussion

Fake hypoglycaemia is a difficult diagnostic psychiatric disorder. This is most often female patients with easy access to hypoglycemic treatments. Only 50% of diagnosed patients admit the dummy catch after confrontation. Psychiatric follow-up is necessary to avoid recurrences that may be life-threatening in this situation.

Conclusion

Dummy hypoglycaemia, which often remains a diagnosis of elimination, is a serious psychiatric disorder that is difficult to diagnose but needs to be discussed in female patients with easy access to insulin.

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EP56

Diabetic foot in images

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Introduction

The diabetic foot is considered as the crossroad of degenerative complications of diabetes (neuropathy, arterial disease, deformity). This is a public health problem with socio-economic implications. The objective of this work is to illustrate the different lesions of the diabetic foot in images.

Materials and methods

We included all hospitalized patients in the Endocrinology Department of the University Hospital of Casablanca during 18 months (September 2017 to December 2018), who received pictures of their foot injuries during their hospitalization and after their consultation. There are some pictures of 8 patients that represent the main lesions of the foot in diabetics.

Observation

The diabetic foot is characterized by the complex association at varying degrees of peripheral circulatory disorders, peripheral neuropathy including loss of sensitivity and impairment of the autonomic nervous system. The diabetic foot occupies by its gravity and its cost a particular place among the complications related to diabetes. Foot lesions in diabetics, particularly ulcer, plantar perforating disease, osteitis, dry and wet gangrene, bacterial dermo-hypodermatitis, necrotizing fasciitisand Charcot's foot, are exposed to prolonged and frequent hospitalization, which favors the professional or family withdrawal from the patient. The risk of amputation is 15 to 30 times higher in the diabetic than the non-diabetic, with amputations often iterative.

Discussion

The diabetic foot is a degenerative complication with significant clinical or socio-economic consequences. Management of the diabetic foot includes several components: early diagnosis, etiological assessment of ulcerations, treatment of the infection, medical or surgical therapeutic indications, optimization of diabetes balance, local care, education for wound discharge and prevention recurrences.

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EP57

Diabetic foot: screening and prevention

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Introduction

The screening of patients at diabetic foot risk and the implementation of prevention measures are justified by the frequency and severity of amputations. The aim of this study was to:

– Screen diabetic feet at risk.
– List the risk factors associated with the diabetic foot at risk.
– Present the methods of management of diabetic foot at risk in our service.

Patients and methods

It was a prospective and observational study, conducted in our department outside patients with recent type 1 diabetes (<5 years), diabetic pregnancies, and patients with non-neuropathy diabetic. Statistical analysis was performed by SPSS software version 19.

Results

We Included 482 patients whose average age was 47.7 years and sex ratio was 1.6. Type 2 diabetes was predominant in 69% of cases, 58% were sedentary, 40% were obese, 42% were hypertensive patients, 48% were dyslipidemic and 12% were smokers. Diabetic nephropathy was present in 36% of cases. According to the IWGDF classification, 24% were at low risk of ulceration, 22% were at moderate risk, 26% were at high risk and 28% at very high risk. The level of risk was significantly correlated ($P<0.005$) with age, age of diabetes, dyslipidemia, obesity, smoking, physical inactivity and nephropathy. All patients benefited from a therapeutic education. A diabetic foot day was organized every 2nd Wednesday of the month, bringing together an average of 10 to 12 high-grade patients for re-education. Patients with arteriopathy obliterans of the lower limbs were put on treatment and referred for specialist advice. Long-lasting footwear and adapted prostheses are prescribed in consultation with physicians in patients

with deformity, corrective surgical management is planned. Over 1 year, among 482 patients, 6 patients with multi-complicated diabetes and grade 3 feet developed a foot injury requiring hospitalization.
Conclusion
The gradation of the podological risk is based exclusively on the clinical examination. Thereafter, patient awareness and education about PD are paramount.

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EP58

Epidemiological and clinical features of the diabetic foot in the elderly

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Introduction
The diabetic foot is a major public health problem with amputation risk is important. Diabetes podiatric complications of are dominated by diabetic neuropathy, diabetic arterial disease and infection. The aim of this study was to identify the epidemiological and clinical characteristics of the diabetic foot in the elderly.
Patients and Methods
It was an observational prospective study, conducted in our department between January and December 2018, including 164 diabetic patients aged 65 and over, collected at the service. Statistical analysis was performed by SPSS software version 19.
Results
We collected 164 patients whose average age was 68 ± 12 years and the sex ratio was 1, 3. Type 2 diabetes was dominated in 89% of patients, with a mean duration of progression of 9 ± 6 years and insulin therapy in 52%. Among our patients, 78% were sedentary, 62% were hypertensive, 40% were dyslipidemic. Diabetic nephropathy was present in 66% of patients. According to the IWGDF classification, 18% were at low risk of ulceration, 24% were at moderate risk, 26% were at high risk and 32% at very high risk. The level of risk was significantly correlated ($P < 0.005$) with the age of diabetes, dyslipidemia, obesity, sedentary lifestyle and nephropathy.
Conclusion
Foot damage is polyfactorial and the various elements acting synergistically. Minimal lesion of the foot in an elderly diabetic patient can threaten the functional and probably vital prognosis of the patient.

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EP59

Prevalence and characteristics of metabolic syndrome in diabetics

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Introduction
Metabolic syndrome (MS) is a high-risk vascular risk situation. The aim of this study was to assess the prevalence of MS in a population of diabetic patients.
Methods
It was a descriptive study conducted from March to September 2017 on 122 diabetics hospitalized at the National Institute of Nutrition. The SM is defined according to the IDF 2005 criteria. All patients underwent careful questioning, a complete clinical examination with anthropometric measurements.
Results
The average age of our population was 52.4 ± 7.3 years. The sex ratio was 0.96. All patients in our population were type 2 diabetics. The average waist circumference was 94.4 ± 11.1 cm and the mean BMI was 28.8 ± 4.8 kg/m^2. The prevalence of MS was 65.2% with female predominance (71%). The mean BMI in this group was 31.5 ± 4.8 kg/m^2 and the average waist circumference was 103.1 ± 9.9 cm. 45.1% of patients were hypertensive, 37.4% had hypertriglyceridemia and 21.6% had low HDLemia. In our population, 36.7% had a severe MS (defined by the presence of at least 4 criteria) and 6% of the patients met all the criteria of the MS. Microangiopathic degenerative complications of diabetes were present in 64.5% of patients with DM whose 54.8% of patients were in the renal failure stage, 53.2% had neuropathy and 32.2% had diabetic retinopathy. Of the macroangiopathic complications, 5.7% had a history of stroke, 4.9% had a history of MI, and 11.5% reported unexplained chest pain.
Conclusion
The consequences of the SM imply its effective diagnosis for a global management of the comorbidities detected. An adapted education program would contribute to better screening and case management.

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EP60

Kidney failure without proteinuria in a population of diabetic women: can we incriminate diabetes?

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Introduction
The pathophysiology of diabetic nephropathy is characterized by proteinuria which often precedes the decline in creatinine clearance. The objective of our study was to describe the clinical and metabolic characteristics of a population of diabetic femele patients with renal failure without proteinuria.
Methods
This is a retrospective study that included 37 diabetic women who had been hospitalized at the National Institute of Nutrition of Tunis (Departement B) for diabetes equilibration. Clinical and metabolic data were collected from medical records. All patients had at least two normal 24 H microalbuminurias. No patient had a clear etiology that explains renal impairment. Creatinine clearance was calculated by the formula CKD-EPI.
Results
The mean age was 57.8 ± 6.5 years. Diabetes was type 2 in 100% of cases evolving since 13.8 ± 2.9 years on average. The average BMI was 33.3 ± 2.8 kg/m^2. 45.04% of patients were dyslipidemic. 62.16% were hypertensive, poorly balanced in more than 60% of cases. 35.15% were polymedicated with an average of 4 drugs per prescription. Degenerative complications Diabetes was myocardial infarction (8.1%), stroke (10.8%), chronic arteritis of the lower limbs (2.7%) and diabetic retinopathy (43.24%). The mean HbA1C was 11.8 ± 1.3%. The mean creatinine clearance was 53.5 ± 12.6 mmol/L.
Conclusion
Diabetes remains the most common etiology of kidney failure worldwide. In our population, normal proteinuria and the presence of other factors that can alter kidney function, made us retentive before retaining the diagnosis of diabetic nephropathy. Other studies with larger numbers are needed to better characterize similar cases of nephropathy.

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EP61

Comprehensive approach towards pediatric diabetes management: policy initiatives in developing country

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Issues
In developing nations diagnosis of diabetes brings mental-trauma/depression in family. Focused treatment for pediatric age-group is unavailable in developing-countries. 26% of diagnosed diabetics are children's. Adequately trained physicians/Nurses in issues of pediatric-diabetes provide continuity of care, relief from depression and smooth transition from diagnosis to treatment. Qualitative collaborative relationship between these makes diabetics life bearable. Our NGO-project highlights significance of relationship between nurses and diabetic-children in community clinic setup of rural India. For Diabetes, its assumed that depression is inevitable sequel to diagnosis. Retrospective analysis of past studies shows—counselling improves QOL & attitude towards diabetes-treatment.

Aims
To describe care issues in diabetic-children's. Observe/modify nature of relationship between nurse and child. To evolve comprehensive treatment plan for patients and families.
Methods
A retrospective analysis of data base from 7 rural health-clinics. Specialized therapy/support to pediatric-age-group not available at any center. Total 117 children's [4–13 years] diagnosed with diabetes. 23 had additional endocrine/metabolic problems. Nursing/medical care plan analyzed. No specialized trained personal in rural/tribal India. Opinion/needs from patients families collected on feedback questionnaire. Then we trained 10 nurses & 2 physicians for handling pediatric cases [4 weeks training].
Results
Out of 117, 41 discontinued Rx due to improper counseling/guidance. 3 died. Patient/family's feedback highlights: Better access to newer drugs-delivery-systems, psycho-social support, follow-up-plan. Nurses/physician be sensitized in pediatric care-issues. Main issues of concern were: [1] illness and coping with their feelings. [2] Initial impact of diagnosis and a search for solution? Expectations for future life & its quality? [3] Concerns of cost of RX [4] Availability of proper follow-up centers in rural areas of developing nations.
Conclusion
Multifaceted Relationship between physician/nurse and Diabetics children's is crucial. Follow-up must be given priority. This relationship provides better continuity of treatment. We show concerns/difficulties while working in Asian set-up for pediatric diabetes to international experts/seniors at ECE-2019-congress.

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EP62

Impact of the month of Ramadan on the metabolic profile of non-fasting diabetic patients

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Introduction
Ramadan is the 9th month of the Islamic calendar, where Muslims are fasting from dawn to sunset. The diabetic patient is exposed to multifactorial risks. Few studies have examined the effect of Ramadan on non-fasting people. The objective of our study was to determine the effects of the fast on the metabolic profile of non-gambling diabetic patients.
Patients and methods
Prospective study including 50 non-fasting patients recruited within the Endocrinology department during the month of Ramadan 2018. The clinical and biological parameters were on two periods before Ramadan (T0) and three weeks after the end of Ramadan (T2). Statistical Analysis by Spss version 25.0.
Results
The characteristics of our patients were a mean age of 52.56 ± 11.51 years, a sex ratio of 1.08 H/F, a family life of 82.4% and a low level of education in 37.3. %. The average body mass index of 33.45 ± 7.5 kg/m^2. Average seniority of 8.72 ± 7.74 years, average HbA1c of 7.9%. The degenerative complications were: retinopathy (37.3%), nephropathy (21.6%), neuropathy (25.5%), dyslipidemia (31.4%), coronary artery disease (7.8%). The dietary survey revealed an average caloric intake of 1743.4 ± 425.86 Kcal/J. There was no difference between the mean weight of patients before and after Ramadan at 86.4 ± 19.35 kg, nor any change in blood pressure. The mean blood glucose level was stable at 1.51 ± 0.46 g/l. An LDL decrease of 0.2 g/l and an increase of 0.1 g/l. In addition, no difference was noted between serum calcium, proteinemia, albuminemia and serum uricemia. Treatment regimens before Ramadan were monotherapy (23.5%), dual therapy (37.3%), three (2%), bedtime (19.6%), diet alone (4%) and after Ramadan monotherapy (60%), biotherapy (35%) and diet alone (5%). The use of hospitalization was necessary in 12 cases (24%), of which 3 were admitted to intensive therapy.
Conclusion
According to these results, the fasting of the month of Ramadan significantly alters the glycemic balance and the lipid balance in non-fasting type 2 diabetics. Hence the interest of sensitizing the diabetic and the practitioner of the importance of pre-Ramadan consultation.

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EP63

Correlation of body composition and glycemic profile of diabetic patients

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Introduction
The incidence of diabetes mellitus is increasing worldwide and is a major public health problem. The aim of our study was to determine the relationship between fat and visceral mass with the glycemic balance of diabetic patients.
Patients and methods
A prospective study, conducted over 9 months from March to December 2018, in the endocrinology department of Ibn Rochd University Hospital of Casablanca, in 75 patients with type 2 diabetes and type 1 with more than 10 years of evolution the day hospital. The body composition was interpreted by the OMROM BF 508 impedance meter, according to the standards of use based on WHO recommendations. Statistical analysis made by Spss software version 25.0.
Results
The participants had a mean age of 47.71 ± 11.15 years with a female predominance (58.7%), a mean waist circumference (104.4 ± 21 cm), an average BMI of 31.34 kg/m^2 et a predominant DT2 (80%). Average HBA1c (9.5%). Degenerative complications Retinopathies (55%), Nephropathy (25%), Neuropathies (20%). The comorbidities HTA (30%) and Dyslipidemias (40%). The thresholds of the impedancemetry were for mean body fat (37.20 ± 8.32%) and visceral fat (13.3 ± 5%). Degenerative complications were statistically higher in patients with increased body and visceral fat (35%, $P = 0.03$). We found a strongly positive correlation between body fat, visceral fat, waist circumference, and HBA1c ($P < 0.0001$, r: 0.7).
Conclusion
These results suggest that body composition may be predictive of insulin resistance, requiring a more rigorous follow-up aimed at improving the management of diabetic patients.

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EP64

Intensive treatment for obesity at our hospital

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Since 2006 at our hospital, lifestyle modification, such as diet and exercise, for obese patients has been provided through a team approach with a physician, dietician, physical therapist and psychologist. From 2016, a surgeon, anesthesiologist and nurse were added to the team for metabolic/bariatric surgery. The aims of this study are to clarify the effectiveness and problems of lifestyle modification, and to clarify the characteristics of patients who transferred for surgical treatment. The diet menu is as follows: intake energy is (resting energy expenditure + exercise energy) $\times$ 0.9, and nutrients/total energy is 55–60% carbohydrates, 15–20% protein and 20–25% fat. The exercise is performed as follows: regular exercise more than 3 times per week or more than 5000 steps per day, and if possible, more than 10000 steps per day. Until now, 150 obese patients (mean age of 50 years and mean body mass index (BMI) of 31) have received medical management, and the mean BMI significantly decreased by 1.2 over 3 months. Twenty patients (13%) have transferred for surgical treatment. Ten patients have diabetes with a BMI of 31–47 and HbA1c 8–9% despite intensive insulin therapy. Four with a BMI of 41–60 have bilateral knee osteoarthritis and require total knee replacement, and two with a BMI of 36–51 have severe sleep apnea. Diabetic patients need a lower BMI for metabolic/bariatric surgery compared with non-diabetic patients.

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EP65

Addressing issues of diabetes patients community: evaluation in resource poor settings

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Issues
Adolescent diabetes social stigma in India. Such diabetics needs proper guidance/information/treatment-counselling outlets. This is burning issue in developing-nations like India. Hence we all need to unite & form a comprehensive diabetes care & counselling policy plan at ECE conference. Treatment options must be suitable for developing-nations considering cost of Rx. Incorporating NGO's in such efforts is very effective.
Our Project Methodology
This is a policy paper. Our 10 year-old-NGO started Diabetes education-project in rural India from 2014. we started s education & surveillance project to analyze social & anthropological issues facing those affected by adolescent diabetes. Total 162 adolescents subjects enrolled by Feedback questionnaires to get their feedback on special needs, perceptions, social attitude on diagnosis of diabetes. Factors like community-inhibition, social-ostracism, economic-difficulties, marital discord, non-availability of treatment-guidance centres, lack of trained-staff analysed & draft policy is recommended to Govt-agencies.
Lessons learned
Adolescent diabetes management must include care of nursing & psycho-social needs. Here role of NGO's in diabetes education is very effective in terms of cost-management, better impact & better-compliance of young diabetics. Community mass intervention projects has proven useful in rural communities of resource poor-nations. ECE participants can collaborate with NGO-activists to address this issue. Uniform public health policy needed to implement & expand newer strategies to include broader range of diabetes care-issues.
Recommendations
Promoting dialogue between Government-health-services & NGO's accelerates diabetes education/awareness programs. NGO participation improves cost-efficacy of such initiatives in economically poor populations. This would reduce difficulties faced by young diabetics from Asian countries. It is essential that WHO/ESE makes common guideline manual on this issue affecting developing-countries. We graphically present our NGO's project on diabetes patients education project in four phases to ECE participants.

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EP66

Whole-body insulin resistance (WBIR) evolving in four stages and its evolutionary effect on the body weight

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Insulin resistance (IR) may be defined as the physiological condition, in which insulin signaling is somehow deranged somewhat irreversibly such that insulin is of little use to cells or tissues. Specific roles of insulin are quite different in the muscle tissue, adipose tissue, and liver. Accordingly, detailed aspects of IR would be very tissue-specific. Meanwhile, IR may develop first in the muscle tissue with a relatively low cell turnover and then progress, in sequence, to the subcutaneous adipose tissue, to the visceral adipose, and to the liver with higher cell turnovers. The cells in a tissue with a lower cell turnover would be exposed longer in average to potential IR-inducing agents and therefore more readily develop IR. Given that IR can hardly be considered a global parameter, it would be essential to subdivide IR into tissue-specific IRs: muscle insulin resistance (MIR), subcutaneous adipose insulin resistance (s-AIR), visceral adipose insulin resistance (v-AIR), and hepatic insulin resistance (HIR). Sequential development of tissue-specific IRs, producing tissue-specific metabolic disruptions, would amount to nothing but the whole-body insulin resistance (WBIR) evolving in four main insulin-resistant stages denoted by IR-I, IR-II, IR-III, IR-IV, respectively. WBIR evolution starts with development of MIR (in the IR-I stage), which would effectively enhance adipose glucose uptake and adipose de novo lipogenesis (ADNL), thereby contributing to rapid weight gain; and then advances to the IR-II stage with additional development of s-AIR, which would effectively enhance visceral adipose glucose uptake and v-ADNL, thereby contributing to visceral obesity; and then advances to the IR-III stage with additional development of v-AIR, which would let the visceral adipose tissue as well undergo uninhibited lipolysis, thereby leading to rapid weight loss; and then advances to the IR-IV stage with additional development of HIR, which would let the liver undergo unsuppressed hepatic glucose generation (HGP), thereby elevating severely even the fasting hyperglycemia for eventual diagnosis of diabetes. In conclusion, particularly the effect of WBIR evolution on the body weight largely refutes the entrenched notion of the so-called lipid-induced insulin resistance (LIIR). Instead, the finding that the time-averaged plasma glucose (PG) elevates steadily with WBIR evolution suggests that hyperglycemia itself has an effect of inducing as well as enhancing IR in a vicious cycle.

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EP67

Vitamin D as a predictor of insulin resistance in PCOS

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Introduction
PCOS is the most common female endocrine disorder with a prevalence of approximately 5–10% in women of reproductive age. PCOS includes hyperandrogenic features, infertility and insulin resistance among others. Lately, Vitamin D has been involved in the etiology of various disorders.
Objective
The aim of our study is to define the role of vitamin D as an etiological and predictive factor in PCOS.
Materials and methods
The study comprises 25 cases of PCOS diagnosed on the basis of Rotterdam criteria. The parameters assessed include HOMA-IR, vitamin D besides the routine anthropometric and biochemical parameters.
Results
The study population was divided into 3 groups according to vitamin D status. Insulin resistance was most severe in the sub group with vitamin D deficiency.
Conclusion
Vitamin D has an important role in the pathogenesis of insulin resistance in PCOS.

Keywords: vitamin D, insulin resistance, polycystic ovarian syndrome
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EP68

Lack of definite association of vitamin D deficiency with diabetic neuropathy: Investigation in Greek and in Bangladeshi patients

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Aim
Determination of the 25(OH) vitamin D levels in Greek-born and in Bangladeshi immigrant patients in Greece with diabetes with and without polyneuropathy.
Materials and methods
The method for the detection and staging of polyneuropathy proposed by Dyck, 1988 was used.
Results
A total of 111 Bangladeshi immigrants and 101 Greek diabetic patients took part in the study. Vitamin D levels were significantly lower in Bangladeshi than in Greek diabetic patients, and were significantly lower in Greek patients with small-fiber neuropathy. In Bangladeshi patients, there was no statistically significant difference in the subgroup of patients with polyneuropathy in comparison to those without polyneuropathy.
Conclusion
The association of vitamin D deficiency only with a small number of Greek patients with exclusively small-fiber neuropathy does not allow us to draw a definite conclusion on the role of vitamin D in the pathogenesis of diabetic neuropathy.

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EP69

Multiple causes of hyponatremia, which one is the most severe? – case report

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Introduction
Hyponatremia is a frequently encountered electrolyte disturbance in clinical practice. The etiology should be searched and revisited properly to be able to guide the appropriate management.
Case-report
A 39-years old woman with type 1. diabetes since childhood, after combined pancreas-kidney transplantation with good stable functions of both organs, was admitted to our internal ward for overall fatigue, fever, unspecific abdominal pain with nausea, suspect urinary infection. In a month she lost 5 kilos on weight and was slightly dehydrated. Laboratory findings at the admission: natrium 122 mmol/mol, kalium 3.9 mmol/mol, chlorides 92 mmol/mol, pH 7.366, bicarbonate 25 mmol/l, total protein 62 g/l, albumin 31 g/l, CRP 72 mg/l, urea 7 mmol/mol, creatinine 127 umol/l, CKD-EPI 0.76 ml/s- stable renal function since transplantation, liver-pancreatic tests normal, euglycemic, mild leukocytosis with a left shift, haemoglobin 98 g/l, thrombocytes in norm, urine smear was clear. Chest X-ray was normal, abdominal ultrasound detected slightly distended small intestine with retroperitoneal and mesenteric lymphadenopathy, on a CT scan the maximal diameter of the lymphadenopathy was 13 mm. After rehydration and empiric antibiotic therapy, no proven microbiological agent was detected and a tendency to hyponatremia 125 mmol/mol persisted with subfebrile temperatures. Hypocortisolism was ruled out and chronic levothyroxine substitution for autoimmune thyroiditis was slightly increased to 150 ucg daily as TSH was 14 mIU/l, fT4 11 pmol/l. With suspicion of a malignancy associated syndrome of inappropriate antidiuretic hormone secretion (SIADH) a PET/CT scan was performed and meanwhile, salt tablets were administered at home. The scan revealed pathology in small intestine mostly in left mesogastrium with intraperitoneal nodules max. diameter 35 mm. The clinical status of the patient worsened rapidly in 14 days leading to readmission for cachexia, fevers, natrium 118 mmol/mol, chlorides 89 mmol/mol, CRP 170 mg/l. Hypertonic saline was administered and due to lack of peripheral lymphadenopathy, negative blood flow cytometry, negative colono/gastroscopy a surgical laparotomy was performed in the abdomen to reach the final diagnosis- diffuse large B cell lymphoma. The patient was referred to the hematooncological department.
Conclusion
Hyponatremia is sometimes overlooked by clinicians, even though it could serve as a warning sign. In our case malignancy associated SIADH due to a posttransplant lymphoproliferation with B-symptoms was found.

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EP70

Influence of obesity on glycemic balance in type 2 diabetics

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Introduction
Obesity poses a significant health risk and is linked to several comorbidities, including diabetes. The aim of our study was to evaluate the impact of obesity on glycemic control in type 2 diabetics.
Methods
It was a descriptive and analytical study, conducted in 200 diabetic patients hospitalized at the National Institute of Nutrition of Tunis. Each patient received a biological assessment including glycated hemoglobin (HbA1c) and a glycemic cycle during his hospitalization. Obesity is defined by a body mass index ≥ 30 kg/m^2.
Results
We included 200 patients with type 2 diabetes. The mean age was 52.78 ± 14.2 years, 58.5% were female. The mean duration of diabetes progression was 12 ± 8.41 years. The mean HbA1c in this population (both obese and non-obese patients combined) was 9.9 ± 2.09%. The prevalence of obesity was 39%. This prevalence was significantly higher in women than in men ($P < 0.005$). For fasting blood glucose, it was significantly higher in the obese than in the non-obese ($P < 0.005$). Similarly, postmeal glycaemia measured at the same time of the day in all hospitalized patients was significantly higher in the obese than in the non-obese ($P < 0.005$). The analytical study also showed that mean HbA1c was significantly higher in obese patients ($P < 0.005$).
Conclusion
Recent studies have shown that the increase in obesity worldwide is associated with a parallel increase in the development of type 2 diabetes and poor glycemic balance. Control is then necessary especially for diabetics.

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EP71

Multidisciplinary approach for diabetes management: developing nations healthcare model

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Background
This is a patient advocacy effort by a Non-government-Organization from developing nation. In addition to drug treatment, patients' improvement in health status and quality of life may depend on their ability and willingness to adhere to all their therapies and undertake self-care activities.
Methodology
Traditionally, life style changes have been promoted through hospital delivered interventions. However, to reach larger number of people with arthritis, recent attention has been directed toward developing community-based interventions, which takes place in nonclinical settings and is provided by health professionals, paraprofessionals or lay persons. care must be targeted to prevent development of complications. educational efforts to promote life style changes, information and motivation strategies needs to be developed. Further, written contracts between patients and health care practitioners regarding health promotion activities, and telephone- or internet follow-up may enhance patients' adherence.
Health promotion
Health promotion enables people to increase control over their health and its determinants, and thereby improve their health smoking, obesity, poor physical fitness and depression, economic burden of treatment are major hurdles in diabetes management. Diabetes is associated with severe psychological distress and major depression and they are a leading cause of morbidity and disability, giving rise to enormous healthcare expenditures and loss of work.
Depression
Diabetics have higher levels of depressed mood & its independent predictor of mortality.
Current status
Currently various lifestyle changes are indicted in diabetes outcome. People with diabetes have significantly worse health-related quality of life (HRQOL). There is considered to be a 'window of opportunity' to improve outcome by the early diagnosis and treatment.
Obesity
Obesity, (BMI > 30 kg/m^2) is a risk factor for diabetes, as well as for cardiovascular disease.
Cardiovascular disease
Several studies has shown that diabetes is associated with increased risk of cardiovascular death compared with general population.
Health promoting interventions
Several studies have also demonstrated that weight loss improves sugar control. Being active is also a mean to prevent depression, as it has been shown that declines in the ability to engage in recreational activities and social interactions significantly increase the risk of depressive symptoms.
Conclusion
Based on current research, it is evident that health promotion is important, while health promotion is important to prevent poor outcomes of the disease & have better QOL. ESE must work towards formation of policy paper on this aspect of diabetis control.

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EP72

Nutritional support in diabetic gastroparesis

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Woman, 40 years old. Smoker and habitual drinker, history of toxic consumption, anxiety-depressive syndrome, postsurgical hypothyroidism after total

thyroidectomy for multinodular goiter in substitution treatment. Diabetes mellitus type 1 diagnosed in 2001 as a result of pregnancy, unstable, with poor chronic glycemic control, requiring frequent admissions to our hospitalization plant due to episodes of ketoacidosis. It requires high insulin requirements and does not present micro or macrovascular complications. Chronic diarrhea occurs since 2013, with up to 4 stools per day, accompanied by nausea and vomiting of food content, which worsens the control and glycemic stability, with frequent moderate-severe inadvertent hypoglycemia and hyperglycemia that was usually complicated by episodes of ketoacidosis moderate-severe diabetic To this is added the development of severe malnutrition, with a loss of 14 kg in the last 6 months. The complementary tests ruled out celiac disease, bacterial superinfection and other causes of chronic diarrhea. Abdominal CT, colonoscopy, TEGD without findings. The EDA checked food debris in the gastric chamber after 12 hours of fasting and autonomic neuropathy test showed an expiration/inspiration index, index 30/15 and abnormal Valsalva index confirming the diagnosis, without being able to rule out a certain component of associated diabetic enteropathy. Due to the important and severe metabolic and nutritional repercussion, we decided to start nutritional support. Which route of administration and type of formula will be the most suitable for our patient to manage?

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Interdisciplinary Endocrinology

EP73

Steatosis in chronic hepatitis C: prevalence and therapeutic impact

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Introduction
Steatosis has become an important issue in hepatitis C, due to the injury it can cause in a chronically ill liver. In chronic hepatitis C patients, the prevalence of steatosis ranges from 40–86%. Steatosis was significantly associated with the lack of response using PEG-IFN and ribavirin. The aim of our study was to determine the prevalence of hepatic steatosis in chronic hepatitis C and determine its impact on the therapeutic response using new direct antiviral agents (DAA).
Material and methods
This is a retrospective study conducted in the Hepatogastroenterology and Infectious Diseases Departments of Farhat Hached University Hospital, collecting all patients with chronic hepatitis C treated with DAA between October 2016 and May 2018. Steatosis was diagnosed by abdominal ultrasound. Treatment efficacy was assessed by the early virological response rate (EVR) at 4 weeks after the start of treatment and the sustained virological response rate (SVR) at 12 weeks after the end of treatment.
Results
Fifty four patients with a median age of 52 years, divided into 32 women and 22 men, were included. Non-insulin-dependent diabetes, portal hypertension and dyslipidemia were present in 13, 7 and 4 patients, respectively. The clinical manifestations were dominated by arthralgia and asthenia. Genotype 1b was dominant with a frequency of 76%. The average pretreatment viral load was 1 457 542 IU/ml. Fourteen patients (28%) were in the cirrhosis stage. Steatosis was present in 11 patients (20.3%). The duration of treatment was 12 weeks in 37 patients (74%) and 24 weeks in the remaining 13 patients (26%). An early virological response (EVR) was obtained in 71% of cases. A sustained virological response (SVR) was noted in all patients. EVR and SVR rates were comparable between patients with and without steatosis.
Conclusion
Steatosis was present in 20.3% of patients and it does not influence the response to treatment with direct antiviral agents.

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EP74

Cardiovascular manifestations and risk in acromegaly: experience of diabetology-endocrinology department of Oujda's Mohammed VI university hospital

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Introduction
Acromegaly is a rare chronic, and disfiguring endocrine disorder characterized by growth hormone excess, that carries a significant burden of cardiovascular morbidity and mortality; and still unfortunately one of the most important cause of death in acromegaly. The purpose of this study is to describe the cardiovascular events and risk factors concerning patients with acromegaly who are followed up in the endocrinology department of Oujda's Mohammed VI university hospital.
Materials and methods
This is a retrospective data analysis of 10 acromegaly patients followed up in in the endocrinology department of Oujda's Mohammed VI university hospital. The cardiovascular risk was estimated by the Framingham scoring system.
Results
Mean age at diagnosis was 48 years with a female predominance. Usually there was a delay of 7,67 years from the apparent onset of the disorder until the diagnosis was made. The cardiovascular risk was respectively high, intermediate and low in 4, 3 and 2 patients. Diabetes was diagnoses in 5 patients and intolerance to carbohydrates in 1 patient. Dyslipidemia was present in 8 patients; class 1 obesity in 3 cases and obstructive sleep apnea syndrome in 5 patients. Hypertension was observed in 4 patients. Electrocardiographic abnormalities were noticed in 6 cases; standing for atrial fibrillation, left ventricular hypertrophy, and repolarization abnormalities. A transthoracic echocardiographic examination revealed a mitral and aortic insufficiency, besides a concentric/eccentric hypertrophy in 4 patients. A tritroncular coronary lesion was observed in 1 patient and the ankle-brachial pressure index was normal in all cases.
Conclusion
Acromegaly is associated with premature cardiovascular mortality and the control of this endocrine disorder lead to a significant improvement of cardiovascular risk factors and to a reduction of the Framingham risk score.

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EP75

Short stature revealing Thomsen's disease: a case report

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Introduction
Thomsen's disease is a non-dystrophic congenital myotonia with autosomal dominant inheritance. Its association with short stature attributed to growth hormone deficiency (GHD) has never been reported in literature to our best knowledge.
Case report
A 14-years-old Moroccan boy, with no particular medical history, presented for evaluation of a short stature. On physical examination, the patient had a height of 141 cm (−2.5 s.d. on presumed growth curve) and a weight of 33 kg (−3 s.d.). His bone age was estimated at 10 years (4-year differential with chronological age). The etiologic assessment concluded to an isolated GHD. In addition, the patient has an 'athletic' appearance with a stiffness of the abdominal muscles, increased by cold. The family history revealed the presence of a similar family case (the maternal uncle). Electromyography showed typical mytonic bursts. All these typical features pointed to the diagnosis of Thomsen's disease. In concert with neurologists, the patient was treated with carbamazepine (200 mg×2/day) and growth hormone (0.035 mg/kg/day). The follow-up noticed an improvement of the neurological symptomatology and a weight gain of 3 cm after 3 months of treatment.
Discussion
Thomsen myotonia belongs to the broad group of muscle channelopathies, caused by mutations in the chloride channel gene (CLCN1), which is located on chromosome 7. Its association with GHD suggests the presence of intricate biomolecular factors. A mutation in the growth hormone-releasing hormone receptor gene (GHRHR), located on the same chromosome, seems a plausible hypothesis to explain this association.

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EP76

Rare variant of benign premature pubarche in a 6 months old boy

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Introduction
Premature pubarche is defined as early appearance of pubic or axillary hair without any other signs of puberty, before 8 years of age in girls and 9 years in boys. We present the case of a 6 months old boy who came to us with scrotal hair since birth with moderate progression until present.
Case presentation
A 6 months old male patient was referred to our clinic to investigate the presence of thick scrotal hair, affirmatively present at birth, with moderate progression until now. He was a healthy, term newborn who was born to nonconsanguineous parents, and had appropriate weight and length. He had history of prolonged neonatal jaundice and G6PD deficiency. Physical examination showed an infant in good condition with normal psychomotor development, with long thick pubic hair on the scrotum, without hyperpigmentation or enlargement of the penis, both testis of 3 ml, normal height (−0,84SDS), and weight (p10–25), with no apparent acceleration in growth rate. Blood tests showed low values of dehydroepiandrosterone sulfate (DHEA-S) and testosterone levels, normal plasma LH and FSH and borderline elevated 17-OH-progesterone: 1.96 ng/ml (RV: <1.7), but not high enough to justify ACTH-stimulation according to current guidelines. He had normal levels of ACTH and cortisol and negative/normal values of β HCG, AFP and CEA.
Conclusions
The hormonal parameters show a benign condition previously reported in infancy as isolated scrotal hair which is usually self-limited. Therefore, our patient needs careful monitoring to confirm this diagnosis.

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EP77

Effect of diets rich in n-3 or n-6 polyunsaturated fatty acids on fibrinogen and haptoglobin on the acute phase response

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Background
Diets rich in polyunsaturated fatty acids (PUFA) n-3 may change the fluidity and composition of membrane phospholipids, leading to different prostanoids formation, decreasing IL-1β and TNFα releases and increasing the basal levels of corticosterone, important factors to promote acute phase response (APR) to stimuli. This study proposes to verify if PUFA n-3 or n-6 rich diets alters the APR of fibrinogen and haptoglobin after turpentine stimulus.
Methods
Three male Wistar rat groups were differently fed, one with standard chow diet (control group), another with standard chow diet plus 15% of soybean oil (PUFA n-6) (soybean group), and the last one with standard chow diet plus 15% of fish oil (PUFA n-3) (fish group), for seven weeks. Each experimental group was split into four different induction procedures: standard APR, APR under sham-adrenalectomy (6th week of diet treatment), APR under adrenalectomy (6th week of diet treatment), and APR under indomethacin (5.54 mg/mL–1 mg/100 g rat weight, 7th week of diet treatment). The APR was induced in the by turpentine (0.5 mL, sc) on the 7th week of diet and blood samples were collected before and 24 hours after turpentine, under ether anaesthesia. IL-1β and TNFα were collected 90 min after stimulus and corticosterone plasmatic samples were collected at baseline and one hour after turpentine stimulus.
Results
The corticosterone baseline levels were significantly elevated in the fish group and, the response to turpentine was similar among the three experimental groups. The fibrinogen and haptoglobin baseline levels were significantly increased and the response of this proteins to turpentine was significantly reduced in fish group, compared to control groups. These findings were not altered by sham-adrenalectomy nor by adrenalectomy, suggesting that adrenocortical hormones are not responsible for the changes observed in fish group. IL-1b and TNFa plasmatic were not detected after turpentine stimulation. After LPS stimulus, IL-1b was reduced in the fish group compared to the control one. When indomethacin was administered, the response of fibrinogen and haptoglobin was statistically reduced in control groups compared to the related standard procedure animals, suggesting that prostanoids participate in the full acute phase response of these proteins. The reduced response of fibrinogen and haptoglobin observed in the fish group disappears on the indomethacin treated animals.
Conclusions
PUFA n-3 are precursors for less inflammatory series of prostanoids and probably they compromise a full acute phase response of fibrinogen and haptoglobin observed in fish group.

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EP78

Assessment of cardiovascular diseases awareness and knowledge among people living with diabetes

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Actuality: Diabetes is one of the largest global health emergencies of the 21st century. Each year more and more people live with this condition, which can result in life-changing complications. In addition to the 415 million adults who are estimated to currently have diabetes, there are 318 million adults with impaired glucose tolerance, which puts them at high risk of developing the disease in the future (International Diabetes Federation, 2015). The prevalence of patients with diabetes, consisting in dispensary registration in the Regional Endocrinology Dispensaries for the Republic of Uzbekistan in 2011 amounted to 128968 patients, whereas by 2015 this indicator increased to 169002. In prospective observational studies of FinnDiane, Verona Diabetes Study, increased variability in HbA1C and glycemia was associated with cardiovascular complications. Cardiovascular disease is one of the leading causes of death among people with diabetes, in particular, coronary artery disease (CAD).
The aim of the study
Assessment CVD awareness and knowledge among people living with diabetes and understanding people living with this disease.
Materials and methods
We have surveyed 45 adults with diabetes. 24 of them were male compared to 21 female aging from 40 to above 70 years old. Questionary had following 6 sections with 17 questions. Some of the questions had sub questions as well.
Results
From our research we found out that patients estimate their level of risk for cardiovascular disease as following: 20% - Low, 33.3% - Below average, 6.7% - Average, 26.7% - Above average, 13.3% - High. Moreover, we have found out that most of the patients learnt the risk for CVD several years after they have been diagnosed with diabetes. Where other options of replies were significantly lower such as: Before type 2 diabetes diagnosis – 20%, At the time of type 2 diabetes diagnosis – 6.7%, Soon after type 2 diabetes diagnosis – 20%, After several years of type 2 diabetes diagnosis – 40%, When I was diagnosed with CVD – 6.7%.
Conclusion
1 in 3 respondents living with diabetes consider their risk of CVD to be low. Nevertheless, diabetes in anamnesis is already a high risk of the CVD development.
40% of respondents had received information on CVD several years following their diabetes diagnosis.
All of the respondents had discussed their type 2 diabetes and CVD risk with a healthcare professional. However, all of the patients already had CVD with diabetes at the time of the survey.

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EP79

Hidradenitis suppurativa and endocrine disturbance: a case report

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Introduction
Hidradenitis suppurativa (HS), also known as acne in-versa is a chronic inflammato-ry dermatosis. Emerging evidence suggests that HS is associated with other comorbidities, while data concerning the coexistence of HS and Down syndrome (DS) are scarce. We report the case of a young male affected by DS and HS that suffers from multiple endocrine disturbances.
Observation
A 23-year-old overweight male (BMI 32 kg/m^2) with a 9-year history of HS presented with follicular lesions, most notably epidermal cysts, pilonidal sinus, and comedones (Hurley stage 2) in axillae, intergluteal folds, scalp and back. According to the Canoui-Poitrine classification, the patient presented the phenotype «follicular ». Laboratory investigations revealed glucose intolerance, hypercholesterolemia and hypothyroidism requiring treatment with L-thyroxine.
Discussion
HS is a systemic inflammatory disease that could be as-sociated with other comorbidities such as metabolic syn-drome, chronic intestinal diseases, and depression. New studies suggest the association of this dermatosis with other comorbidities. A syndromic con-dition including both HS, DS and various endocrine abnormalities has been previously described, but only in a few studies. Indeed, a retrospective study including 783 affected by DS estimates the prevalence of SH in these patients, up to 14.6% against 1% in the general French

population. The underlying molecular mechanisms ex-plaining the association of HS with DS, are not still com-pletely known. Evidence suggests that the increased ex-pression of amyloid precursor protein, encoded by a gene located on chromosome 21, might enhance keratinocyte activity, leading to impaired Notch signaling and the development of cutaneous lesions resembling to HS. DS is the most common chromosomal disorder, with a phenotype including a wide range of congenital heart defects, neurological abnor-malities, dermatological disorders such as alopecia areata and acne, as well as a variety of endocrine disorders. There is frequently an obesity in both diseases, HS and DS. Hypothyroidism are more common thyroid disturbance in DS, usually autoimmune hypothyroidism, sometimes Graves' disease. An international multicenter study report 56 cases affected by both DS and HS, 32% of them suffers from hypothyroidism.

Conclusion

Various endocrine abnormalities could occur during HS, more common in patients affected by DS. Further studies are needed to support this hypothesis, as well as research focused on the involved inflammatory mechanisms, so to develop novel therapeutic options for this debilitating disease and its comorbidities.

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EP80

Hypercortisolemia in Rothmund Thomson syndrome with RECQL4 mutation

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Introduction

Rothmund-Thomson syndrome (RTS) is a rare autosomal recessive genodermatosis, with specific clinical features. Herein, we report a case of RTS with RECQL4 mutation, unusually associated with hypercortisolemia.

Case report

An 18-year-old girl, born to consanguinous parents, with a history of xeroderma pigmentosum (XP) in two cousins, has been followed-up for RTS, since the age of 3 years. The diagnosis of RTS was made based on photosensitivity, poikilodermatous rash, sparse scalp hair, eyelashes and eyebrows, verrucous hyperkeratosis of hands and feet, short stature and various skeletal anomalies (small hands, hypoplastic thumbs, hypoplasia of the patella, diffuse osteoporosis). Molecular analysis for RECQL4 mutations, revealed a nonsense homozygous p.GLN757X mutation. During a follow-up visit, the patient reported a secondary amenorrhea. Cushing's syndrome was suspected, since the patient displayed central obesity with high levels of cortisol and corticotrophin-releasing hormone. This diagnosis was however discarded given the negativity of dexamethasone suppression test in addition to the normality of thoraco-abdominal tomodensitometry and pituitary magnetic resonance imaging.

Discussion

RTS is caused, in 65% of cases, by homozygous or compound heterozygous mutations in the RECQL4 helicase gene, determining a defect in helicases functioning, that is found in a number of genetic disorders with genomic instability and predisposition to cancer as common features. XP is one of these characteristic genodermatosis, which explains the family history of XP in our patient. The nonsense exon 14 mutation c.2269C > T (p.Gln757X) seems to be the second recurrent mutation shown on the world map. Cutaneous and skeletal manifestations noticed in our patient are common among RTS patients. Endocrinological disorders are less frequently reported. Hypercortisolemia with central obesity has not been described in RTS patients. Given her genetic predisposition to cancer, our patient was suspected to have a paraneoplastic syndrome. The negativity of hormonal and radiological investigations suggested the diagnosis of cyclic Cushing's syndrome.

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EP81

Epilepsy induced by severe hypoglycemia: about three cases

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Introduction

When hypoglycemia is deep and repeated, it can induce various neurological disorders, including epileptic seizures. The link between hypoglycemia and epileptic phenomena is complex and poorly explained. We report 3 cases of epilepsy induced by repeated episodes of deep hypoglycemia.

Cases report

Mr D.M, 48 years old, with a history of 3 episodes of hypoglycemic coma, admitted for status epilepticus with a blood glucose level of 0.4 g /l; cerebral CT was normal. The encephalogram showed a slowing of the background rhythm with paroxysmal fronto-central bilateral anomalies. Biological test shows endogenous hypersecretion of insulin; echoendoscopy revealed an hypoechogenicity of 2 cm/2.5 cm at the head of pancreas. The second case is a 38-year-old patient treated for epilepsy for 2 years, admitted for a major generalized tonic-clonic seizure with left hemiplegia. MRI brain was normal, glycemia was at 0.3 g /l, insulin levels and peptide C were too high, an Octreoscan is required; an endocrine tumor of the pancreas secreting insulin is strongly suspected in these two patients. The third case is a 22-year-old patient, diabetic type 1, receiving insulin for 6 years, he has a history of hypoglycemic coma and he is hospitalized for a new episode revealed by generalized tonic-clonic seizures. The encephalogram showed a slowing of the background rhythm with paroxysmal fronto-central bilateral anomalies. Cerebral MRI showed an hypersignal in T1 and T2 of the basal ganglia.

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EP82

Effectiveness and safety of candesartan cilexetil/hydrochlorothiazide combination in jordanian hypertensive patients at risk of cardiovascular disease

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Rationale and objectives

Validation of new therapeutic regimens in the treatment of hypertension, particularly in poorly controlled patients at high risk for cardiovascular disease, is urgently needed. We evaluated the efficacy and safety of two doses of the candesartan cilexetil/hydrochlorothiazide combination (Blopress Plus®) in hypertensive patients in Jordan.

Methods

An observational, multicenter, prospective, open-label study of Jordanian adult (18 years or older, $n = 390$) hypertensive patients attending outpatient clinics was conducted over eight weeks. Patients were stratified according to their cardiovascular disease risk into low/moderate- and high/very high-risk groups. Two doses of Blopress Plus® (16/12.5 or 8/12.5 mg) were started at baseline, and blood pressure readings and adverse events were subsequently analyzed at the 4- and 8-week time points.

Results

Mean systolic and mean diastolic blood pressures were significantly reduced 4 and 8 weeks after treatment with Blopress Plus®. Overall, 85.6% and 94.6% of the patients achieved target blood pressure at the 4- and 8-week time points, respectively. Proportion of patients achieving target blood pressure was not significantly different between the two cardiovascular disease risk groups. 1.3% of patients reported non-serious adverse events, of which only dizziness was perceived as related to the study drug.

Conclusion

Blopress Plus® is an effective and safe antihypertensive drug therapy, with a considerably high success rate in achieving target blood pressure in patients with high/very high cardiovascular risk.

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EP83

Hyperprolactinemia

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Introduction

Hyperprolactinemia may be physiological or caused by discontinuation of normal prolactin regulation because of certain drugs or by other diseases such as kidney, ovarian and thyroid diseases.

Materials and methods

This is a retrospective study of 30 patients presenting with hyperprolactinemia.

Results
The average age was 30 years old. 20 patients married, 10 no married (30%). The indication of the prolactin dosage was primary or secondary amenorrhea in 5 cases (16.5), isolated galactorrhoea in 8 cases (26%) or associated in 9 cases (30%), cycle disorders in 18 cases or primary or secondary sterility in 5 cases. The clinical examination was normal in 10 cases and abnormal in 16 CAS. The etiological investigation of hyperprolactinemia was based on MRI in 16 cases (53%), 11 of which were pathological, one in 10 cases (37%), 2 of which were pathological, one sella turcica in 4 cases (13%), 8%), mammary cytology in 2 cases and mammography in 8 cases. The driving was based on medical treatment, other treatment in 8 cases; discontinuation of drug intake in 3 patients; a patient was referred to neurosurgery.
Conclusion
Prolactinemia remains an essential biological examination for diagnostic orientation in certain pathologies. MRI is now the only way to confirm the diagnosis of pituitary adenomas.

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EP84

Osteoporosis issues & complementary Indian medicine: three years experiences in Asian population

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Issues
No specific centre in asia for Osteoporosis patients treatment/rehabilitation. We used locally available Complementary Indian Medicines [CAM] for providing home based care in rural/tribal areas.
Aims
To provide CAM to poor patients in collaboration with Traditional-faith-hearers. Evaluated cost-efficacy of CAM & response of pain of fractures to CAM alongside analgesics.
Methods
This was a cross sectional, observational analysis study. from April 2014 to November 2018, 122 patients [$n=122$] of RA aged 34–67 years enrolled. 68% females, 32% males. 43% returned to villages after prolonged therapy in city hospitals on allopathic drugs. 12% physical deformities. self report questionnaire distributed to patients attending NGO clinics with consent from state ethics committee and patient's consent...Our NGO nurses treated patients with TFH in providing CAM. Mud therapy 21%, Bach-flower remedy 40%, Accupressure/Accupuncture 57%, Hydrotherapy 24%, Hypnotherapy 75%, ayurvedic therapy 82%, 26% on Unani Medicines, 61% on Homeopathic medicines, 72% on Herbal-Oil-TFH massage therapy, 58% Aromatherapy.
Results
We treated patients in 16 sessions CAM. feedback Performa given to subjects & responses evaluated periodically to modify treatment methodology. Our free NGO clinic module in functioning stages shown graphically to IOF-2010 conference participants. Average pain recorded weekly on a scale of 1 to 10. mean score pain fell from 8.2 (S.D. 1.4) to 3.8 (S.D. 2.7) points, which is highly significant ($P<0.001$). Symptom relief ($n=90$), Gr-1 wanting to find alternatives to drugs ($n=95$). Cost of CAM 52% cheaper compared to Allopathic medicines & islocally & has high acceptance
Conclusion
122 of patients used & preferred CAMs. Cost wise cheaper & patient compliance better. 12% dropped out of sheer frustration/fatigue. Patients need Psychosocial-Rx, Palliative-care-centers. Realizing divergent versions of CAM, multicentre study on this burning issue must be carried out. At ECE-2019, We shall form group with researchers from USA/Europe to substantially improve CAM approach. We NGO-representatives from developing nations need exposure to research technicalities/methodologies used by European/American experts in management of osteoporosis. This is indeed possible by my participation at 2019 ECE congress.

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Pituitary and Neuroendocrinology

EP85

The frequency of subclinical cushing's syndrome in women with polycystic ovaries syndrome

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Aim
The aim of investigation to study of the features of the Cushing's subclinical syndrome in women (CS) with metabolic syndrome (MS)
Material and methods
Under our supervision in the Department of neuroendocrinology of the Center of Endocrinology of MPH out-patient clinics with primary or secondary infertility in the period from September 2015 to July 2016 were examined 120 patients of childbearing age with metabolic syndrome in polycystic ovary syndrome (PCOS). The average age of patients was 25.5 ± 4, 3 years. 20 healthy women of the appropriate age were included in the control group. All patients underwent a set of studies, including the clinical (General blood and urine analysis), biochemical (blood glucose, glucose tolerance test), hormonal (LH, FSH, prolactin, estradiol, progesterone, free testosterone, dehydroepiandrostenedione (DHEA), 17-oxyprogesterone (17 OKS), antimuller hormone (AMG), insulin on day 14), determination of the cycle), cortisol in the blood and free cortisol in the daily urine.
Results
It was found that the patients were divided into three groups: 1 Gy. - patients with primary PCOS-23 cases (19%), 2 Gy. - patients with secondary PCOS in obesity-89 cases (74%), 3 g. - patients with secondary PCOS and subclinical SC - 8 cases (7%). In 1 group of patients there was a significant decrease in both pituitary and ovarian hormones in the background of hyperandrogenemia. Further, in the second group of patients was also revealed a significant decrease in pituitary hormones on the background of hyperandrogenemia, while ovarian function was within normal limits. In the third group of patients was also revealed a significant decrease in pituitary hormones on the background of hyperandrogenemia, hypercortisolemia, hyperinsulinemia.
Summary
Thus, in all groups on the 14th day of the cycle, there was a significant decrease in the basal values of LH, FSH, IGF-1, progesterone, estradiol against the background of hyperandrogenemia. At the same time, hyperinsulinemia was observed in groups 2 and 3. Only patients of group 3 had significantly increased values of DHEA, 17 OKS and cortisol of blood. Mean values of prolactin, AMH was normal.

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EP86

Prognostic interpretation of four different dynamic biochemical tests of growth hormonal status for acromegaly

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Acromegaly is an insidious disease that results from excessive growth hormone (GH) secretion from the pituitary tumor. Major advances have occurred in the understanding of some aspects of acromegaly, such as the biology of pituitary tumors, physiology, molecular mechanisms of GH secretion. In a point of GH producing pituitary adenoma, it was located in a pituitary gland, even though macroadenoma. Macroadenoma was bigger than normal pituitary, remnant normal pituitary gland existed with shrunken state. So, GH was secreted from the both pools of GH of the normal remnant pituitary gland and GH producing adenoma respectively. These GH secretory phenomena by blood glucose were interpreted as physiologic response with pituitary GH pools. Neuroendocrinologist must investigate characteristics and dynamic patterns of these two different pools of GH at the time of diagnosis for the GH behavior of acromegalics. The physiologic GH pools were mainly regulated by blood glucose levels. Hyperglycemia could suppress GH secretion from the normal pituitary via somatostatinergic pathway, and somewhat influence to block GH secretion from the GH producing pituitary tumor. For checking it, we used oral glucose tolerance test (oGTT) with 75 grams of glucose solution. Also, hypoglycemia below 40 mg/dL induced by regular insulin (insulin tolerance test, ITT) could stimulate GH secretion from the normal pituitary gland at 60 to 90 minutes after insulin injection. The GH secretory dynamic pattern would be normal, if the peak GH level was over 5 μg/L during test. These GH secretory phenomena by blood glucose were interpreted as physiologic response with pituitary GH pools.
During medical treatment, we also tested previously mentioned 4 different active tests reflected to GH secretory status from the normal pituitary and tumor tissues.

Average treatment period was 10.5 (6.3–24.5) years for cured patients and 9.4 (4.9–14.0) years for uncured patients. After medical treatment, cured patients showed that complete responder rate was 100% (8/8) for TRH stimulation test (TST), 87.5% (7/8) for insulin tolerance test (ITT), and 100% (8/8) for octreotide suppression test (OST). Uncured patients showed that complete responder rate was 75% (6/8) for TST, 75% (6/8) for ITT and 25% (2/8) for OST. Fully completed responders of these 3 dynamic tests revealed that 50% (4/8) from cured group, and 25% (2/8) at the time of pre-treatment. After treatment, full responded patients of these 3 different tests were 87.5 (7/8) from cured group, and only 12.5% (1/8) from uncured group.

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EP87

Studying of a condition of reproductive function of patients with the inactive pituitary adenomas (IPA)

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At IPA development of a tumor leads to various of pituitary dysfunction, including violates the gonadotropic function of the pituitary gland and there are disorders of sexual and reproductive function. The purpose of our research was studying of a condition of sexual system and gonadotropic function of a hypophysis at patients with is IPA.

Results and discussion

In the analysis of a condition of sexual system at 126 women with it is IPA to 50-year age the following groups are revealed: 1) patients from the oligomenorrhea – 46/126 (36.5%), at 38 of which were present clinical and biochemical signs of a polycystic ovary syndrome (the small-cystic ovaries with ultrasound of the pelvic organs, a high rate of a ratio of LH/FSH raised or supranormal concentration of LH, 8 of them, according to ultrasonography, had a uterus hypoplasia); 2) patients from the secondary amenorrhea – 52/126 (41.3%), at 6 from which at ultrasound of bodies of a small p ultrasound of the pelvic organs the hypoplasia of ovaries and a hypoplasia of a uterus, at one — polycystic ovaries, and in blood serum - low concentration E is revealed; 3) patients with a preserved menstrual cycle and no changes in the pelvic organs at ultrasound (28/126 patients – 22.2%), but at the 3rd of them were raised concentration E and T, and at one the hirsutism was observed. Clinically men with it is IPA as well as women, depending on a condition of sexual system represent three groups: with a normal state of sexual glands (48.6%); hypogonadotropic hypogonadism (40.2%) and reduction of volume of small eggs (11.2%). Existence of high concentration of FSH in blood in combination with increase in volume of small eggs allows diagnosing an active gonadotropic tumor of a pituitary for men.

Conclusions

So, on a condition of sexual system at the time of establishment of the diagnosis it is IPA men and women can be presented by three groups: with a secondary hypogonadism (40.7%); with a normal state of sexual system (22.0%); with polycystic ovary syndrome (36.5% of women) and reduction of volume of small eggs (11.2% of men).

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EP88

Secondary amenorrhea as unique manifestation of acromegaly due to giant pituitary adenoma

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Introduction

Pituitary adenomas are considered to be benign tumors that are diagnosed by its sympthoms (secondary to compression or hormonal secretion) or incidentally in an imaging technique performed because of another reason. 'Silent' somatotrophinomas are very rare. This type of adenoma is typically large and despite it presents with mild or no acromegalic features it usually develops hormone secretion.

A case report

A 29-year-old spanish female with no previous disseases asked to her primary care doctor because of secondary amenorrhea. After that, she was studied in gynaecology consult by an exhaustive ultrasonography examination that was absoloutely normal and a blood test which rouled out pregnancy and showed low gonadotropine (LH and FSH), estrogen and prolactine levels with a normal kariotype (46 XX). With this findings, gynaecologists asked endocrinology department for its cooperation. She had no visual fields deffects, optical coherence tomography (OCT) was normal and she denied headache or other sympthoms of pituitary volumen expansion. No hyperandrogenism signs. Continuing with secondary amenorrhea study, endocrinologist ordered a pituitary MRI, that revealed a giant pituitary adenoma (41 mm high, 30 mm wide and 24 mm deep). It extended up and out of the sella turcica, stretching the optic chiasm, both cavernous sinus and pituitary infundibulum. A complete hormonal blood test revealed high somatomedin C (IGF-1) levels, without growth hormone (GH) supression at an oral glucosa tolerance test (OGTT). Waiting for surgery, somatostatin agonists treatment was performed, without any changes in tumour size. Endoscopic transsphenoidal surgery was performed in october 2018. However, the tumour was not completely removed. Some weeks after surgery visual fields and OCT were normal. Three months after surgery the patient doesn't have nor clinical nor biochemical hypopituitarism and she hasn't noticed any visual defects, despite it can still be found on MRI tumor remnant.

Conclusion

Giant pituitary adenomas (more than 4 cm adenomas) are commonly diagnosed by its clinical manifestations, that's why we should pay special atention to each sympthom isolated. This is a remarkable case of acromegaly with secondary amenorrhea as its only manifestation, which demonstrates the importance of a complete pituitary hormonal study in patients presenting with apparently nonsecreting macroadenomas.

References

1. Sidhaye A, Burger P, Rigamonti D, Salvatori R. Giant somatotrophinoma without acromegalic features: more 'quiet' than 'silent': case report. Neurosurgery. 2005;56:E1154. doi: 10.1227/01.NEU.0000157961.67867.E5.

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EP89

Pituitary neuroendocrine tumor/pit 1 with gh producting cells

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GH secreting adenomas could be associated with clinical acromegaly with or without hyperprolactinemia, being rare cases of non functioning adenomas. They correspond a 25–30%of pituitary adenomas, generaly presented as macroadenoma.Frequently, they have another hormones production, often prolactin and TSH. Almost 75% of cases are macroadenomas. A 48-year-old Caucasian patient admitted complaining of facial craniofacial alterations, polyarthralgia, holocranial headache and paresthesia in cuffs several years ago. Amenorrhea since the age of 30. Associated comorbidities: Type 2 diabetes one year in treatment with insulin and metformin, arterial hypertension, anxiety. No family history suggestive of endocrinopathy. The physical examination showed the following randomness: cervical acanthosis and bilateral peri-ocular, mild hepatomegaly and fingers and feet in the form of sausage. Galactorrhea bilateral mamillary expression. Hemodynamically stable. Confirmed by hormonal dosages diagnosed with acromegaly, resonance of the pituitary region showed an expansive suprasellar lesion with involvement of the entire left carotid, compressing the optic chiasm and measuring 3, 1×2, 5×2, 6 cm. Initiated treatment with Octreotide LAR and forwarded to neurosurgery. The patient evolved with central hypothyroidism and was treated with levothyroxine. He performed debulking of the lesion hypophyseal eight years after the indication, in this period remained in use of the analogs of somatostatin and cabergoline. Immunohistochemistry revealed positivity for GH, PIT-1 e cytokeratin 8 with negative E-cadherin. KI-67 positive in less than 1% of the cells. It is noteworthy,that the positivity in paranuclear pattern of CAM5.2, with absence of expression in membrane for E-cadherin is compatible with the subgroup of hypophysis adenomas produced by GH, ultrastructurally characterized, with sparsely granular,exhibiting less indolent behavior in this family of tumors, this neoplasm exhibits a lower response to treatment with somatostatin analogues.

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EP90

A metastasis of large B-cell lymphoma mimicking a pituitary adenoma: a case report

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Background
Pituitary metastasis are rare, however, not well-documented. They are usually encountered in elderly patients with disseminated malignant disease. The most frequent are metastases of breast and lung cancer. We herein report a case of an old patient with pituitary metastasis of a mediastinal lymphoma.
Case report
A 88-year-old man with a history of treated prostate cancer and primary hypothyroidism presented to our emergency department with headaches, asthenia and fast progressing bilateral paraplegia. Thoraco abdominal computed tomographic (CT) scan detected a large mass of 73*70*180 mm at the posterior mediastinum with multiple pleural and vertebral metastases. The 18F-*FDG*-TEP scan confirmed the mediastinal mass wich was intensely hypermetabolic and revealed an intensely hypermetabolic mass in the pituitary fossa (SUV max 16.8). Magnetic resonance imaging of the pituitary revealed a sellar mass of 15*9*14 mm involving the pituitary gland which is also extended into the right cavernous sinus. Laboratory tests indicated an elevated LDH level,a normochromic and normocytic anemia of 10 g/dl, a lymphopenia and a normal hormonal profile. A CT-guided biopsy of the mediastinal mass was done and the histological examination revealed that it was the infiltration of a large B-cell lymphoma. Diagnosis of the pituitary metastasis was made by identification of lymphomatous cells in the cerebrospinal fluid. Chemotherapy was then initiated.
Conclusion
This case illustrated a rare cause of pituitary metastasis: the non Hodgkinien lymphoma. This diagnosis is usually difficult to differentiate from pituitary adenoma, meningioma and other sellar lesions. An earlier diagnosis may lead to an appropriate therapy and potentially improving quality of life.

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EP91

Thyroid diseases during acromegaly: about 43 cases

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Introduction
Acromegaly is a relatively uncommon disease and is frequently associated with thyroid diseases whose risk increases with the age of the disease.
Objective
The purpose of our study was to determine the different thyroid abnormalities observed during acromegaly to improve their management.
Patients and methods
Retrospective, descriptive study involving 43 acromegalic patients hospitalized at the Department of Endocrinology, Diabetology and Metabolic Diseases CHU IBN ROCHD, Casablanca from January 2005 to December 2018. All patients underwent morphological and functional exploration of the thyroid.
Results
The meanage of our patients was 48 years (13–73), with sex ratio H / F: 0.53 and a diagnostic delay of 4 years. Goiter was present in 74.4% of cases, of which 16.2% had nodular goiter and 58.1% had multi-heteronodulargoitre. Thyrotropic insufficiency was observed in 32.5%. No cases of primary hyperthyroidism have been reported. And one case of papillary thyroid carcinoma was diagnosed inone patient.
Conclusion
The elevation of the IGF1 level plays a major role in the pathophysiology of thyroid disorders, hence the need for systematic morphological and functional exploration of the thyroid during the discovery of acromegaly and surveillance. regular and possible cytopraction of suspicious nodules is necessary in order to watch for thyroid abnormalities that may appear during the evolution of the disease.

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EP92

Cardiovascular manifestations of acromegaly: about 43 cases

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Introduction
Acromegaly is a rare endocrinopathy, potentially fatal by its metabolic, cardiovascular and neoplastic impact. The aim of this work is to study the cardiovascular impact of acromegaly and cardiovascular risk factors during acromegaly.
Materials
This is a retrospective, descriptive study of 43 acromegalic patients admitted to the Department of Endocrinology, Diabetology and Metabolic Diseases CHU IBN ROCHD, Casablanca from January 2005 to December 2018.
Results
The average age of our patients was 48 years (13–73), with sex ratio H / F: 0.53. HBP was present in 37.2%, glycoregulatory abnormalities in 60% of cases, dyslipidemia in 41% and hyperuricemia in 5%. Cardiovascular examination revealed irregular rhythm in one patient and dyspnea stage II was noted in 32% of cases and stage III in 39%. Obesity was observed in 49% of cases. Cardiac ultrasound found hypertrophic cardiomyopathy in 7% of patients. The association of two risk factors was observed in 26.2%, three risk factors in 13.9% and four risk factors in 13.9%. The other patients a reduction in the number of antihypertensives and an improvement in their metabolic profile were also appreciated.
Discussion
Cardiac involvement is constant during acromegaly. HBP is more frequent and severe as the disease is older and the incidence of other cardiovascular risk factors is higher than the general population requiring multidisciplinary management to improve the cardiovascular prognosis.

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EP93

Etiology of syndrome of inappropriate antidiuretic in patients on parenteral nutrition: prospective multicenter study

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Introduction
Syndrome of Inappropriate Antidiuretic (SIAD) is the most frequent cause of hyponatremia in parenteral nutrition (PN) patients. Moreover, SIAD may be caused by multiple etiologies (drugs; pulmonary, neurological or abdominal disorders; malignant disease; idiopathic…). Our objective was to evaluate the main etiologies of SIAD in patients receiving PN.
Methods
Prospective, non-interventional, multicenter study in 19 Spanish hospitals. Forty-seven patients with SIAD-induced hyponatremia while receiving PN over a 9-month period were recruited. Hyponatraemia was defined as a Serum Na level (SNa) <135 mmol/l. Patient data collected included sex, age, prior comorbidities, use of drugs, cause of hospital admission and serum sodium levels (SNa) before and following PN initiation. Parameters for study of hyponatremia were also included, such as clinical volemia, the presence of pain, nausea, gastrointestinal losses, edema, measurement of creatinine, plasma and urine Osmolality, urinary electrolytes, cortisolemia, and thyroid stimulating hormone.
Results
59.6% were men. The average age was 66.9 (s.d. 11.5). 53.2% had hyponatremia before PN initiation. All patients had diagnostic criteria for the SIAD. Most probable etiologies of SIAD were: malignant disease (55.3%), drugs (23.4%:

antidepressants, pregabalin/gabapentin, opiatas,...), abdominal disorders (10.6%), pulmonary disorders (2.1%), and idiopathic (2.1%). Etiology of SIAD could not be assessed in 3 patients. No patient had SIAD caused by neurologic disorder.
Conclusions
The diagnostic approach of etiology of SIAD is complex. Multiple clinical factors must be taken into account. In our series of patients receiving PN, paraneoplasic secretion of antidiuretic hormone was the most frequent cause of SIAD-induced hyponatremia. Other etiologies were different than in the general population, probably related to specific clinical features of patients on PN.

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EP94

TSH secreting pituitary tumor

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Thyroid hypophyseal adenomas correspond to about 0.5 to 1% of pituitary adenomas. Tumor hypersecretion of TSH may also be present in plurihormonal adenomas that simultaneously secrete growth hormone and/or prolactin or FSH and LH glycoprotein hormones. A 37-year-old patient complaining of ears, hands, feet and face growth for 1 year. He reported amenorrhea for 04 years, sweating and joint pains. Associated comorbidities: Systemic arterial hypertension for 4 years in the use of enalapril and hydrochlorothiazide, pre-diabetes using metformin with diagnosis for 3 months of osteoarthrosis and carpal tunnel syndrome.The physical examination showed acrocodons in the umbilical region. Face with prominence of the zygomatic arch, discrete prognathism and Macroglossia. Galactorrhea in the left breast to digitoexpressao. Laboratory revealing increased IGF-1 and prolactin, TSH in the normality range with elevation of free T4. Basal gonadotropins within the normality range with low estradiol. Normal basal Cortisol. A GH suppression test was performed with glucose revealing not suppression, despite hyperglycemia. Nuclear Magnetic Resonance (NMR) of a hypophyseal region showing enlargement of turcica saddle with glandular indefinition and hypophyseal stem, the costs of large expansive sealing, with supra-sealing extension, predominantly solid, compressing cranially the optic chiasm, insinuating itself to both cavernous sinuses, involving about 180 degrees in both carotid, with discontinuity of the sealing floor, with component of the lesion extending and obliterating the sphenoid sinus It features heterogenous enhancement, measuring $3.9\times4.1\times3.5$ cm. Started treatment with Somatostatin analog, Octreotide LAR, with progressive increase of dose to 40 mg/day and posterior association with Cabergoline. Transsphenoid surgery was performed with immunohistochemistry compatible with pituitary Adenoma producing TSH, GH and prolactin. Ki-67:2%. NMR post surgery: Empty saddle. Colonoscopy without alterations. DXA Osteopenia. It evolved with non-normalized and increasing IGF-1 unresponsive to Octreotide 40 mg monthly, beginning of response after association with Cabergoline. New NMR showed recurrent lesion with FSH/LH, TSH and ACTH preserved axes. In programming for a new surgical intervention. Thyrotropinomas are rare tumors. The exposed case reveals a patient with a plurihormonal adenoma evolving with post-surgical recurrence and lack of response to somatostatin analogs and decreasing IGF-1 levels after introduction of cabergoline.

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EP95

Acute pituitary apoplexy-one year case series

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Objectives
Pituitary Apoplexy, either as a result of haemorrhage or infarction, remains a rare but serious Endocrine Disorder, requiring urgent clinical assessment and management. The British Endocrine Society (BES) has set out recommendations regarding the diagnosis and management of pituitary apoplexy, but there remains little published literature depicting this. The aim of this study was to compare our current Management practise of Pituitary Apoplexy with the recommendations set out by The British Endocrine Society (BES).
Methods
In this study, we retrospectively collected data on all new diagnoses of Pituitary Apoplexy in a 12 month period, ranging from 1/1/2015 to 31/12/2015. We assessed data including patient demographics, presenting symptoms, Type of Pituitary tumour, time to first assessment of visual fields and acuity, time to Specialist Endocrine assessment, time to Neurosurgical assessment, and reassessment of visual fields and acuity at the time of discharge with comparison at presentation. Data was collected from Patient Records and Patient imaging software.
Results
4 male patients were diagnosed with pituitary apoplexy. Mean patient age was 61 years (46 to 76 years). All 4 suffered from diplopia and impaired visual acuity. All 4 were Macroadenomas. All 4 were commenced on IV Saline within 24 hours. 2 out of the 4 (50%) were commenced on Parenteral Hydrocortisone within 24 hours. Mean Time to Endocrine review was 31.6 hours (Range 22.03 hours to 45.5 hours). Mean time to Neurosurgical review was 48.5 hours (Range 25.9 hours to 100.4 hours). All 4 were managed conservatively. Mean time to first formal Visual acuity/field assessment 54.2 hours (Range 31.2 hours to 71.2 hours).
Conclusion
Overall, we are adhering to the BES Apoplexy recommendations. All 4 patients showed objective improvements clinically and in visual acuity following treatment. However, the length of time to specialty input and administration of parenteral Hydrocortisone remained suboptimal.
Disclosure of of Interest
None Declared.

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EP96

Combination of cushing's syndrome and acromegaly: a rare case report

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Cushing's syndrome (CS) is a relatively rare disease characterized by autonomous hypersecretion of cortisol. The incidence of CS is estimated to be equal to 2–3 cases per million inhabitants per year.The incidence of acromegaly is 3–4 patients per 1 000000 per year. The disease is caused by hypersecretion of growth hormone which is mainly caused by benign tumour of the pituitary gland. In our case report we present a 41 - year - old woman suffering from both Cushing's syndrome and acromegaly. The patient was examined in National Institute of Endocrinology and Diabetology Lubochňa for a centripetal type of obesity and hirsutism. Laboratory tests revealed high plasma cortisol levels without circulating variation, hypercortisoluria and elevated plasmatic levels of adrenocorticotropic hormone (ACTH). A 2 mg dexamethasone blockade was performed without adequate cortisol suppression in serum and urine up to 8 mg blockade resulted in cortisolure suppression. A magnetic resonance imaging (MR) scan revealed suspect picoadenoma of the pituitary gland (size 2 mm). Subsequently trans-sphenoidal resection was performed. Histopathological and immunohistochemical examinations did not reveal the ACTH-producing pituitary adenoma. After surgery hypercortisolism persisted with newly revealed high plasma insulin-like growth factor-1 (IGF-1), basal growth hormone (GH) was normal. We subsequently performed oGTT test with GH which was not suppressed after glucose administration. Treatment withKetoconazole at dose 200 mg 1/ 2-0-1 and somatostatin analogues (Lanreotide) at dose 120 mg every 42 days were initiated. Control magnetic resonance imaging of the sella demonstrated small tumour of pituary gland of size 3×5 mm. Later 3 years after first surgery another trans-sphenoidal resection of residue was performed. Histological and immunohistochemical examinations did not confirm adenoma with ACTH and RH secretion.After second surgery, IGF-1 plasma levels were not normalized with persistence of hypercortisolism. The treatment with Lanreotide at the initial dose as well as Ketoconazole was reinitiated (with increased dose of Ketoconazole to 1-1-1 tbl per 200 mg).

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EP97

Restoration of fertility in a woman with giant prolactinoma in response to cabergoline treatment (case report)

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A 32-year-old woman presented with primary amenorrhea, prolactin (PRL) level of 154150 mIU/l (40–530 mIU/l) diagnosed with an endo-supra-infra-laterosellar giant pituitary adenoma measuring maximum 6.2 cm. The patient was prescribed a treatment with cabergoline (CAB) at an initial dose of 0.5 mg per week. The treatment decreased the tumour size and brought to normal the level of PRL. After 7 months of CAB treatment menarche was achieved, after 12 months the patient became pregnant. The pregnancy ended up with a missed miscarriage at 6–7 weeks; an artificial abortion was conducted. Pituitary MRI scan did not show any negative changes. After 18 months from the start of the treatment the patient got pregnant for the second time. At 25 weeks of gestation an MRI scan of the brain was conducted which did not show any increase in the tumour size. At 38 weeks the patient delivered a healthy full-term girl via C-section. There was no breastfeeding; the CAB therapy was resumed after the delivery. During the treatment, prolactin level returned to the normal range and the menstrual cycle was restored. After 3 years the patient got pregnant for the 3rd time. The pregnancy ended up with a delivery of a healthy girl via C-section. The patient did not receive CAB during the pregnancies; the examination did not show any tumour enlargement. After the delivery the patient continued taking CAB. The further MRI scans did not show any tumour enlargement. Therefore, CAB therapy was effective to normalize PRL level, reduce the tumour size, induce menarche and pregnancies which lead to the birth of healthy children in a woman with primary amenorrhea and a giant prolactinoma invading the skull base bones.

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EP98

Effectiveness of somatostatin analogues in the treatment of acromegaly

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Introduction
Somatostatinanalogues (SSAs) are the largest contributor to the direct medical cost of acromegaly management worldwide. The aim of this review was to expose our experience and report available evidence on the effectiveness of SSAs in the treatment of acromegaly.
Methods
This is a retrospective study including ten acromegalic patients followed in the Endocrinology - Diabetology Department at Mohamed VI University Hospital in Oujda, Morocco.
Results
The mean age at time of diagnosis was 49 years with a female predominance. The median delay to diagnosis was 8 years. Etiological diagnosis was pituitary adenoma in all our patients, macroadenoma in 9 patients and microadenoma in one patient. Eight patients had received medical treatment with SSAs: Lanreotide LP 120 mg. This treatment was given pre-operatively in four patients with non-invasive adenoma and in three patients with second line after incomplete tumor removal with persistent tumor residue. The pre-therapeutic evaluation had objected a vesicular sludge in one patient and a lithiasis of the main biliary tract in one patient. Treatment with SSAs has allowed IGF1 to be normalized in 62.5% of cases. During follow up, there was a sides effects, the occurrence of vesicular lithiasis were complicated by cholecystitis in one patient and transit disorders in another patient.
Conclusion
Lanreotide is the only SSAs available in Morocco. It represents a particularly interesting alternative in case of somatotropic hypersecretion after surgery or in inoperable forms.

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EP99

Challenges in management of diabetes insipidus with impaired thirst perception

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A 37-year-old female, referred by gynaecologist with low prolactin and free T4 after work up for secondary amenorrhea despite removal of contraceptive coil 18 months ago. Her only daughter was born seven years ago with no complications. Patient admitted to have tiredness and dizziness for a few years but denied headache or visual symptoms. Pituitary hormone profile confirmed secondary hypothyroidism, secondary hypogonadism, low prolactin, low IGF-1 level but normal adrenal axis. MRI revealed pituitary tumour measuring $6\times4\times2$ cm compressing the optic chiasm. Initial visual assessment demonstrated bitemporal hemianopia and preserved visual acuity. She developed severe headaches and vomiting within a few days and repeat visual assessment suggested rapid worsening of vision. Repeat imaging showed no evidence of pituitary apoplexy and she underwent urgent transcranial surgery. The surgery was challenging as tumour was adherent to hypothalamus, walls of third ventricle and optic chiasm.Post-surgery, she developed diabetes insipidus and symptoms of hypothalamic dysfunction including impaired thirst, hyperphagia, impaired temperature regulation and anterograde amnesia. Treatment of diabetes insipidus with impaired thirst was challenging even with strict fluid allowance and desmopressin. Patients with diabetes insipidus and intact thirst drink appropriate quantity of fluids to replace urine losses driven by hypothalamic thirst mechanisms. While on desmopressin, one must drink to thirst. Achieving optimal fluid and electrolyte balance becomes challenging if thirst perception is impaired. She was started on oral desmopressin 100 microgram twice a day with strict fluid allowance of 750 ml to 1250 ml every 12 hours. She had strict monitoring of input and output, serum electrolytes and serum and urine osmolality. Our patient had predominant polydipsia despite desmopressin intake, no polyuria and low serum sodium. Despite regular monitoring, serum sodium levels fluctuated as she was spotted drinking water from taps of the toilet. It is further difficult to achieve a satisfactory fluid balance at home after discharge even with family support. This case outlines the difficulties in management of patients with diabetes insipidus and unreliable thirst perception. Frequent monitoring of biochemistry, accurate recording of fluid input and output, an acceptable fluid allowance, strict compliance with prescribed desmopressin, good communication with patient's primary care physician, carer supervision and family support are essential.

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EP100

Follistatin is negatively associated with growth hormone and insulin-like growth factor 1 in patients with acromegaly

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Background
Patients with acromegaly usually presented symptoms of the hypersecretion of growth hormone (GH). GH may increase insulin-like growth factor 1 (IGF-1), affect energy homeostasis, and cause complications in cardiovascular, skeletal, or metabolic systems. Follistatin is a glycoprotein with various biologic functions that plays a role in adipocyte differentiation, muscle stimulation, anti-inflammation and energy homeostasis. We evaluated the serum levels of follistatin in patients with acromegaly.
Subjects and methods
Forty acromegalic patients (15 male and 25 female) with a mean age of 52.8 ± 10.1 years were recruited. Correlations between follistatin and GH or IGF-1 were calculated.
Results
Serum levels of follistatin were negatively associated with GH and IGF-1 ($\beta=-0.34$, $P=0.034$, and $\beta=-0.57$, $P<0.001$, respectively).
Conclusions
Follistatin is negatively associated with GH and IGF-1 in patients with acromegaly.

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EP101

Pituitary apoplexy and transient hypopituitarism

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Introdution
Pituitary apoplexy (PA) is a rare clinical syndrome caused by sudden hemorrhage or infarction of the pituitary gland. PA may be the form of presentation of a pituitary tumor or occur during follow-up of a previously diagnosed macroadenoma. A high suspicion índex is required to establish a timely diagnosis.
Case report
A 54-year-old man was referred to Endocrinology department (04/2015) due to a pituitary macroadenoma. He reported sexual disfunction for 2 years and no headache or visual changes. On physical examination he presented normal BP, facial/scalp vitiligo, no stigmata of hypercortisolism or acromegaly and absent visual field defects upon confrontation. Laboratory work-up showed normal pituitary function except slightly hiperprolactinemia - 43.9 ng/ml (3.4–19.4) and magnetic resonance imaging (MRI) (03/2015) revealed a macroadenoma with suprasellar extension (18×11×10 mm) that contacted optic chiasm and signs of small circumscribed intratumoral hemorrhage. Hook phenomenon and macro-prolactinemia were excluded and Neurophthalmology observation was normal. Two months later the patient returned complaining of fatigue, adynamia, anorexia and weight loss of 10 kg. He denied headache or visual disturbance. At this time laboratory work-up showed: serum cortisol 1.1 ug/dl (3.7–19.4); ACTH 19.8 pg/ml (< 46); TSH 0.51 uUI/ml (3.4–19); FT4 0.46 ng/dl (0.7–1.48); total testosterone 0.35 ng/ml (1.4–9.2); LH 0.7 mUI/ml (0.57–12.07); FSH 1.71 mUI/ml (0.95–11.95); PRL 95 ng/ml (3.4–19.4), IGF-1 32.4 ng/ml (87–238). MRI revealed a large sellar lesion compressing optic chiasm and remodeling sellar floor with bilateral extension to cavernous sinus. In medial and right antero-lateral position a hypertense component was found in T1/T2 weights. PA and hypopituitarism were admitted and hormonal replacement therapy was started with prednisolone 7.5 mg/day, levothyroxine 75 mcg/day, testosterone 250 ml/1 ml 4/4 weeks and bromocriptine 5 mg/day. In the following 6 months, a complete recovery of the pituitary function was observed and replacement therapy was gradually withdrawn. Imaging study demonstrated collapse of the cystic/hemorrhagic macroadenoma measuring 14×10 mm with partial reabsorption of the hematic content. Surveillance was continued and at the last visit(10/2018) the patient was asymptomatic without therapy and imaging reevaluation showed expansion of the cystic/necrotic cavity of the pituitary macroadenoma, currently measuring 15×20 mm, with predominantly suprasellar development. Neurophthalmology reevaluation was normal.
Comments
In this patient, subclinical apoplexy of a non-functioning pituitary adenoma with transient hypopituitarism were observed. In the cases described about 80% of patients develop hypopituitarism, being ACTH deficiency the most relevant. In our patient we observed multiple pituitary deficiencies followed by full recovery. It should also be of note the reexpansion of necrotic/cystic cavity and consequent increase of the residual macroadenoma, that precludes a close surveillance.

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EP102

Thyrotropin-producing pituitary adenoma: 3 case reports

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Introduction
Thyrotropin-secreting pituitary adenomas represent less than 1% of all pituitary adenomas. Usually, patients present mild or moderate signs of hyperthyroidism and Hormonal evaluation shows increased free thyroid hormone concentration with detectable, normal or increased serum thyrotropin (TSH) level. Herein we report three cases of thyrotropin adenomas with particular clinical and biological features.
Observations
Three patients, aged 25 38 and 75 years old, presented severe headaches with Visual acuity disturbance. Only one patient presented clinical features of hyperthyroidism such as tachycardia, tremor and weight loss without goiter. However in all the cases, biological assessment showed normal TSH serum level (1.41 to 3 μU/ml), with low or normal free thyroxine (FT4) (5.9 to 12 pmol/l). Two patients had hypopituitarism including corticotropic and gonadotropic axis associated with hypothyroidism in one case. Huge macro adenomas were diagnosed with CT scan and MRI with cavernous sinus invasion and compression of optic chiasma in one case. A transphenoidal surgery was performed in emergency in two cases of apoplexy and in one case because of the visual impairment. After histopathological examination two tumors stained for TSH alone, and one tumor stained for TSH and prolactin. During follow up, hypopituitarism remained under hormonal replacement and a transient diabetes insipidus after surgery. And two patients had tumor recurrence requiring radiotherapy.
Conclusion
Transphenoidal surgery remains the treatment of choice in patients with TSH-secreting pituitary adenomas and somatostatin analogs seem to be an alternative medical treatment to surgery in patients with recurrent macroadenomas or invasive tumors.

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EP103

Non-functional pituitary adenoma

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Introduction
The non-functional pituitary adenoma (NFPA) is a benign tumor, which has a progressive development but it is a severe tumor by its neuro-ophthalmological and endocrine repercussions.
Patients and methods
It is about a descriptive and retrospective study conducted in 35 patients collected in the endocrinology department of Sfax between January 2000 and December 2017. The diagnosis of NFPA was based on the presence of pituitary adenoma on hypothalamic-pituitary imaging and the absence of clinical and biological signs of hormonal hypersecretion.
Results
Thrity-five patients were enrolled including 20 men (57.14%) and 15 women (42.28%). The average age of our patients was 49.23 years old with a sex ratio of 1.33. Pituitary tumor syndrome was the most common mode of discovery (85.7%). On imagery, a micro-adenoma was found in 8.57% of cases, a macro-adenoma in 77.14% of cases and a giant HA in 14.28% of cases. Suprasellar invasion was found in 71.42% of cases. These NFPA were complicated by pituitary insufficiency in 81.5% of cases. Gonadotropic insufficiency was the most common, found in 54.28% of cases. Adrenocorticotropic insufficiency and thyrotropic insufficiency were found in 37.14% and 38.28% of cases, respectively. Hyperprolactinemia of disconnection was observed in 28.57% of cases. The majority of our patients were operated on (62.85%) in the presence of neuro-ophthalmological disorders, endocrine disorders and pituitary apoplexy associated with neurological disorders.The immunohistochemical study showed 7 cases of null cell adenoma and 6 cases of silent pituitary adenoma. It was uninterpretable in 3 cases for almost total necrosis. Surgical complications were dominated by transient diabetes insipidus (18.18%), transient rhinorrhea and postoperative hyperphagia were found in 9.09% of cases each, bleeding and meningitis were found in 4.55% of cases each. Among our operated patients, 15 were regularly followed in the medium and long term, an improvement of the pituitary tumoral syndrome in the majority of patients (66%), an aggravation or appearance of a pituitary insufficiency in 12 patients (80%). Postoperative MRI revealed tumor residue in 6 cases and tumor recurrence in only one case. The average duration of follow-up in postoperative patients was approximately 18 months (extremes: 12 months – 3 years). Therapeutic abstention was indicated in 12 patients. The follow-up of these patients shows a stable clinical, biological and radiological state.
Conclusion
NFPA are benign, rare but serious tumors. It is a heterogeneous group by its clinical manifestations, its hormonal and ophthalmological impact.

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EP104

Corticotroph adenoma associated with a rare infection – case report

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Introduction
Cushing Syndrome have long been recognised to predispose patients to infection diseases, a consequence of the immunosuppression induced by corticosteroids. There is a predisposition to viral, bacterial, parasitic and especially fungal diseases. Opportunistic infections, particularly invasive fungal infections, represent a serious complication associated with an increased risk of mortality.
Clinical case
We represent a 55 years-old woman, poultry farmer, with diabetes diagnosis in January/2017. At September 2017 she was hospitalized at the surgery department (Viseu-Hospital) with an infected diabetic foot ulcer, where she began an intense headache, palpebral ptosis, anisocoria, prostration periods alternated with psychomotor agitation. Cranial CT showed 'a pituitary expansive lesion, with bone destruction and evidence of bleeding'. Laboratory findings: ACTH 1320 pg/ml (4.7–48.8), TSH 0.07 μUI/ml (0.35–5.5), FT4 0.8 ng/dl (0.9–1.8), prolactin 1.0 ng/ml (1.8–20.3). Patient was transferred to neurosurgery department of Coimbra Hospital with clinical suspicion of pituitary apoplexy, medicated with nasal desmopressin 20 μg 2id, L-thyroxin 50 μg id e hydrocortisone 50 mg 2id. At the neurosurgery department, she repeats laboratory tests: TSH 0.068 μUI/ml (0.4–4.0), FT4 0.9 ng/dl (0.8–1.9), ACTH 41 pg/ml (9–52), cortisol 22 μg/dl (5–25), GH 1.2 μg/l (<1.0), IGF-1 −168 ng/ml (81–225), FSH 4.2 mUI/ml, LH 0.2 mUI/ml, estradiol 17 pg/ml, prolactin 1.1 ng/ml. MRI showed a pituitary macroadenoma with apoplexy ($2.7\times2.8\times3.3$ cm). She underwent a transsphenoidal surgery with partial excision of the lesion (October/2017). Neuropathology: a corticotroph adenoma with apoplexy, bone destruction and fungal infection. In February/2017, at the endocrinology department hospitalization, distant fungal infections were excluded with CT scan; blood cultures and HIV were negative. The clinical case was discussed with infectiology physicians and it was decided no initiate anti-fungal treatment. After clinical stabilization, the patient was discharge, medicated with hydrocortisone 15 mg, L-thyroxin 50 μg and sitagliptin 50 mg 2id. She maintains endocrinology and infectiology visits.
Conclusion
The clinical case presented is a rare case of a corticotroph adenoma associated with pituitary fungal infection. The initial clinical suspicion was an apoplexy of pituitary macroadenoma and only neuropathology allowed the correct diagnosis. The pituitary apoplexy associated with surgery allowed the infection removal, the correction of hypercortisolism and glycaemic optimization. The absence of systemic disease made possible to dispense a systemic antifungal therapy. The imaging resolution of the lesion and the persistence of adrenal insufficiency suggest a good prognosis. In conclusion, the professional activity, the hypercortisolism and decompensated diabetes were contributor factors to this rare association.

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EP105

Therapeutic challenges in a case of TSH/GH co-secreting pituitary macroadenoma

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Introduction
Thyrotropin-secreting pituitary adenomas are rare tumors accounting for 1–2% of all pituitary adenomas and the diagnosis is based on the combination of high fT4 levels with normal to high TSH concentration in the presence of a pituitary adenoma. About one third co-secrete other hormones, of which, most frequently growth hormone (16%) followed by prolactin and gonadotropins.
Case report
A 60 years-old male patient presented in 2016 after the incidental finding of an $18\times16\times14$ mm pituitary macroadenoma on a CT scan performed while investigating a lipothymic episode. His medical history revealed arterial hypertension and sinus node dysfunction that required permanent pacemaker. The initial laboratory investigations showed high fT4 (2.23 ng/dl, N: 0.89–1.76) and TSH in the upper normal limit (3.03 μUI/ml, N: 0.4–4) in addition to hypersomatotropism: high IGF1 (404 ng/ml, N: 81–225) unsupressed GH during OGTT (1.39 ng/ml). The clinical examination showed no features of acromegaly and no signs of hyperthyroidism. The thyroid ultrasonography described multinodular goiter and the visual field test were normal. Treatment with somatostatin analogs was initiated with a favorable biological (IGF1 = 222 ng/ml, TSH = 1.12 μUI/ml, fT4 = 1.29 ng/dl) and imagistic response (mild tumor shrinkage: $16\times14\times14$ mm). Considering a surgical intervention, treatment has been disrupted, leading to another increasing of IGF1, fT4 and fT3 levels, which confirmed the suspicion of a mixed TSH/GH cosecreting adenoma. Somatostatin analogs were reinitiated, but despite the initially favorable evolution and the thyroid axis mentained within normal limits, the last investigations showed unsupressed levels of GH (1.206 ng/ml) and high levels of IGF1 (304 ng/ml, N: 51–187), requiring the association of cabergoline (1 mg/4 days).
Discussion
This case highlights the unusual presentation of a TSH/GH co-secreting macroadenoma in an asymptomatic patient. According to literature, surgical cure rate in such cases is less than two thirds due to predominance of invasive, large, fibrous tumors with a high risk of recurrence. In addition, in this patient, considering the surgical risks, treatment with somatostatin analogs seemed to be the proper approach with an initial favorable biological and imagistic response. Despite the sustained response on the thyroid axis, the presence of hypersomatotropism requires the association of dopamine receptor agonists, also considering gamma knife radiotherapy.

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EP106

Central resistance to thyroid hormone coexisting with autoimmune thyroid disease – case report

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Pituitary resistance to thyroid hormone (PRTH) is a rare, genetic cause of hyperthyroidism. It is characterized by a high concentration of free thyroid hormones, coexisting with elevated or normal concentration of thyroid stimulating hormone. The most prevalent features of this syndrome are typical symptoms of hyperthyroidism and goitre. Diagnosis of this condition does not exclude other comorbidities of the thyroid gland, including these of autoimmune origin. We present the case of a 55-year old woman with symptoms of hyperthyroidism, in the clinical picture seen as tachycardia and thyroid laboratory tests suggesting secondary thyroid disorder. During the diagnostic process focal lesions in the thyroid were ruled out, and TRH stimulation test revealed more than 10-fold rise in TSH concentration. What is interesting, an autoimmune thyroiditis was diagnosed. Thyroid ultrasound showed an unenlarged thyroid gland (total volume 12.3 ml) with a diffusely decreased echogenicity. The patient received thiamazole at first, however due to malaise and poor tolerance the antithyroid treatment was discontinued. Due to the elevated fT3 and fT4 levels and minimal symptoms of hyperthyroidism, the patient was given bromocriptine at a dose of 2.5 mg per day. After 5 months of treatment the patient was euthyroid and has remained in this state to this day.

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EP107

Pituitary stalk interruption syndrome: about 9 case report

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Introduction
Pituitary Stalk Interruption Syndrome (PSIS) is characterized by the presence of a thin or absent pituitary stalk, associated with hypoplastic or aplastic anterior pituitary and ectopic posterior pituitary (EPP) on magnetic resonance imaging (MRI). The objective of this study is to describe the clinical, hormonal and radiological aspects of PSIS.
Patients and methods
This is a retrospective longitudinal study of 9 cases of PSIS collected in the Endocrinology-Diabetology Department of Oujda's Mohammed VI University Hospital.
Results
Seven out of 9 patients with PSIS were male. The average age was 9,5 years and there were no familial cases. No history of the neonatal incident was found. The reason for referral was a short stature in all patients. An impuberism was found in 4 cases, and 2 cases had associated diabetes insipidus. Clinical examination revealed severe growth retardation in 55% of the patients and micropenis in 57% of the cases. The hormonal evaluation showed isolated GH deficiency in 33.3% of the cases and combined GHD in 66.7% of the cases. Pituitary MRI findings were pituitary stalk for all patients, and was associated with anterior pituitary hypoplasia in 2 cases, an ectopic posterior pituitary in 4 cases and absence of posterior pituitary in 1 case. The evolution was favourable with an average height gain of 10 cm after one year of GH therapy.
Conclusion
The signs and symptoms of PSIS during the neonatal period and infancy are often overlooked and therefore diagnosis is delayed. Early diagnosis and treatment of this rare disease can prevent permanent short stature of the patient and thus pledge an excellent opportunity to reach their normal height after GH therapy.

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EP108

Central diabetes insipidus in children: difficulties of etiological diagnosis

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Introduction
Central diabetes insipidus (DIC) is defined by the excretion of large volume of diluted urine, secondary to an absolute or relative deficiency of endogenous vasopressin. We report three observations of children with central diabetes insipidus.
Results
This study reports the case of three patients whose average age was thirteen years old (11, 13 and 15 y). The occurrence of polyuria-polydipsia syndrome was the main reason for consultation and hypotonic polyuria was present among all children. The physical examination was normal and the Minirin® test made it possible to diagnose DIC in all the cases. Concerning the MRI findings, 2 patients showed changes in the size of pituitary stalk thickness with the absence of posterior pituitary bright signal in one case; the other patient's MRI showed loss of the bright signal from the posterior pituitary gland without any other abnormalities. The biological assessment made mainly of alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (BHCG) and other autoimmune tests were screen negative.
Discussion
The central DI is rarely observed among children; the clinical presentation is often abrupt, making its diagnosis more or less easy. On the contrary, the etiological diagnosis usually stays unmasked long enough after the diagnosis is made, justifying prolonged and through follow up.

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EP109

Idiopathic short stature in a female patient

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Idiopathic short stature (ISS) is a condition characterized by a height more than 2 standard deviations below the corresponding average height for a given age, sex and population, without any identifiable systemic, endocrine, nutritional, or chromosomal disorder, and normal stimulated growth hormone (GH) levels. We report a case of a 17-years-old female, admitted to the hospital for endocrinology reevaluation. She was firsty reffered to endocrinologist for short stature at the age of 5 when laboratory and hormonal testing showed no abnormalities (normal hemogram, liver and renal function test, thyroid and cortisol axes; peak GH 20.6 μg/L). Her karyotype was a normal 46XX. Her birth height and weight were adequate but the past medical history was significant for 18 months imobilisation for Perthes disease at the age of 4. After primary evaluation, the patient avoided recommended regular checkups. According to her parents, her height velocity was 4.5 cm per year. She was reevaluated at the age of 11, when the anthropometric parameters showed height 125.5 cm (3rd percentile) and weight 46 kg (86 percentile). Laboratory investigations and hormonal analysis were without abnormalities. Her bone age was found to be at 10–10.5 years. On current admission, her height was 132.5 cm, weight 53 kg, body mass index (BMI) 30.42 kg/m^2, with waist and hip circumferences of 75.5 cm and 90 cm respectively. She achived menarche at age 11 with regular menstrual periods. Laboratory tests are still within normal limits. Her insulin-like growth factor (IGF)-1 level of 428 ng/dl was good and so the other hormonal analysis. This case focuses on clinical dilemmas raised during the irregular patient follow-up. The management of ISS remains a challenge since its treatment options are controversial. In documented studies, only modest evidence for efficacy with use of recombinant GH is noticed, but the therapy is generally not been shown to affect health related quality of life.

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EP110

A rare pituitary adenoma: silent corticotroph adenoma

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Introduction
Silent corticotroph adenomas (SCAs) are uncommon pituitary tumors, immunoreactive for ACTH, but without clinical evidence of hypercortisolism and present with local mass effects and some endocrine dysfunction. Case 43 years old male patient was diagnosed with pituitary tumor which was 5×3 cm in size. In history, 6 months ago he applied to another hospital with syncope and operated transsphenoidally. But these datas are unreachable. He had been suffering from weakness, impotence under the medication of testosterone and levothyroxine. There were no clinical symptoms about Cushing Syndrome. It was accepted as recurrent pituitary tumor and we decided to pterional craniotomy operation under the stress dose steroid treatment. Pre and postoperative, the hormone levels were found as ACTH: 151.34 (5–60 pg/mL), cortisol: 11.4, 0.89 (3.09–16.6 μg/dL), prolactin: 6.7, 9.27 (5.8–7.2 ng/mL), fT4: 0.94, 1.46 (0.89–1.76 ng/dL), total testosterone:176, 124 (241–827 ng/dL), IGF-1:183, 139 (101–267 ug/L), FSH: 2.3, 0.831 (1.4–18.1 IU/L), LH: 2, 0.123 (1.5–9.3 IU/L), respectively. In histopathological examination adenoma showing positive staining for ACTH diffuse (+), GH (−), FSH (−), LH (−), Prolactin (−), p53: %1 (+), Ki67 proliferation index: %3. By asking him to come to the controls, he was discharged with desmopressin, levothyroxine, hydrocortisone and testosterone replacement treatment.
Discussion
SCAs are very rare pituitary mass lesions. SCAs stain for ACTH, but do not secrete sufficient ACTH to cause Cushing disease. Like this case, SCAs carry a more aggressive biological behavior, increasing in size and higher potential for recurrence.

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EP111

A case of primary autoimmune hypophysitis associated with hashimoto's disease, alopecia areata and chronic hepatitis

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Background
Primary autoimmune hypophysitis (PAH) is a rare chronic inflammatory condition of the pituitary gland that occurs more commonly in females during pregnancy or in the post-partum period. It is strongly associated with other autoimmune disorders. The various forms of hypophysitis are misdiagnosed as pituitary adenoma in 40% cases.
Objective
First of all, we propose to present a case of PAH associated with other autoimmune diseases. Our second aim is to review the current literature about autoimmune disorders with a tendency toward familial aggregation.
Case presentation
We report a case of a 59 year-old woman who was diagnosed in post-menopause with Hashimoto's disease, hypothyroidism, alopecia aerata, chronic hepatitis and PAH. Her mother was also diagnosed with liver cirrhosis, Graves and Addison's diseases. Laboratory tests revealed a very low FT4 levels (<0.35 ng/dL) with slightly elevated levels of TSH (8.84 mIU/L) and thyroid peroxidase antibody (62.3 IU/ml, normal range <5.6. U/L), hypocortisolism (3.63 µg/dL), hypoglycemia (58 mg/dL), elevated red blood cells sedimentation (24/h) and lymphocytosis. The other pituitary hormones (prolactin, ACTH) and IGF-1 were in normal range. FSH (1.5 UI/L) and LH (0.1 UI/L) levels was very low and inadequate for post-menopause. MRI of the hypothalamic-pituitary region showed glandular parenchyma with diffusely reduced contrast. Hormone replacement therapy with levothyroxine and prednisone was initiated. Patient presented also an episode of fulminant, but reversible autoimmune hepatitis. Conclusion: PAH clinical diagnosis remains an exclusion diagnosis. Association of PAH with another autoimmune disorders occurring before, after or concurrently with PAH emphasizes the importance of close follow-up of such patients.
Keywords: autoimmune hypophysitis, alopecia areata, Hashimoto's disease
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EP112

Short stature and undescended testis in pituitary stalk interruption syndrome

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Objective
Pituitary stalk interruption syndrome (PSIS) is a rare congenital abnormality of the pituitary that is responsible for multiple anterior pituitary hormone deficiencies with the estimated incidence of 0. 5/100,000 live births. We report the a case of PSIS from Saudi Arabia.
Case report
A 16 year old Saudi boy with short stature and undescended testis, status post bilateral orchidopexy presented to our endocrine clinic. He was delivered by caesarean because of breech presentation and birth asphyxia. Investigation revealed underdeveloped secondary sexual characteristics with decreased facial and pubic hair growth. The patient height was 134 cm whereas the bone age was 9–11 years. Pelvis examination showed a scrotum with bilateral 1 mL testes and the stretch penile length was 3 cm. The patient laboratory investigations showed hemoglobin level of 13 g/dL, serum sodium 140 mmol/L, serum potassium 4.1 mmol/L, serum chloride 102 mmol/L, calcium 91 mg/dL, random blood sugar 110 mg/dL and albumin 3.8 mg/dL. A pituitary hormone profile showed hypopituitarism with thyroid, and adrenal sparing. The patient free T4 was 17.3 pmol/L (9–25 pmol/L) and synacthen test revealed a morning baseline cortisol level of 6.5 µg/dL (normal = 4.3–22.4 ug/dL) with adrenocorticotrophic hormone of 9.8 pmol/L (1.1–13.2 pmol/L). Insulin-like growth factor 1 level 50 ng/dL (normal = 193.0–731.0 ug/L), follicle-stimulating hormone 0.35 µIU/mL (normal, 0.0–10.0), and leutinizing hormone 0.4 µIU/mL (normal = 1.2–7.8). The patient's morning testosterone level showed 8 ng/dL (normal = 280–800 ng/dL) and prolactin 116 mIU/L (normal = 86–324 mIU/L). There were no symptom suggestive of posterior pituitary involvement like polyuria and polydipsia as urine and serum osmolality. The MRI examination showed no pituitary gland identified in the sella turcica and no clear pituitary stalk. A T1 hyperintense focus with post-contrast enhancement was identified posterior to the optic chiasma representing an ectopic posterior pituitary gland. The growth hormone and testosterone therapy were added to medical therapy of the patients and no thyroid or hydrocortisone replacement therapy was given. It should always be kept in the differential diagnosis of patient presenting with short stature. Patients with this disease have an excellent opportunity to reach normal height if they present before the joining of epiphyses.
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EP113

The case of recurrence of the growth non-functional pituitary macroadenoma with hypopituitarism

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The aim
To examine the case of relapse, the growth of non-functional pituitary macroadenoma (NFPA).
Material and methods
Under our supervision was a patient Bekieva Karomat, born in 1985 with the diagnosis: Macroadenoma of the pituitary gland with a total growth option. (NFPA) State after the transnasal hypophysisectomy (23.01.08, TGE). Continued growth of the tumor. Re TGE (26.11.11). Hypopituitarism. Secondary hypogonadism, secondary hypocorticism, secondary hypothyroidism. Bitemporal hemianopsyia. Primary infertility. Functional hyperprolactinemia.
Complaints
No field of view from 2 side, headaches, no period, constant weakness, worse in the evening, decrease in blood pressure to 90/60 mm Hg From the anamnesis: the beginning of disease associates with marriage in 2007. The patient was operated in 2008 with supra - infra - literaterary growth. Histologically, small cell installed chromophobe adenoma. In the early postoperative period there was an improvement in vision. In the late postoperative period, neuroendocrine disorders remained without dynamics, as the patient was observed irregularly, took Cabergoline irregularly for 6 months, for the purpose of hormone replacement therapy was not. The patient refused radiation therapy. The deterioration of the state noted the last 6 months, when the above complaints intensified.
Objectively
Height 156 cm, weight 55 kg. skin pale, dry. BP 110/70 mm Hg Pulse 72 beats/min. In the analyses: STH – 0.13 ng/ml, FSH −0.94 mu/L, TSH– 4.0 Miu/L, LH – 0.46 mu/L, prolactin – 307 ng/ml, cortisol is 55.1 ng/ml, IGF-1 – 88 ng/ml, estradiol of 17.4 PG/ml For established MRI pituitary adenoma size 5.6 cm×4.3 cm×5.4 cm Marked loss of visual field entirely with 2 St to green and red, more to the left. The white – bitemporally hemianopsia. The patient was re-performed TGE prof. M. P. Powell. In the early postoperative period, the patient noted a complete improvement in visual fields. Appointed hormone replacement therapy (HRT): prednisolone, levothyroxine, femoston 1/10.
Conclusions
1) small cell chromophobic adenoma in patients of reproductive age are characterized by a recurrent course after TGE. 2) in order to prevent recurrence of growth, radiation therapy of the pituitary gland or HRT is necessary.
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EP114

sLiving with acromegaly: depicting acromegaly treatment evolution in 18 years period

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Introduction
Pituitary adenomas are benign intracranial tumors. However, some of them are resistant to multiple medical treatments and are clinically considered to be aggressive.

Case report
Twenty years old male patient presented with symptomatic hyperglycemia and general weakness. With suspected diagnosis of type 1 diabetes patient was hospitalized in Kauno Klinikos, Endocrinology Department. In further clinical observation acromegalic appearance noticed. After additional investigation elevated STH 126.05 ng/l (ULN < 10) determined, pituitary MRI revealed 2.0×3.0 mm microadenoma. Patient was diagnosed with acromegaly and transsphenodal pituitary adenoma surgery was performed in 2000. However, 4 months after surgery STH 34 ng/ml (ULN < 10) and IGF-1 951 nmol/l (ULN ×2) remained elevated. Pituitary MRI revealed 0.9×0.9 cm adenoma's regrowth and invasion into cavernous sinus. Despite of initiated treatment with dopamine agonist -Bromocriptine and dose escalation up to 35 mg/per day, no positive clinical effects were observed. One year after surgery hormones markedly increased STH 268 ng/ml (ULN×26), IGF 1613 nmol/l (ULN×3). Pituitary MRI revealed tumor extension 1.0×0.9×1.3 cm - second transsphenoidal pituitary adenoma surgery was performed, continuing treatment with Bromocriptine as well. 3 years after diagnosis of acromegaly, patient visited endocrinologist complaining of low libido, erectile dysfunction, headache and sweating. STH persisted elevated STH 30 ng/ml (ULN < 20), MRI disclosed recurrence of pituitary adenoma, PRL (< 10 mLU/l (LLN 50 <) was suppressed due to continuation of treatment with dopamine agonists. As initial treatment with surgerys and dopamine agonist was insufficient radiotherapy was started. One year after RT MRI disclosed empty sella syndrome. Since modern medical treatment for acromegaly became available in 2007, treatment with subcutaneous injections of somatostatin receptor ligands was started. 3 years later patient developed hypopituitarism (1.97 mU/l (LLN 10 <), 3.56 nnmol/l (LLN 20 <), TTH 2.75 mU/l (ULN 3.6), FT4 8.5 pmol/l (LLN 10 <), Cortisol 43.2 nmol/l (LLN 61), Testosterone < 0.17 nmol/l (LLN 9.26), LH 1U/l (LLN 1), FSH < 0.17 U/l (LLN 1.3), HbA1c 6% - with no diabetes treatment. Hormone replacement therapies with L-Thyroxine, Testosterone and Hydrocortisone were started.
Conclusions
This is a challenging patient's clinical case which illustrates the acromegaly treatment evolution during 18 years period and difficulties to achieve stable remission.

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EP115

Pseudo-tumoral hypophysis: what can it be?

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Introduction
Lymphocytic hypophysitis is a rare inflammatory disorder of the pituitary gland with autoimmune origin, related to a diffuse infiltration of the pituitary gland, sometimes resulting in severe hypopituitarism. It is common in young women in late pregnancy or postpartum, however, its occurrence in men is rare with only a few cases reported in the literature. We report the case of a lymphocytic hypophysitis in a young male patient who presented for a pituitary macroadenoma.
Observation
A 31- year-old male patient, having a sister followed for lichen, presented, 10 days before admission, brutal headache, strabismus of the left eye, ptosis and a slight decrease in visual acuity with clinical signs of corticotropic and gonadotropic deficiency, pituitary MRI showed an intrasellar process of 17 * 20 mm with deformation of the sellar floor, repression of the stem and the chiasma with partial filling of the optochiasmatic cistern. The hormonal assessment showed corticotropic, thyrotropic and gonadotropic deficiency. The patient was put in substitution and sent to neurosurgery for adenomectomy, meanwhile the patient presented a spontaneous resolution of headaches and visual disturbances, the MRI control showed a regression in size of the pituitary adenoma of 9 * 10 mm, with persistence of hormonal deficits. Autoimmune exploration have shown positive anti-nuclear and anti-DNA antibodies and the patient was sent to internal medicine department where he was put on steroids.
Conclusion:
Lymphocytic hypophysitis is a rare autoimmune disorder, predominant in young women most often manifested by headache, visual disturbances or hypopituitarism. This observation shows the interest of thinking about it in front of a context of pituitary adenoma even in a male patient.

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EP116

Association of accelerated coronary atherosclerosis and steroid induced hyperglycemia in craniopharyngeoma operated patient: 15 years follow up patient

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Introduction
Rapid progression of atherosclerosis is classicaly described after e.g. percutaneous transluminal coronary angioplasty or it is defined as an diameter reduction of a preexisting stenosis. However, both initiation and perpetuation mechanisms are rarely descibed in patients on supraphysiological dosages of glucocorticoids (GCs).
Case report
We present male patient, 53-year old, after transsphenoidal operation of hypophysis pp. craniopharyngeoma with consequtive total hypopituitarism, when he was 41-years old (2004y.). Pronison substitution therapy started with 5 mg, but soon, because od polyarthralgia and polymyalgia, switched to antiinflammatory dosage of 20 mg. Diabetes mellitus (type 2) developed after 2 years of such a therapy (HbA1c 7.6%, FBG 5.7 and 2 h pp. 10.7 mmol/l). Inferior ST segment elevation myocardial infarction (STEMI) developed after 5 years (2009.y.), as an occlusion of the ramus intermedius artery (RIM). Drug-eluting stent (DES) was placed in the medial segment of ramus interventricularis anterior (RIA) which was with stenosis of 95%. Myocardial perfusion scintigraphy with Tc-99m sestamibi showed reversible anterolateral wall ischaemia. Because HbA1c of 10.2% evening dose od intermediate-acting insulin of 12j. was introduced as add on therapy to gluformin 2500 mg and glimepirid 2 mg. Patient stopped smoking and atorvastation of 20mg was introduced. After 3 years (2012y.) new anteroseptal STEMI developed as a consequence of RIA occlusion. DES was placed in RIM. Right coronary artery (ACD) showed new stenosis of 40%. Scintigraphy did not show viability of apex but the other parts of the left ventricle were viable. HbA1c was 9.9% with charcteristic pattern of BG: fasting 5.9 and 2 h pp. 14.4 mmol/l. We decided to return GCs on subtitution doses of 5 mg prednison and to leave only insulin sensitizing therapy. Latest HbA1c is 7.1% and BG 6.6 and 2 h pp. 8.9 mmol/l. He is in good condition. Left ventricle ejection fraction improved from 38%, after second STEMI, to 50% on latest control in 2018.y.
Conclusion
Hypercortisolism saturating 11 βHSD type 2 abolishes protective convesion of cortisol into inactive cortisone, so though through mineralocorticoid receptors perpetuating atherosclerotic process. In the presence of repetitive glucose spikes during GC therapy the molecules are expressed via protein kinase C and mitochondrial superoxide production. Any dosages of glucocorticoids in Addison's patient which are above subtitutional should be patiently weighted between antiinflammatory effects on atherosclerosis but also possible negative promotive atherosclerotic effects.

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EP117

Primary amenorrhea at age 37 – case report

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A female patient was first referred to the Endocrinology department due to primary amenorrhea at age 37. She mentioned trans-sphenoidal surgery at age 15 due to a craniopharyngioma and the indication to be supplemented with hydrocortisone (HC) and DDAVP, that she adhered to until age 20, when she abandoned all appointments. Apart from that, she mentioned normal pubertal development and said she was generally healthy. She denied any episodes compatible with Addisonian crises. From the interview it was clear she was polyureic ($\geq$2 mictions every night), depressed, asthenic. Her complains were unspecific muscle-joint aches, tiredness, lack of drive, easy crying. Observation revealed short stature (142 cm; target 159 cm), obesity (84 kg) of android distribution, peripheral chronic edema of the limbs and face, puffy hands (indicis ring size of 24.5 mm), hypokinetic movements, BP 94/66 mmhg, HR 64 bpm, unpalpable thyroid, external female genitalia. Breast tissue was soft and no gland bud could be palpable. She was extremely reluctant to start HC because of the fear of weight gain, but after a comprehensive explanation, finally agreed on making blood tests the next day and start HC immediately after. Laboratory: glucose 76

(80–100) mg/dl, Na 137 (135–124) mmol/l, K 4.35 (3.5–4.5) mmol/l, PRL 24 (10–28) ng/ml, TSH 10 mIU/L, fT4l 6 (10–24) pg/ml, fT3l 2.76 (8–12) pg/ml, FSH and LH <1 mIU/ml, E2 <5 pg/ml, GH 0.14 ng/ml, IGF1 <40 ng/ml, ACTH 5.4 (10–52) pg/ml, cortisol 0.6 (5–25) ug/dl, 24 h urinary volume 6300 ml, urine density 615 mOsm. The Pelvic-US revealed an infantile uterus of $60\times15\times18$ mm ($L\times AP\times T$) without visible endometrium or ovaries and the breast-US confirmed the presence of adipose tissue. Bone health was compromised with a lumbar and femoral Z score of -3.2 and -2 respectively on dual-energy x-ray absorptiometry. The thyroid-scan showed a normal gland with 19 cc of volume. After 1 week, under HC substitution, there was a dramatic improvement of vigour, activity and well-being. She seemed euthymic. Nocturia was controlled with DDAVP at night. Levothyroxine was then started and after 2 weeks a estradiol patch was initiated together with calcium and vitamin D. TD estradiol was prescribed as for puberty induction regimens but up-titrated every 4 months. After one year she lost 7 kg, has a gynoid fat distribution, significantly less peripheral edemas (indicis of 23 mm), shows a positive attitude towards life, has no complaints and adheres daily to treatment.

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EP118

Familial hypogonadotropic hypogonadism: about a family

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Introduction
When hypoglycemia is deep and repeated, it can induce various neurological disorders, including epileptic seizures. The link between hypoglycemia and epileptic phenomena is complex and poorly explained. We report 3 cases of epilepsy induced by repeated episodes of deep hypoglycemia.
Cases report
Mr D.M, 48 years old, with a history of 3 episodes of hypoglycemic coma, admitted for status epilepticus with a blood glucose level of 0.4 g/l; cerebral CT was normal. The encephalogram showed a slowing of the background rhythm with paroxysmal fronto-central bilateral anomalies. Biological test shows endogenous hypersecretion of insulin; echoendoscopy revealed an hypoechogenicity of 2 cm/2.5 cm at the head of pancreas. The second case is a 38-year-old patient treated for epilepsy for 2 years, admitted for a major generalized tonic-clonic seizure with left hemiplegia. MRI brain was normal, glycemia was at 0.3 g/l, insulin levels and peptide C were too high, an Octreoscan is required; an endocrine tumor of the pancreas secreting insulin is strongly suspected in these two patients. The third case is a 22-year-old patient, diabetic type 1, receiving insulin for 6 years, he has a history of hypoglycemic coma and he is hospitalized for a new episode revealed by generalized tonic-clonic seizures. The encephalogram showed a slowing of the background rhythm with paroxysmal fronto-central bilateral anomalies. Cerebral MRI showed an hypersignal in T1 and T2 of the basal ganglia.
Discussion
The deep hypoglycemia can induce convulsive crises as far as it can predisposes to the development of epileptogenic foci. The induced seizures are mainly generalized and tonic-clonic and the described abnormalities predominate in the frontal and temporal lobes, which joins the cases of our 3 patients.

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EP119

Pitutary apoplexia: a cause of spontaneous remission of Cushing's disease with cyclic secretion

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Introducion
Pituitary apoplexy is an endocrine emergency that is a rare complication of pituitary adenomas and exceptional in ACTH adenomas. We report a case of apoplexy on corticotropic adenoma with intermittent secretion.
Case report
The patient was 41 years old woman, she presented in 2012 a period of symptomatic hypercortisolism. Urinary free cortisol was elevated to 113 µg/24 h, Low-dose dexamethasone testing was negative, ACTH was elevated to 40.2 pmol/l, the high-dose dexamethasone suppression test was positive, a pituitary MRI and a thoraco pancreatic scanner were normal; These finding led us to a Cushing disease with normal MRI. The patient was revaluated 5 months later, she was clinically better and biochemically presented an eucorticism. 1 year later she presented relapsed symptoms and a biochemical recurrence of hypercortisilosm (high urinary cortisol: 125.7 µg/24 h and negative Low-dose dexamethasone testing). an intermittent Cushing was suggested. Brutally the patient presented a sudden tumor syndrome, pituitary MRI revealed an intrasellar arachnoidocele approving the apoplexy of an adrenocorticotropic pytuitary adenoma that was unnoticed on the previous pituitary MRI. Endocrine and ophthalmological examinations were normal.The patient was revaluated 6 months later and she was clinically better, The Urinary free cortisol and pituitary function testing showed a good pituitary hypothalamic function.
Conclusion
Apoplexy adenomatosis is a rare complication. Evolution can be marked by a cure of Cushing's disease, a persistence of Cushing's syndrome due to a tumor residue, or a remission followed by a recurrence of Cushing's disease. In our case, the clinical, biological and radiological evolution was in favor of an intermittent Cushing syndrome spontaneously regressive by apoplexy of a corticotropic adenoma.

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EP120

Management challenge of child hood Cushing disease

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Introduction
Cushing's syndrome (CS) is rare in children. The most common cause of CS in children is exogenous or iatrogenic CS. The most common cause of endogenous CS is Cushing disease (CD). Pediatric CD is almost always caused by a pituitary microadenoma. Here we present a rare case of (CD) related to pituitary macroadenoma.
Clinical observation
An 11 year old boy presented with complaints of excessive appetite and progressive weight gain. He had chushingoid face, skin thinning and purplish striae. He has no growth retardation. Laboratory investigations revealed an over production of cortisol (2089 pg/ml) and non-suppressive value after low-dose dexamethasone suppression test (1912 pg/ml). ACTH was 262 pg/ml. Pituitary magnetic resonance imaging (MRI) revealed an extensive macroadenoma sized $20\times18\times13$ mm. The patient underwent a trans-sphenoidal resection. The postoperative MRI showed a subtotal tumor resection. One year later, in the follow-up, the investigations exhibit a relapse of Cushing disease and the recurrence of the macroadenoma on the pituitary MRI. The patient underwent a second operation. However 4 months later, the patient presented behavioural changes and persistent cushing disease. A third surgery was indicated followed by a radiotherapy.
Conclusion
Our case highlights the challenge of Cushing disease in children with macroprolactinoma. In several studies remission rates is poor after first transsphenoidal operation. Moreover, outcome was dismal with a second transsphenoidal operation and postoperative radiotherapy.

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EP121

Delayed diagnosis of acromegaly: a two-year journey

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Aims
To present the case of a 69-year-old female patient who was diagnosed with acromegaly two years following the initial onset of facial and acral symptoms, having already developed colonic hyperplastic polyps, one of the complications associated with acromegaly, one year prior to diagnosis.
Material
Case report and literature review.

Method
Acromegaly was diagnosed based on clinical suspicion, raised IGF-1 level, absence of GH suppression following OGTT, brain MRI and histology.
Results
After recognition of phenotypical, particularly facial and acral, features of acromegaly, IGF-1 level was elevated at 624 nmol/L, OGTT failed to suppress GH nadir levels, and brain MRI showed a pituitary macroadenoma which was identified histologically as a mixed, sparsely granulated somatotroph and lactotroph adenoma.
Discussion and conclusion
The onset of acromegaly can be insidious in older patients leading to complications and delayed diagnosis. Early diagnosis of acromegaly and effective screening and monitoring for its complications decreases morbidity and mortality and improves overall prognostic outcomes and quality of life. Had the hyperplastic polyps detected on colonoscopy in our patient been recognised as a feature of acromegaly, the diagnosis may have been established earlier. Therefore, it is crucial to raise the awareness within other specialties of all the features and complications of acromegaly.

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Reproductive Endocrinology

EP122

Severe pulmonary tromboembolism and klinefelter syndrome

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Introduction
Klinefelter syndrome (KS) is the most common congenital abnormality causing primary hypogonadism. KS has a tendency for hypercoagulability.
Case report
A 48 year old man diagnosed as having KS during the sterility test was admitted to our hospital emergency department after suffering a syncopal episode at work. He complained of difficulty breathing during the last two weeks and he was receiving bronchodilator therapy. He had suffered deep vein thrombosis in 2014 with normal hypercoagulability workup. At the emergency room his blood pressure and pulse were 116/75 mm Hg and 76 rpm. Phisycal exam reveal no sings of deep vein thrombosis (DVT). Electrocardiography revealed findings of ST depression in V1 V3 areas. The results of arterial blood gas analysis showed hypoxemia (pO2 68, pCO 33, bicarbonate 28, pH 7.4). With the suspicion of possible pulmonary tromboesbolism, contrast enhanced chest computed tomography was carried out which show up submassive pulmonary embolism. Vascular ultrasound of inferior limbs did not find DVT. The patient was transferred to the intensive unit care where he underwent anticoagulation therapy with low molecular weight heparin and warfarin. A complete work up for thrombophilia was made again with normal results. After the patient was discharged from the hospital, he was put on warfarin for anticoagulation therapy and followed up on a outpatient basis.
Conclusions
KS is associated with high risk for venous tromboembolism (VTE). Given the increased incidence of VTE in KS, in patients with dynpnea, Pulmonary thromboembolism must be considered. KS could be considered to be a genetic hypercoagulable state per se. This has clinical implications for the prevention and diagnosis of VTE among patients with KS. We suggest thrombophilia screening in men with KS before starting hormonal treatment.

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EP123

Klinefelter syndrome and hypogonadotropic hypogonadism: an unusual presentation

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Introduction
Klinefelter syndrome (KS) is the most common genetic form of male hypogonadism, despite becoming evident only after puberty. The syndrome is characterized by a primary gonadal defect, which results in small testes due to hyalinization of the seminiferous tubules, low to low normal range of serum testosterone levels and elevated serum gonadotrophins. Paradoxically, a few cases have been described, presenting with hypogonadotropism.
Case-report
A 52-year-old male was referred to the endocrinology outpatient's department due to obesity grade 3 (BMI 55.6 kg/m^2, Height 1.80 m, Weight 180 kg). He had past history of hypertension, schizophrenia and chronic venous insufficiency and was polimedicated, namely with fluoxetine, risperidone, biperiden and haloperidol. There was no history of visual disturbances or anosmia, but the patient complained of diminished olfaction. Physical examination revealed sparse facial hair, gynecomastia, central obesity, small, soft testes, and the penile length was 5 cm. Laboratory evaluation showed normal levels of gonadotrophins (FSH 6.5 U/l; LH 4.8 U/l), despite low total (31.7 ng/dl) and free (1.5 pg/ml) serum testosterone. Estradiol level was low (E2 $<$ 10 pg/ml) and prolactin level was within normal range (9.4 ng/ml). The remaining anterior pituitary hormonal profile was normal, and the pituitary MRI did not display any lesion. A diagnosis of hypogonadism hypogonadotropic was assumed and the patient started testosterone replacement therapy responding positively, with improved virilization and a weight loss of about 35 kg in 6 months. Posteriorly, a LHRH test was performed, which showed subnormal FSH and LH responses. Initially, a Kallmann Syndrome was hypothesized, however genetic test came back negative, and surprisingly peripheral karyotyping revealed a 47 XXY pattern, confirming a Klinefelter syndrome.
Conclusion
Only a few cases of Klinefelter Syndrome presenting with hypogonadism hypogonadotropic have been reported in the past. The pathophysiology remains unknown, although it has been suggested that this occurred due to exhaustion of the gonadotrophs as a result of prolonged hypersecretion. The use of psychotropic drugs has been associated with hypogonadotropism, however this is mainly through hyperprolactinemia. Additionally, male obesity secondary hypogonadism has been described, although usually associated with high estradiol levels, and an improvement after weight loss has also been reported. Since these factors could not explain the hypogonadotropism, and a pituitary tumor was also excluded, the case reported might represent a rare variant of KS.

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EP124

Klinefelter's syndrome (47,XXY) in male systemic lupus erythematosus

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Introduction
Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that predominantly affects women. The coexisting Klinefelter's syndrome (47,XXY) and SLE was rare.
Observations
We report a case of a middle-aged male had SLE discovered by arthralgia. He presented hypogonadism. Hormonal examinations showed a low serum testosterone level (0.3 ng/ml), and high follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels (24.1 mIU/ml and 20.2 mIU/ml. Chromosomal analysis revealed a 47,XXY. The diagnosis was therefore Klinefelter's syndrome (KS) and systemic lupus erythematosus (SLE).
Discussion
This case illustrates that male with Klinefelter Sydrome (KS) may develop SLE manifestations. KS is occasionally associated with autoimmune diseases, such as SLE. A genetic polymorphism on the X chromosome might help explain the female predominance in SLE. This hypothesis could explain the co-existing Klinefelter's syndrome (47,XXY) and SLE. This autoimmune disease could also be improved by testosterone administration.
Conclusion
Increased diagnostic vigilance of KS in male with SLE is important in order to recognize this diagnosis, the effects of hypogonadism and effects of replacement treatment. Screening for other autoimmune diseases should be recommended.

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EP125

A rare case of hypergonadotrophic hypogonadism by 47,XXY/46,XX mosaic

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Introduction
Klinefelter syndrome (KS) represents the most common cause of hypergonadotrophic hypogonadism, with an estimated prevalence of 1:500 to 1:1000 men. This syndrome is characterized by the presence of an additional X chromosome. Eighty percent present with a 47,XXY karyotype and the remaining 20% present with a 47,XXY/46,XY mosaic or with multiple X chromosome aneuploidies, often with additional Y chromosomes. The presence of a 47,XXY/46,XX mosaic with male phenotype and characteristics of KS has been reported in less than a dozen cases. In addition, several other phenotypes associated with this mosaicism have been described including female phenotype or anomaly of ovotesticular sexual differentiation. We report a case of patient with KS phenotype presenting as a 47,XXY/46,XX mosaic – discovered while investigating a male primary infertility.
Case presentation
The patient, a 53-year-old house-builder, with a male phenotype and a primary school degree, was referred to the Endocrinology department because of gynecomastia and infertility. He had a history of epilepsy, degenerative discopathy and varicose vein surgery. At the age of 28, he was investigated for infertility. Hypergonadotrophic hypogonadism was detected and a spermogram revealed azoospermia. Due to non-attendance to the appointment he was not supplemented with testosterone. Currently he had no complaints suggestive of hypogonadism. On physical examination he had an eunucoid habitus, a BMI of 23 kg/m^2, scarce beard, adipomastia and bilaterally diminished, firm testicles, without masses. Analytically: free testosterone 1.51 pg/ml (6.60–30.00), LH 14.0 mIU/ml (1.2–8.6), FSH 60.9 mIU/ml (1.3–19.3), hemoglobin 13.5 g/dl (13.9–16.3), with normal glucose and lipid profile. Testicular ultrasound: diminished testicular volume (right 2.6 ml and left 3.2 ml). Breast ultrasound: adipomastia. Normal bone densitometry. He started supplementation with testosterone 250mg every 3 weeks with normalization of testosterone values. The peripheral blood lymphocytes karyotype revealed mos: 46,XX[10] /47,XXY[40].
Discussion
KS is not uncommon, but it is often underdiagnosed, possibly because it is not clinically evident until puberty. This diagnosis should be considered in patients with hypergonadotrophic hypogonadism even when discovered in adulthood. The particular aspect of this case is related to the patient's karyotype with cell lines 46,XX and 47,XXY. The phenotype in these patients is influenced by the proportion of Y chromosome gonadal cells that is not always the same as in peripheral blood. We have no data regarding the gonadal karyotype in this patient, although, given the phenotype, we suspected that most gonadal cells will contain a Y chromosome, promoting this male sexual differentiation.

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EP126

Analysis of quality of life in women of reproductive age with polycystic ovarian syndrome

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Objective
To study the quality of life in women of reproductive age with different phenotypes of polycystic ovarian syndrome (PCOS).
Materials and methods
68 women with diagnosed polycystic ovarian syndrome aged 18–44 and 30 practically healthy women of the comparable age. According to the patient's phenotype the main group was divided into 2 subgroups: patients with PCOS and obesity of varying severity (BMI $>$ 25 kg/m^2) and patients with PCOS and normal body weight (BMI $<$ 25 kg/m^2). The quality of life was assessed with the use of SF-36 questionnaire.
Results and discussion
The average figures for the mental health component in patients with PCOS in group I were 59.25 $\pm$ 5.1 points; in group II they were 63.25 $\pm$ 3.4 points and were significantly lower compared to the figures in practically healthy individuals — 91.66 $\pm$ 4.3 points. The average figures for the physical health component (PH) in patients with PCOS in group I were 69.25 $\pm$ 4.7 points; in group II they were 73.25 $\pm$ 4.3 points and were also significantly lower compared to the figures in practically healthy individuals $-$96.66 $\pm$ 1.4 points.
Conclusion
The obtained results indicate a decline in the quality of life indicators in women of reproductive image with PCOS and obesity of varying severity. It has been found that in patients with PCOS and obesity, both the physical and psychological components of health are affected. But the psychological component plays a more prominent role in the quality of life of the patients in the study group.

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EP127

The role of transcription factors in control of ovarian functions

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We are the first who studied the control and the role of transcription factors in the regulation of reproductive functions. Our presentation represents a short review of original data concerning external (temperature, calories restriction) and internal (hormones, protein kinases, RNA interference) in control of selected transcription factors (p53, NFkB, STAT1, CREB1), as well as their role in control of basic ovarian cell functions (proliferation, apoptosis, secretory activity, response to hormonal stimulators). It was shown, that stress (high temperatures, food restriction), hormonal regulators of reproduction (gonadotropins, GH, oxytocin, some growth factors), pharmacological or genomic regulators of protein kinases (protein kinase A, MAP kinase, CDC2 and other kinases), si RNAs and miRNAs control the expression of these transcription factors within porcine, rabbit and human ovarian cells. Furthermore, the transfection-induced overexpression of these transcription factors altered the proliferation (markers of cell cycle PCNA, cyclin B1, MAP kinase, CDC2 kinase/p34), both nuclear (TdT) and cytoplasmic (bax, bcl-2, caspase 3, p53) apoptosis, release of steroid (progesterone, testosterone, estradiol) and peptide (oxytocin, IGF-I) hormones and prostaglandins (F and G) by cultured ovarian granulosa cells, as well as their response to stress and hormonal treatments. Comparison of cDNA constructs encoding phosphorylable and non-phosphorylable CREB1 showed no substantial differences in their action on the majority of analyzed ovarian functions. These observation demonstrate (1) the presence of transcription factors in ovarian cells, (2) the hierarchy of upstream regulators of ovarian transcription factors (environmental factors – hormones-protein kinases – miRNA – transcription factors), (3) the involvement of transcription factors in control of basic ovarian cell functions (proliferation, apoptosis, secretory activity and response to hormones), and (4) that phosphorylation of some transcription factors is not necessary for their action.

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EP128

Reproductive disorders in women with morbid obesity

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Background
Obesity is significantly associated to several reproductive disorders in women. However, the molecular mechanisms involved in this association are complex and still not completely understood. The aim of our study was to determine the prevalence of reproductive disturbances in a group of women with morbid obesity.

Methods
We conducted a cross sectional study in 50 women with a body mass index (BMI) ≥ 40 kg/m^2 collected in the endocrinology department of La Rabta hospital over a period of 6 months (October 2017–March 2018). Patients with hypothyroidism and Cushing syndrome were excluded. Clinical, biological and ovary ultrasound findings were collected in all participants.
Results
The average age of our patients was 34.2 ± 7.51 years. Their mean BMI was 44.53 ± 3.97 kg/m^2 and their waist circumference was 123.38 ± 10.89 cm. Menstrual cycle disturbance were found in 46% of our population: 42% had spaniomenorrhea and the remaining 4% had secondary amenorrhea. Twenty seven percent of cases had infertility: it was primary in 20% and secondary in 7%. The prevalence of hyperandrogenism was 46%. Polycystic ovary syndrome was diagnosed in 40% of our patients. During pregnancy, a history of miscarriage was found in 57% with a mean number of abortion of 1.1 ± 1.5. Furthermore, women with morbid obesity had an elevated risk of complications during pregnancy as gestational diabetes mellitus and pregnancy induced hypertension were present in 37% and 22%, respectively.
Conclusion
Female morbid obesity affects reproductive function by altering the hypothalamic- pituitary-ovarian axis, oocyte quality, endometrial receptivity and causing adverse pregnancy outcomes. This can be explained by the presence of a condition of functional hyperandrogenism and hyperinsulinaemia, which accompanies the insulin-resistant state in severely obese patients. Weight loss can improve reproductive potential in these patients.

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EP129

A case of post-menopausal hirsutism

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Introduction
Hirsutism is the presence of excess hair growth in females as a result of increased androgen production and/or increased skin sensitivity to androgens. In a postmenopausal female presenting with hirsutism, a high level of clinical suspicion, a detailed history and physical examination, substantiated by focused biochemical and morphological confirmation is necessary.
History
The authors present a case of a female with a longstanding history of recurrent hirsutism that had worsened over a short number of weeks. A 61-year-old, post-menopausal lady, with a past medical history of PCOS, was referred to the endocrine outpatients with a two-year history of hirsutism and markedly elevated serum testosterone. Accompanying symptoms included increased libido, weight gain, baldness, generalised pruritus and deepening of the voice.
Investigations
On examination the patient was normotensive, with central adiposity and male pattern baldness. A hormone profile revealed a markedly elevated serum testosterone of 18.3 nmol/L, androstenedione of 5.3 ng/mL (0.35–2.49 ng/mL) and a free androgen index 67% ($<6.6\%$). Cortisol, prolactin, growth hormone and thyroid function tests were normal. A CT scan of the abdomen and pelvis carried out two years previously had shown a 12×15mm left ovarian cyst and normal adrenal glands. A recent ultrasound of the uterus and ovaries was performed by the referring gynaecologists, but failed to show any pathology (including the previously reported left ovarian cyst). An MRI was later performed and confirmed the presence of a 17mm left ovarian mass.
Results
The patient underwent a total abdominal hysterectomy with salpingo-oophorectomy. Histology confirmed the presence of a Leydig cell tumour, confined to the left ovary, with no malignant features. The tumour was deemed to have an excellent prognosis.
Discussion
Hyperandrogenism after menopause is a rare condition that needs careful evaluation in order to avoid misdiagnosis. This is a case of relapsing hirsutism initially due to PCOS and later due to an ovarian secreting, androgenic tumour. Whilst DHEAS levels are usually raised in adrenal tumours, androstenedione levels are usually raised in ovarian tumours. On the other hand, 17-hydroxyprogesterone (17-OHP) may be raised with both adrenal and extra-adrenal tumours. This can help guide to the possible source of androgen excess and hence direct further imaging. Ovarian and adrenal vein sampling may be used to determine the source of hyperandrogenism with variable success.

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EP130

Ovarian ultrasound features in women with morbid obesity

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Background
Obesity is an increasingly common health problem which has been found to affect female reproductive function in several aspects. The aim of our study was to determine the ovarian ultrasound features in women with morbid obesity.
Methods
We performed a cross sectional study in 50 women with a body mass index (BMI) ≥ 40 kg /m^2 collected over a period of 6 months (October 2017–March 2018). For each woman, a sus-pubic ultrasound was performed during the early follicular phase. In each ovary, the total number of small follicles (2–10 mm) was counted and the ovary volume was determined.
Results
The average age of our patients was 34.2 ± 7.51 years and their mean BMI was 44.53 ± 3.97 kg/m^2. The mean volume of the right and left ovary was 10.3 ± 5.8 ml and 10 ± 5.5 ml, respectively. Thirty four percent of our women had an ovarian volume greater than 10 ml. The mean antral follicular count was 5.0 ± 3.8 follicles in the right ovary and 4.8 ± 3.5 in the left one. This antral follicular count was greater than 12 in 12% and correlated positively with the BMI ($r = 0.29$, $P = 0.06$), insulinemia ($r = 0.5$; $P = 0.001$) and the Homa index ($r = 0.57$; $P < 0.001$). Thirty six percent of our patients had a polycystic ovary aspect at ovarian ultrasound. Polycystic ovary syndrome (PCOS) was diagnosed in 40% of cases. Only the ovarian volume >10 ml was significantly associated with PCOS (OR = 11, $P = 0.001$).
Conclusion
This study showed that the ovarian morphology may change in obese patients specifically the finding of a multifollicular appearance or enlarged ovaries. This may be explained by the effect of hyperinsulinemia and the excess of LH caused by obesity on ovarian size.

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EP131

Secondary amenorrhea: epidemiological, clinical and etiology profile at the university hospital center Mohammed VI Oujda

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Secondary amenorrhea is defined as the cessation of regular menses for three months or the cessation of irregular menses for six months (1). Most cases of secondary amenorrhea can be attributed to polycystic ovary syndrome, hypothalamic amenorrhea, hyperprolactinemia, or primary ovarian insufficiency the aim of this study to analyze the clinical, biological, etiological profile of secondary amenorrhea (2).
Patients and methods
We conducted a retrospective descriptive study of 47 patients hospitalized or followed in consultation with the endocrinology department of the Mohammed VI hospital center of Oujda for a secondary amenorrhea.
Results
The mean age is 31.5 years ± 8.4 years, the history have revealed tuberculosis, postpartum haemorrhage, autoimmune diseases such as dysthyroidism, diabetes, thrombocytopenia and Crohn's disease. clinical examination we found malnutrition in 6 patients with BMI less than 18 kg/m^2, moderate obesity in 5 cases, hyperandrogenism is found in 7 cases, clinical signs of dysthyroidism in 5

patients, and galactorrhea are found in the majority of patients (24 cases). Biological investigations allowed us to retain: hypogonadotropic hypogonadism in 21 patients including 5 cases of panhypopituitarism, 19 cases hyperprolactinemia, hypergonadotropic hypogonadism in 2 patients. After radiological assessment, the most common etiology was pituitary adenomas, followed by isolated hyperprolactinemia, polycystic ovary syndrome, and 1 case of sheehan syndrome, primary ovarian failure in 2 cases, 3 cases of hyperthyroidia, and the rest was secondary to unbalanced chronic diseases. Patients with primary ovarian insufficiency can maintain unpredictable ovarian function and should not be presumed infertile. Patients with hypothalamic amenorrhea should be evaluated for eating disorders and are at risk for decreased bone density. Patients with polycystic ovary syndrome are at risk for glucose intolerance, dyslipidemia, and other aspects of metabolic syndrome.

Conclusion

Thus secondary amenorrhea, which is very frequent, makes it necessary to review the major chapters of the endocrinology of reproduction. Their etiological diagnosis may seem complex because the list of their causes is long (3).

Bibliography

1. DAVID A.and Uniformed Services University of the Health Sciences, Bethesda, Maryland: Amenorrhea: An Approach to Diagnosis and Management. Volume 87, Number 11, June 1, 2013.

2. Azziz R and *et al*.; Androgen Excess Society. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab. 2006;91(11):4237–4245. 42.

3. ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41–47.

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EP132

Major getational hypertriglyceridemia

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Introduction

The disturbance of the lipid balance during pregnancy is common. Nevertheless, major hypertriglyceridemia during pregnancy is rare and can not be attributed to pregnancy.

Methods

We report the case of a pregnant woman hospitalized at the national nutrition institute of Tunis (departement A) for the management of a major hypertriglyceridemia.

Results

This is a 28-year-old female patient with ovarian stimulation-induced pregnancy, followed for gestational diabetes mellitus with insulin therapy,hospitalized at 24 weeks of amenorrhea for management of major hypertriglyceridemia (16 mmol/L). She has no other pathological history, neither personal nor familial,particularly dyslipidemia. Acute pancreatitis was eliminated. She had a preconceptional weight of 80kg, a weight gain of 0.6 kg/month. The average HbA1C was 6.7%. Other lipid parameters, hepatic, renal and thyroid status were normal. The patient was put on a hypo-lipid diet with an adjustment of insulin doses, with a favorable evolution and a decrease of triglyceride to 4.6 mmol/L.

Conclusion

Induction of pregnancy seems to be the most likely etiology of this hypertriglyceridemia, related to the stimulation, by high levels of estrogen, of hepatic synthesis of very low density lipoprotein (VLDL). Thus, such rare causes of hypertriglyceridemia should not be ignored, given the risks involved, including acute pancreatitis, which may affect maternal and fetal prognosis.

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EP133

Hirsutism in women of reproductive age from the oriental region of eastern Morocco: what features?

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Background

In clinical practice, hirsutism is commonly seen among women of fertile age and defined as the presence of terminal hair with male distribution in women.

Objective

The aim of the study was to assess the clinical, biochemical and etiologic features of hirsutism in women from the oriental region of Morocco.

Materials and methods

36 female patients presenting with hirsutism at Department of Endocrinology, Mohammed VI Hospital, Oujda, from 2012 to 2018 were assessed using the recently approved diagnostic guidelines for hyperandrogenic women with hirsutism.

Results

Polycystic ovary syndrome (PCOS) was the cause of hirsutisme in 25 patients (69.4%) followed by idiopathic hirsutism (IH) in 7 patients (19.4%). Others causes of hirsutism included cushing's syndrome in 3 patients (8.4%), and late onset congenital adrenal hyperplasia in 1 patient (2.8%). Age at presentation of PCOS was 25 ± 5. 6years (mean $\pm$ SD) and 61% of the subjects were overweighted or obese. Besides, 21 (84%) of patients with PCOS had an oligo/anovulatory cycle while the remaining 4 patients (16%) maintained normal regular menstrual cycle. Luteinizing hormone and total testosterone were significantly higher in patients with PCOS than in those with IH.

Conclusion

We find that PCOS is the commonest cause of hirsutism in our clinical practice and PCOS is prominent amongst young obese female. However, more studies are needed to verify our findings.

Keywords: hirsutism, polycystic ovary syndrome, idiopathic hirsutism

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EP134

Primary amenorrhea: clinical, biological, etiological and therapeutic features

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Introduction

Primary amenorrhea is an uncommon presentation in reproductive medicine requiring rigorous investigation. Primary amenorrhea is defined by the absence of menstrual cycle in girls after the age of 15 years, with or without the development of secondary sexual characteristics. The objective of the study is to determine the clinical, biological, etiological and therapeutic profile of primary amenorrhea in the Endocrinology-Diabetology department of Mohammed VI University Hospital in Oujda.

Patients and methods

A retrospective study about 9 female patients with primary amenorrhea who attended the Endocrinology-Diabetology department during a 4 years period.

Result

The mean age at the diagnosis was 19 years. Primary Amenorrhea was associated with short stature in 7 patients, clinical features of Turner's syndrome in 2 cases, a headache in 1 case and obesity in 1 case. The causes of primary amenorrhea in our series was related to hypogonadotropic hypogonadism and hypopituitarism in the context of a combined GHD in 33.3% the cases, of which 2 cases were due to an interruption of the pituitary stalk and 1 case had a normal MRI, prolactinoma in 1 case, Prader-Willi syndrome in 1 case, 2 cases were caused by chronic diseases, while 2 cases were related to Turner's syndrome. We noted 3 cases of spinal osteoporosis as a complication of estrogen deficiency. Therapeutic management is based on estrogen-progestogen hormone replacement therapy, osteoporosis treatment, and etiological treatment.

Conclusion

The most common causes for primary amenorrhea are related to chromosomal abnormalities followed by endocrinological causes like Hypothalamic Hypogonadism and pituitary disease. The other causes include Mullerian abnormalities, congenital adrenal hyperplasia and poly cystic ovarian syndrome (PCOS). Treatment depends on the cause with emphasis on the immediate and long-term wellbeing of the patients.

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EP135

Clinical, malformative and cytogenetic profile of mosaicturnersyndrome at Mohammed VI University Hospital Centre Oujda

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Introduction
Turner syndrome is a chromosomal abnormality that affects phenotypic females who have one intact X chromosome and complete or partial absence of the second sex chromosome. In this genetic disease, the karyotype ranges from complet 45, X to forms of mosaicism in which a normal cell line (46, XX or 46, XY) or a second (or third) abnormal cell line is found. Mosaic turner syndrome (MTS) has a heterogeneous clinical presentation as well as a varied presence of malformations and associated diseases [1]. Our aim was to describe the clinical, malformative and the cytogenetic characteristics of MTS in our Hospital centre.
Patients and methods
Descriptive, transversal study of female patients followed for MTS in Mohammed VI University Hospital Centre Oujda.
Results
This study included 5 patients. The average age at diagnosis was 24.04 ± 17.05 years. MTS was diagnosed before puberty in 2 patients and in adulthood in 3 patients. Patients had a short stature (100%), primary amenorrhea (40%) and a characteristic facial appearance of TS (60%). Cytogenetic analysis showed for all patients, a form of mosaicism with a double cell population, including one monosomy X. An isochromosome of long arm of X chromosome was found (40%) as well as a deletion of long arm of X chromosome. Analysis by fluorescent *in situ* hybridization (FISH) detected, in one patient, the presence of an X chromosome without SRY (30% of cells observed) and a copy of the X chromosome with two copies of the SRY locus on a small chromosomal marker related to an isochromosome of the short arm of the Y chromosome. Diseases associated with MTS were diabetes mellitus (20%), autoimmune peripheral hypothyroidism (20%), celiac disease (20%), arterial hypertension (20%) and repetitive otitis with repetition with transmission deafness (40%). Our patients had not cardiac and renal malformations. Growth hormone therapy was initiated in two patients whose disease had been diagnosed before puberty.
Discussion and conclusion
MTS is a rare genetic condition. Its diagnosis is made inperi-pubertalperiod or in adulthood in our context, following exploration of a short stature or a primary amenorrhea. Its clinical presentation is heterogeneous and according to cytogenetic profile. Malformations do not seem common in patients with this disease
Reference
1. Claus H Gravholt, Niels H Andersen, Gerard S Conway and *et al.* Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol 2017; 177: G1–G70.

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Thyroid

EP136

Evaluation of thyroid function in obese adults with non-alcoholic fatty liver disease attending at Tanta university hospitals

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Background
Non-alcoholic fatty liver disease (NAFLD) is considered most common cause of end stage Liver disorder that needs liver transplantation worldwide**.** NAFLD is considered the hepatic aspect of metabolic syndrome. The association between thyroid dysfunction and NAFLD has increasingly become interesting focus of research.
Objective
Evaluation of thyroid function in obese adults with non-alcoholic fatty liver disease attending at Tanta university hospitals from July 2017 to February 2018.
Patients and method
Our study patients was classified into 2 groups first includes 60 obese with non alcoholic fatty liver (NAFLD) patients, second group includes 60 obese non NAFLD patients recruited from endocrinology, diabetes and metabolism outpatient clinics and inpatient wards,Internal medicine department at Tanta University Hospitals. Serum thyroid stimulating hormone (TSH), Free thyroxine (FT4), Free Tri-iodiothyronine (FT3) by ELISA, Anti thyroid peroxidase (ANTI-TPO), Anti thyroglobulin (Tg Ab), NAFLD fibrosis score for NAFLD group and thyroid ultrasound are done for both groups.
Results
TSH levels showed statistically significant difference higher within normal range in obese NAFLD group $P = 0.001$ with mean values 2.72 ± 0.77 in obese NAFLD group, 1.93 ± 0.66 in obese Non-NAFLD group. Also FT4 levels showed statistically significant difference lower within normal range in obese NAFLD group $P = 0.006$ with mean values 1.08 ± 0.22 in obese NAFLD group, 1.25 ± 0.42 in obese Non- NAFLD group. As regard FT3 levels, ANTI-TPO levels, Tg Ab levels and thyroid ultrasound characters did not show statistically no significant difference between the two groups.
Conclusion
We concluded that there was elevation in levels of TSH within the normal range (0.4–4.2 mIU/l) in obese NAFLD group over obese Non-NAFLD group. Also FT4 results was within normal range (0.8–1.8 ng/dl) with lower levels in obese NAFLD group than obese Non-NAFLD and we still need further research on large scale.
Keywords: Non-alcoholic fatty liver, obese, thyroid dysfunction
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EP137

Differential diagnosis of thyrotoxicosis syndrome in postpartum period

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Introduction
Thyrotoxicosis syndrome is a clinical syndrome, associated with the negative effect of strong thyroid hormone excess on the organism. In most cases women with thyrotoxicosis syndrome in postpartum period have postpartum thyroiditis, caused by reactivation of the immune system after gestational suppression. However sometimes Graves disease can manifest during the postpartum period, this condition also results in thyrotoxicosis syndrome and requires radical thyroidectomy. Thus determining the cause of the thyrotoxicosis syndrome is an important part of the diagnostic process and, consequently, choosing of treatment tactic in patients with thyroid pathology in postpartum period.
Clinical case
A 23-year-old woman presented with discomfort and dryness of eyes, tremor, constant feeling of heat and stuffiness, excessive sweating, rapid heart rate, weight loss, irritability and nervousness, headache, increased frequency of stools. In October 2016 she had a baby and complains has developed since March 2017, a thyroid ultrasound revealed increased thyroid volume (26.3 cm^3) and diffuse changes similar to autoimmune thyroiditis. The symptoms have become worse since September 2017: heart rate increased, there were significant changes in periorbital region and the patient consulted an endocrinologist. It's known from social history that the patient smokes. Physical examination: thyroid gland was visually enlarged, firm, homogeneous. The patient was presumed to have the thyrotoxicosis syndrome, and the laboratory examination showed decreased level of TSH (0.005 mIU/l) and increased levels of: fT3 (>41.0 pmol/l), fT4 (>76.0 pmol/l) and TSH-receptor antibodies (TRAb) (>40 IU/l). Thyroid ultrasound revealed enlarged thyroid gland (66.6 cm^3). The thyroid radioactive iodine uptake test also showed significantly enlarged thyroid gland and diffusely increased iodine uptake, especially in the right lobe. Taking into consideration low TSH level, high levels of fT3 and fT4 and TRAb, ultrasound and thyroid radioactive iodine uptake test findings, Graves disease was diagnosed and thyroidectomy was performed in September 2017. Pathological analysis of the patient's lesion confirmed the diagnosis of Graves disease. L-thyroxin 75 μg was administered 1 time a day 30 minutes before breakfast and taking other medications. TSH and free T4 monitoring was planned 3 months later after administration.
Conclusion
This case shows how important is proper and early diagnosis of causes of the thyrotoxicosis syndrome in postpartum period, such as diffuse toxic goiter and postpartum thyroiditis. These actions have allowed to choose the right treatment tactic and to perform surgical resection of the thyroid gland, and as a result, to achieve a positive prognosis.

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EP138

Severe primary hypothyroidism as a cause of reversible renal failure

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Introduction
Hypothyroidism is not a common cause of renal failure which remains under-appreciated. Herein we report a case of acute renal failure in a patient with a severe primary hypothyroidism in whom hormone replacement therapy with Levothyroxine has significantly improved renal function.
Observation
A 72-year-old man was referred to our department for primary hypothyroidism. His past medical history included a coronary heart disease with a heart failure.Four weeks ago, he was diagnosed with a renal failure. He presented to our department with generalized weakness, constipation, hearing loss and night snoring. On examination, he had a myxoedema with a puffy face, a macroglossia and a peripheral non-pitting edema, a psychomotor slowdown, a bradycardia, a dry skin and slow relaxing reflexes. The thyroid gland was not palpable. The diagnosis of hypothyroidism was confirmed by the *thyroid function test*s showing increased *thyroid-stimulating hormone* (TSH)$>$100 mUI/l (0.35–4.95) and decreased Free T4 at 0.75 pmol/l (N:9–20). Routine blood tests disclosed a moderate renal failure with a serum creatinine at 18 mg/l (the clearance of creatinine was estimated at 39 ml/mn), normal natremia and kalemia levels, an elevated lactate dehydrogenase (LDH) level at 554 U/l (N: 125–245), a normal creatine phosphokinase (CPK) level and hepatic cytolysis. The patient received Levothyroxine replacement with initiation dose of 12.5 µg per day then we increased the dose gradually by 12.5 µg every 7 to 10 days. After one month of treatement, the control of serum creatinine was at 11 mg/l with a significant improvement in creatinine clearance to 70 ml/min.
Discussion and conclusion
In our patient, thyroid hormone replacement therapy resulted in renal function improvement which confirms the relationship between hypothyroidism and renal failure. Although the physiopathology of this association remains poorly understood, the decreased cardiac output and renal blood flow leading to a reduction in glomerular filtration rate represents the main mechanism. Other factors have been implicated such as rhabdomyolysis and hydro-retention. Since treatment of hypothyroidism can improve renal function, evaluation of thyroid function in patient with unexplained kidney failure is recommended.

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EP139

Case report: Myxedema coma after radiotheraphy for Laryngeal cancer

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Introduction
Since the thyroid myxedema coma is rarely seen nowadays, its diagnosis can be overlooked.
Case
The patient with tracheostomy who underwent total laryngectomy and bilateral neck dissection and radiotherapy (RT) at the neck region 10 years ago due to Larynx cancer was admitted to the intensive care unit the diagnosis periorbital edema, hypotension, hypothermia, consciousness disorder and pneumosepsis. Treatment was started for Acinobacter, which was produced in the blood culture of the patient. The patient was found to have tongue growth and diffuse body edema and other hypothyroid findings. TSH: 52 (N: 0.27–4.2 mIU/l) free T4: 0.039 (N: 0.93–1.7 mIU/l), free T3: 0.527 (N: 2–4.4 mIU/l) was found in laboratory tests for suspected hypothyroidism. In thyroid ultrasonugraphy, both lobe size increased and heterogeneity in parenchyma. When these findings were evaluated together, the patient was accepted as hypothyroidism coma. IV levothyroxine was demanded to be introduced in our country, but 200-400 mcg/day oral LT4 and iv hydrocortisone treatment was started with 100 mg every 6 hour intervals. After treatment was begun, freee T4 levels reached normal levels 3 weeks later (1st 0.139 mIU/l, 2nd 0.5 mIU/l, 3rd 1.43 mIU/l). The patient showed significant improvement in hypothermia, hypotension and tongue swelling. However, the patient died because of DIC (disseminated intravascular coagulation) developed during the follow-up of the patient.
Conclucion
As the absorption of reduced oral levothyroxin due to edema from the bowel will delay the increase in free T4, faster euthyroidism can be achieved with IV levothyroxin preparations in the mix edema coma. On the other hand, it should be kept in mind that hypothyroidism may develop in patients receiving RT in the neck area and the patient should be kept in follow-up.

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EP140

Significance of testing anti-thyroid peroxidase in euthyroid patients

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Autoimmune thyroid disease is the common autoimmune disorders. It is more commonly in women. 2% to 4% of women and up to 1% of men are affected worldwide The prevalence increases with advancing age. Detection and quantification of the antibody titers help in establishing an autoimmune etiology.
Objectives
We study the prevalence of thyroid hormone dysfunction especially TSH and positive anti-TPO antibody titers in patients suspect for thyroid-related disorders.
Materials and Methods We study about 54 patients. These patients had clinical symptoms and anamnestic elements suspected for disorders of thyroid. The assay for anti-TPO antibodies is an immunoassay based on the principle of electro-chemiluminescence The upper limit of the normal range for anti-TPO is $>$30 IU/ml. TSH, was estimated by chemiluminescence. The normal range for TSH is O.3–4.5 IU/ml. The results of 54 subjects were analyzed. The rage age was 20–55 years old. Most of them were females 52 patients or 98%. Two of them were males or 2% The total 54 patients: 21 patients had TSH normal and anti TPO high value (38.8%). 16 were euthyroid TSH normal antiTPO normal value. (29.6%) 8 had TSH high and antiTPO normal value (14%), 6 patients had TSH high and antiTPO high value (11.1%) and only 3 were TSH low and antiTPO high value (5.5%).
Conclusion
Autoimmune thyroid diseases occur due to immune-mediated alterations in the thyroid gland. Chronic thyroid dysfunction i.e. hyperthyroidism (Grave's disease) and hypothyroidism (Hashimoto's Thyroiditis) occur secondary to the actions of antibodies. Anti-TPO antibodies are the most prevalent and is present in 80–90% of Hashimoto's Thyroiditis, 65–75% of Grave's disease and 10–20% of nodular goiter or thyroid carcinoma. Even 10–15% of normal individuals can have an elevated antibody titer. In our study we have noticed that the present of antiTPO was high level in 38.8% of euthyroid patients. In our study the majority of euthyroid patients had an elevated anti TPO titer, so we suggested that we could detected the antiTPO even in the patients without thyroid related disorders. This may be due to well-compensated thyroid function at present with a future risk of dysfunction in them. So we concluded the important role of antiTPO titer even in the euthyroid patients. Its important to screen the antiTPO not only in supscted patients with Hashimotos Thyroiditis or Graves disease, but to screen even in normal individual. This importance of screening is compounded by the fact that anti-thyroid antibodies may be positive in a significant percentage of normal people.

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EP141

Association of a toxic thyroid nodule and papillary microcarcinoma: case report

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Hyperthyroidism is rarely associated with malignancy. Some cases of co-existing between hyperthyroidism and thyroid carcinoma have been described. We report a case of association of a toxic thyroid nodule and papillary microcarcinoma.
Observation
A 50-year-old male was referred to the endocrinologist for hyperthyroidism (TSH: 0.01 mUI/l, FT4: 22.8 pmol/l, FT3: 17.1 pmol/l). Thyroid ultrasonography showed a nodule of 38 mm in the left lobe. 99 mTc thyroid scintigraphy imaging showed a hot area corresponding to the nodule with lower uptake in the remaining thyroid tissue. After return to euthyroidism with methimazole treatment, a total

thyroidectomy was performed. Histopathological examination of the nodule revealed papillary microcarcinoma of 1 mm. Levothyrox treatment was prescribed without adjunct iodine therapy or lymph node dissection.
Comment
The association between hyperthyroidism and thyroid carcinoma is no longer exceptional. Some cases of Graves' disease (1) and toxic multinodular goiter (2) and autonomously hyperfunctioning thyroid nodule (3) associated with thyroid carcinoma have been described. Our observation supports the hypothesis of non-protection of hyperthyroidism against thyroid carcinoma. The association of the two pathologies is therefore possible.
References
1. Leghlimi S. *et al*., Association between Graves' disease and differentiated thyroid carcinoma. Annals of Endocrinology, Vol 75, Issues 5–6, october 2014.
2. Marcello M. *et al*., Anaplastic carcinoma and toxic multinodular goiter: an unusual presentation. Eur Thyroid J. 2014 Dec; 3(4): 278–82
3. Lima M.J. *et al*., Autonomously hyperfunctioning cystic nodule habouring thyroid carcinoma- Case report and literature review. Int J Surg Case Case Rep. 2018;42:287–289
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EP142

Primary thyroid lymphoma: a differential diagnosis to be considered
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Introduction
Primary lymphoma of the thyroid (PTL) is a rare cause of malignancy, accounting for 5% of thyroid malignancies, with an annual estimated incidence of 2 per 1 million. Women are more commonly affected than men (2–8:1). Patients typically present in the sixth or seventh decade of life. Most thyroid lymphomas are non-Hodgkin's lymphomas (NHLs) of B-cell origin. Patients with Hashimoto's thyroiditis are at greater risk for developing PTL. Treatment and prognosis of PTL depend upon the histology and stage of the tumor at diagnosis.
Case report
We present a 50 years old man with a rapidly enlarging neck mass with compressive symptoms including dyspnea and stridor, requiring intubation. The cervical ultrasound revealed a sub-sternal goiter with heterogeneous, hypoechoic echostructure, and the fine-needle aspirating cytology was consistent with lymphocytic Hashimoto thyroiditis. The computed tomography (CT) scan revealed an enlarged thyroid gland with tracheal deviation as well as right neck lymphadenopathy. Thyroid function studies show thyroid-stimulating hormone 8.1 μIU/ml (reference, 0.27 to 4.20 μIU/ml), free thyroxine 13.7 ng/dl (reference, 12 to 22 pmol/dl), and positive anti-thyroperoxidase (TPO) antibodies. The core needle biopsy of the thyroid grand for combined pathology and immunohistochemistry revealed diffuse large B cell non-Hodgkin's lymphoma with germinal center B-cell subtype.
Conclusions
Thyroid lymphoma is a rare cancer but must be considered in the differential diagnosis of patients presenting with an enlarging neck mass and a history of Hashimoto's thyroiditis. Advances in both diagnosis and treatment in recent years have altered our approach to the management of this disease.
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EP143

Clinical case of giant goiter with chronic lymphoid leukemia
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Introduction
Lymphoma of the thyroid gland is an uncommon condition occurring primarily in older women. Most patients have a short history of enlarging thyroid or a neck mass causing tracheal compression. There is also a strong association between thyroid lymphoma and Hashimoto's thyroiditis. The diagnosis is established by biopsy. The conventional approach to treatment is combination of radiation therapy with multi-agent chemotherapy, while there is no significant role for extirpative surgery in the management of thyroid lymphoma. Prognosis of localised tumours (stage IE, Ann Arbor classification) is excellent. Extrathyroidal involvement (stage IIE-IVE) reduces the 5-year survival rate to about 70%, provided that current therapy regimens are respected. In this clinical case, the different stages from Hashimoto's thyroiditis and thyroid lymphoma are demonstrated by histology. We describe a rare case of Hashimoto's thyroiditis in a woman with chronic lymphoid leukemia.
Case report
A 65-year-old woman suffering from goiter and hypothyroidism for 9 years, treated with levothyroxine 125 mcg, followed in our Centre in May 2018. The blood tests revealed that she had euthyroidism (TSH – 2.3 mU/l). In blood test there was lymphocytic leukemia, found early about 6 months ago. Ultrasound confirmed Hashimoto's thyroiditis and an enlarged thyroid with no nodules. The CT scan additionally revealed multiple paratracheal ganglia, intrathoracic extension and tracheal compression. Cytology was compatible with chronic lymphocytic thyroiditis (Bethesda II). In our case Hashimoto's thyroiditis was diagnosed with chronic lymphocytic leukemia, and surgical treatment was recommended. Definitive treatment was made by performing total thyroidectomy. And histological examination confirmed the diagnosis of chronic lymphocytic thyroiditis.
Conclusions
It is important to choose correct way and treatment in differential diagnostic between chronic lymphocytic thyroiditis and chronic lymphoid leukemia.
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EP144

The rare association of graves disease with chronic spontaneous urticaria
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Background
Chronic spontaneous urticaria (CSU) is defined by the presence of recurrent urticaria (also called hives or wheals), angioedema, or both, for a period of six weeks or longer. CSU affects just 1% pf the general population and its etiopathogenesis is not well understood. CSU is known to be associated with various autoimmune conditions. However the association CSU and Graves Disease is very rarely seen in clinical practice.
Clinical case
In this case report we present a 48 year old woman with Graves Disease who developed recurrent episodes of urticaria with angioedema. She was extremely sensitive to even minute doses of carbimazole. This resulted in very fluctuating thyroid functions over a six month period with TSH levels being as low as 0.05 to as high as 90. Her TSH receptor antibodies and Thyroid peroxidase antibodies were positive. Additionally, her thyroid ultrasound favoured an autoimmune cause of her hyperthyroidism. It was observed that she had episodes of urticaria with swelling around the eyes which responded very poorly to high doses of antihistamines. However, a positive correlation was seen between normalisation of thyroid hormones and the resolution of urticaria.
Conclusion
Clinicians should be wary of the association between CSU and Graves Disease and are advised to exclude hyperthyroidism as a cause if the CSU is not responding to conventional treatments.
Keywords: Chronic Urticaria, Graves Disease
DOI: 10.1530/endoabs.63.EP144

EP145

Correction of androgen deficiency in men with hypothyroidism
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The aim
Is to investigate the effectiveness of therapy with testosterone undecanoatein patients with hypothyroidism and androgen deficiency.
Material and methods
Substitution therapy with testosterone was performed on 55 men with hypothyroidism and clinically or laboratory confirmed androgen deficiency. The age of the patients was from 35 to 69 years, the duration of hypothyroidism – from 3 to 16 years.
Results
The average total testosterone level in the patients' blood before the start of treatment was 9.3 ± 0.6 nmol/l and was significantly lower than the control group level (20.02 ± 0.81 nmol/l), $P > 0.05$. Indicators of total testosterone levels in the patients were in the range from 3.9 nmol/l to 10.7 nmol/l, with a level of hormone below 8.0 nmol/l (sign of absolute androgen deficiency) was observed in only 11

patients. Three months after the administration of testosterone, a significant increase in the mean total concentration of testosterone in the blood of the examined patients was observed up to 14.9 ± 0.87 nmol/l. At the same time, there were significant fluctuations of the indicator – from the mean normal values to those that were within the lower boundary of the normal values of testosterone in the blood of healthy men. A more pronounced increase in the average blood level of total testosterone in patients was observed after 6 months up to 17.24 ± 0.73 nmol/l. On the background of substitution therapy with testosterone, stabilization of the level of total testosterone at the reference level in the blood of men with hypothyroidism was observed after 9 months of follow-up (after the fourth injection) (16.83 ± 0.75 nmol/l) compared with the indicator before treatment.

Conclusions

The average total testosterone level in the blood of patients before the start of treatment was significantly lower than that of the control group. On the background of substitution therapy with testosterone, stabilization of the level of total testosterone at the reference levels in the blood of men with hypothyroidism was observed in 9 months of follow-up compared with the indicator before treatment. The use of long-acting injectable long-term testosterone undecanoate results in the normalization of total testosterone levels in men with hypothyroidism and androgen deficiency.

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EP146

Investigation of blood groups in benign thyroid diseases in Turkey

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Background

İt is known that there is a relationship between some diseases and blood groups.

Objective

The objective of our study is to investigate how often ABO and Rh blood groups are seen in benign thyroid diseases, especially in autoimmune-mediated thyroid diseases, and hence whether there is an association between blood groups and thyroid diseases.

Method

A total of 958 patients who were followed due to any benign thyroid disease were included in the study.

Results

The study population comprised 958 patients, 550 with Hashimoto's hypothyroidism, 160 with non-Hashimoto's hypothyroidism, 103 with iatrogenic hypothyroidism, 93 with secondary hypothyroidism, and 28 with Graves' and 24 with non-Graves' hyperthyroidism. Of the patients, 47.1% belonged to the O blood group, 30% to the A blood group, 15.2% to the B blood group, and 7.7% to the AB blood group while 90% were Rh-positive. The ratio of those with the O blood group was determined to be significantly higher in the Hashimoto's hypothyroidism group compared to the other disease groups. In the non-Hashimoto's hypothyroidism group, however, the ratio of the AB blood group was statistically significantly higher. While autoimmune diseases were more common in those with the O blood group, they were significantly lower in the AB blood group ($P < 0.001$).

Conclusion

In our study, we determined that the ratio of the O blood group was significantly higher among patients with hypothyroidism due to Hashimoto's thyroiditis. This suggests that the O blood group might be a risk factor for Hashimoto's disease.

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EP147

A rare variant of Hashimoto's thyroiditis

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Hashimoto's thyroiditis (HT) is the most common inflammatory condition of the thyroid gland. In addition to the classic variant of HT, several other subtypes have been identified, such as the fibrous variant (HTFV).

Case history

A 38 years old man noticed a rapidly enlarging lump in his neck month ago. This resulted in discomfort with choking sensation and mild dysphagia. He mentioned weight loss, tiredness and night sweats. He was a smoker and drank alcohol in moderation. He had no other past medical history. On examination he had palpable hard thyroid mass. The USS of the neck showed diffusely enlarged thyroid gland, with uniform alteration in echotexture. There was strikingly mixed reflectivity. The thyroid capsule was intact, with no infiltration into the overlying muscles. The most likely diagnosis was thought to be amyloid goitre. Patient had a core biopsy of the thyroid. CT scan of the neck and thorax confirmed diffusely enlarged thyroid with heterogenous enhancement with no retrosternal extension. There was no significant tracheal deviation or narrowing. His Thyroid function tests showed primary hypothyroidism with FT4 of 6.2 pmol/l (10.8–25.5), FT3 1.7 pmol/l (3.1–6.8) and TSH of > 100 mU/l (0.27–4.20). His C reactive protein was 71 mg/l (0–5). He had high titres of Thyroid peroxidase antibodies 1779 IU/ml (0–109) and TSH receptor antibodies were negative. The core biopsy showed marked fibrosis with lymphocyte, eosinophil infiltartes. Immunochemistry showed B and T lymphoid infiltrates with a large population of plasma cells. Features were suggestive of Reidel's thyroiditis but there was no significant expression of IgG4 within the plasma cells. This is usually high in Reidel's thyroiditis. A diagnosis of Fibrous variant of Hashimoto's thyroiditis was made and that would fit with high TPO antibodies. The fibrosclerotic process is the key feature of several thyroid diseases like Reidel's thyroiditis (RD). Differential diagnosis between HTFV and RT is based on histological criteria established by Beahrs *et al*. In HTFV the fibroinflammatory process involves a part or whole gland and it does not include the adjacent tissues. In conclusion, this case shows that the differential diagnosis between HTFV and RD is difficult due to the partial clinical and morphological overlapping and the poor efficacy of conventional cytology as well as presurgical biopsy.

Reference

1. G. Iannaci, R. Luise, P. Sapere, V. *et al*. Fibrous Variant of Hashimoto's Thyroiditis as a Diagnostic Pitfall in Thyroid Pathology. Case reports in Endocrinology 2013.

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EP148

Rhabdomyolysis as clinical presentation of hypothyroidism

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Introduction

Asymptomatic, mild or moderate elevations of creatine phosphokinase are frequently found in hypothyroidism, but rhabdomyolysis is rare, and even more so when it constitutes its clinical presentation.

Clinical case

A 26-year-old male who regularly practiced sports, with no family or personal history of interest, went to the emergency room referring to myalgia, generalized cramps, and muscular weakness in the previous two weeks which had not improved with an anti-inflammatory treatment. The symptoms appeared after resuming training, which had been suspended due to severe asthenia one month before. The physical examination was normal and in the biochemical exam, the following were observed: CPK 1.494 U/L (MB 46 U/L), aldolase 9 U/L (2–7.6), LDH 812 U/L, creatinine 1.84 mg/dl, myoglobinuria 0.38 ($N < 0.171$), GOT 103 U/L, GPT 103 U/L, urates 7.89 mg/dl, cholesterol 293 mg/dl, calcium 10.5 mg/dl, ionic calcium 4.32 mg/dl, total proteins 9.53 g/dl and polyclonal hypergammaglobulinemia. Cortisol, serology and anticardiolipin and smooth muscle antibodies were normal. The electrocardiogram showed sinus bradycardia, the echocardiogram a minimal pericardial effusion, the thyroid ultrasonography, reduced size and glandular echogenicity and the neurophysiological study increased the latency of the F waves in nerves of the lower limbs. Severe autoimmune primary hypothyroidism was confirmed (free-T4 < 0.2 ng/dL, TSH 120.65 mIU/L, antithyroglobulin and antimicrosomal antibodies > 5.000 U/ml) and replacement therapy with sodium levothyroxine was initiated. A few weeks later all the analytical parameters were normalized, the pericardial effusion disappeared and the patient was asymptomatic.

Discussion

Rhabdomyolysis is an infrequent manifestation of hypothyroidism and, in most cases, such as above described, exercise, previous chronic renal failure or lipid-lowering drugs are identified as precipitating factors. A threshold myoglobinuria level related to the development of renal failure has not yet been defined. It is believed that dehydration and low urinary pH are involved in its pathogenesis since uric acid can precipitate in the distal tubule in the presence of acid urine and

high levels of lactate. This could explain why alterations of the renal function appeared in this patient in spite of the moderate elevation of the muscular enzymes. Since rhabdomyolysis can become a severe medical issue when complicated by acute renal failure, it could be cost-effective to perform thyroid functional tests on all individuals who perform intense physical exercise.

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EP149

Primary thyroid lymphoma: about two cases

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Introduction
Primary thyroid lymphomas are rare (2–5% of thyroid cancers and less than 5% of extra-ganglionic lymphomas). The most frequent types are B-cell lymphoma and MALT lymphoma. Posing a diagnosis problem, including differential diagnosis with anaplastic cancer. We report two different cases of thyroid lymphoma.
Observation
Case 1: Women 64-year-old, followed by 7 years for Hashimoto's thyroid consulted for a cervical mass, of rapid evolution and compressive signs, cervical ultrasound: thyroid diving in the mediastinum exceeding 200cc and right lymph node, cervico-thoracic CT: tracheal stenosis with compression, bronchial or oesophageal breccia and mediastinitis. The biopsy found lymphoma diffused into large B cells. The patient dies quickly before initiating treatment.
Case 2: Man 78-year-old with no history, consults following the appearance of a cervical mass, cervical ultrasound: thyroid nodule eutirads 5, cervico-thoracic CT: large goitre diving into the thorax with mass syndrome on tracheoesophagea, the biopsy evokes an aggressive type B thyroid lymphoma. The patient had chemotherapy based CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) with good locoregional evolution.
Discussion
The risk of developing thyroid lymphoma is multiplied by 67 in case of lymphocytic thyroiditis. Because of their rarity and their clinical polymorphism, thyroid lymphomas have revealed diagnostic difficulties. Therapeutic conduct is currently well codified. Their prognosis, depending on the histology and stage of the disease, was favorable with a 5-year survival rate of 70 to 80%.
Conclusion
Due to the different therapeutic management, thyroid lymphoma is a diagnosis that must be mentioned in front of any cervical mass with rapid evolution, especially if there is a history of thyroiditis.

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EP150

Mixed histiocytosis with BRAF (V600E) mutation and papillary thyroid carcinoma

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Langherhans cell histiocytosis (LCH) and Erdheim-Chester (EC) are two histiocytic disorders which occurrence in the same patient has rarely been described. Thyroid involvement of LCH is rare, and concurrent papillary thyroid carcinoma (PTC) exceptionally reported. We report a case of a 73 year old man who presented a diagnosis of mixed histiocytosis LCH and EC. The patient suffered of insipidus diabetes since 1 year without pituitary abnormality but clinical examination showed periorbital xanthelesma. Systemic involvement was confirmed with bilateral sclerotic bone lesions, retroperitoneal fibrosing disease.Bone biopsy showed infiltration of histiocytes with kidney-shaped nuclear and eosinophilic cytoplasma. Histiocytes were CD1a, protein S 100 positive and CD 68 negative and expressed mutation BRAF V600E. Treatment with vemurafenidwas started. Also this patient had two thyroid nodules (27 and 14 mm) hypoechogenic, Tirads 4 without fixation on the Pet/CT - Ultrasound-guided fine needle aspiration (FNA) of the thyroid was suspicious for malignancy (Bethesda 5). Total thyroidectomy was performed. There was no thyroid histiocytosis involvement but an incompletely capsulated papillary carcinoma with follicular pattern and capsular minimal invasion without BRAF V600E mutation. No lymph node invasion was noted.Radioactive iodine therapy (30 mci) under recombinant TSH was delivered with efficacy: 6 months later, thyroglobulin was undetectable without circulating antibody and neck ultrasound was normal. LCH can involve thyroid and cervical lymph nodes, and could coexist with other thyroid diseases such as chronic lymphocytic thyroiditis. PTC may be exceptionally associated and should be considered in the differential diagnosis. Moreover, FNA cytological diagnosis of LCH is difficult. Activating missense mutation BRAF V600E has been identified in multiple neoplasms including melanoma, colorectal carcinoma but also papillary thyroid carcinoma and histiocytosis (LCH, EC). Two cases reported LCH associated with a BRAF V600E mutation in PTC. Unfortunately this mutation was absent in our case of PTC.

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EP151

Multicentric papillary thyroid carcinoma with concomitant rare dedifferentiation in the lymph node metastasis

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Introduction
Papillary thyroid carcinoma (PTC) is a differentiated thyroid carcinoma accounting for approximately 80% of all thyroid malignancies; in contrast only 1–2% of thyroid cancers are anaplastic. While the transformation of papillary thyroid carcinoma to the more aggressive anaplastic carcinoma represents a well known occurrence, the transformation of metastatic PTC in a distant location is an uncommon finding, but new insights from the *BRAF(V600E)* mutation studies could explain such an event.
Case report
We present the case of a 50 years old woman with medical history of surgically removed anaplastic axillary lymph node with 18F-FDG PET/CT which revealing increased values with high probability of malignancy only in the left thyroid lobe. Further investigations: euthyroid state and normal calcitonin; cervical regional ultrasound examination showed a hypoechogenyc mass in the left thyroid lobe which was biopsied by fine needle aspiration with malignant result (Bethesda Category IV-B IV). Total thyroidectomy was performed and histopathological evaluation revealed multicentric papillary thyroid carcinoma. The high level of postoperatory thyroglobulin was an indication for radioactive iodine ablation. The patient also started chemotherapy.
Discussion
A pertinent question would be: it was the same disease? In our case, based on the imunohistochemical phenotype and the results of the PET/CT, a diagnosis of anaplastic dedifferentiation in a axillary lymph nodes metastasis from a multicentric papillary thyroid carcinoma is the most probable diagnosis.
Keywords: papillary, dedifferentiation, anaplastic

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EP152

Hyperthyroid Graves' disease without detectable thyrotropin receptor antibodies

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Introduction
Detection of TSH-receptor autoantibodies in the diagnosis of graves disease is well established. however these autoantibodies may not be always present in some forms of correctly observed autoimmune hyperthyroidism. Here, we

describe a patient with hyperthyroid Graves' disease without detectable thyrotropin receptor antibodies.
Case report
She was A 55-year-old woman, presented with a 2 years history of increased sweating, palpitations, polyphagy and insomnia with weight loss of 10 kg. Clinical examination revealed exophthalmos and lid lag, a fine tremor of her fingers, the pulse was 100/min and a small diffuse goiter without trill. Blood tests demonstrated high FT4 = 55.3 pmol/L (NR 12–22), FT3 = 29.2 pmol/l (3.1–6.8), TSH < 0.005 mIU/l (0.27–4.2), Measurement of her thyroid-stimulating hormone was négatif. Thyroid scintigraphy shows an enlarged gland with homogeneous uptake of radiotracer in both lobes.
Discussion
Immunogenic hyperthyroidism (Graves or Basedow's disease) is a consequence of pathological stimulation of the thyroid gland by stimulating TSH-receptor autoantibodies (TSAbs). In Differentes studies The results show that it is extremely rare to have negative TSH receptor autoantibody in patients with active hyperthyroid Graves' disease. In our case palpation, clinical findings, and the data of thyroid sintigraphy were sufficient to establish the diagnosis of Graves disease despite of TSH receptor autoantibodies were undetectable. Other mechanisms can also activate graves disease than antibody-dependent ones or a local production of antibodies within the thyroid can be suggested.

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EP153

Surgical treatment for graves' disease: about 39 cases

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Introduction
Graves' disease represents an autoimmune disease of the thyroid gland, which therapeutic management is controversy. The aim of our study is to discuss, after a review of the literature, the role of surgery, especially total thyroidectomy, in the treatment of Graves' disease.
Patients and methods
We conducted a retrospective study of medical records of 39 patients who underwent surgery for Graves' disease at the Department of Otolaryngology Head and Neck Surgery of Farhat Hached University Hospital during 15 years (from 01/01/2001 to 31/12/2015).
Results
Thirty nine patients were operated for Graves' disease, 23 women and 16 men, aged between 13 and 58 years old. All our patients had thyroid goiter and hyperthyroidism, treated with anti thyroid drugs and β blockers. Seventeen of them had Graves' orbitopathy. Our operative indications were dominated by the failure of the medical treatment (72% of cases). All our patients had a total thyroidectomy. Seven patients developed post operative complications: transient hypocalcemia in six cases and recurrent laryngeal nerve paresis in one case. All our patients received thyroid hormone replacement after surgery with favorable evolution.
Conclusion
Total thyroidectomy is the more efficient radical method for treating patients with Graves' disease. It is not accompanied by a higher rate of complications than subtotal thyroidectomy.

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EP154

A case of probable thyroid hormone resistance syndrome

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Introduction
A disturbed thyroid status is a frequent reason for consultation in endocrinology. The typical tables of hypo or hyperthyroidism encountered lead to classical etiological investigations whether central or peripheral. In some unusual situations, the profile encountered may be atypical. We report a case.
Observation
Six years old girl, hospitalized for a goitre evolving since one year without thyrotoxicosis nor compression signs. There was strong consanguinity in the family and the mother has a thyroidectomy. The examination found a homogeneous goiter, without thrill, tachycardia. The balance returned normal TSH at 1.88 μU/ml with a high LT4 level at 58 pmol/l. On cervical ultrasound, an homogeneous goitre, with normal vascularization. In thyroid scintigraphy we found a moderate goitre with very intense fixation, without nodules. The blood stamp found normal prolactin and cortisol levels. Pituitary MRI was without abnormality. The maternal assessment found a normal TSH at 1.74 mU/l, an LT4 at 41.9 pmol/l. The diagnosis of central hormone resistance syndrome was retained.
Discussion
The thyroid hormone resistance syndrome is a rare entity, not very symptomatic. We can evoque it as a differential diagnosis of a thyrotropic adenoma with an unrestrained TSH and an increased level of peripheral hormones, especially in patients with consanguinity (autosomal dominant character). The diagnosis is genetic, not currently used is practice. The treatment is not codified. It can be abstention or thyroidectomy and is based on the presence of signs of thyroitoxicosis.

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EP155

Transient elevation of CA 19-9 due to cessation of levothyroxine in a patient with Hashimoto's thyroiditis

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Serum CA 19-9 (carbohydrate antigen 19-9) is a tumor marker of monosialoganglioside structure. Its level is frequently measured for screening purposes in daily practice by physicians, while its main use is in the study of tumor recurrence and follow-up of recurrences. Although significant elevations in CA 19-9 levels cause suspicion of malignancy, an underlying malignant disease may not always be determined and benign pathologies may also be seen. A 45-year-old female patient being followed for Hashimoto's thyroiditis applied to our clinic with complaints of fatigue, tiredness, and hair loss. Elevations of both thyroid-stimulating hormone (TSH) and CA 19-9 were seen. Normal TSH and CA 19-9 levels were observed after the patient was treated for hypothyroidism, and analysis results were determined to be normal after testing for malignancy. Based on our case, we think that hypothyroidism should be kept in mind in patients with CA 19-9 elevation while making a differential diagnosis.

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EP156

An uncommon debut of graves disease with bilateral gynecomastia: case report

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Gynecomastia is an uncommon clinical manifestation of hyperthyroidism, due to an imbalance between sexual hormones caused by thyroid hormones excess. Recognition of such unusual association is important to ensure appropriate treatment and to avoid unnecessary investigation. In hyperthyroidism, increased serum levels of SHBG binds testosterone with greater affinity than estradiol, resulting in relatively higher free estradiol compared with free testosterone levels and thereby contributing to stimulation of breast tissue and gynecomastia. A 52-year-old man with no medical history was referred to endocrinology department because of painful enlargement of his breasts. He also complains about palpitations, tremor and 10 kg weight loss in the last 3 months. The patient was not from endemic area for goiter and had no family history of thyroid disease. Physical examination revealed enlarged thyroid, tremor of both hands,

tachycardia (110/min), painful breasts enlargement with about 2 cm of palpable tissue. Laboratory findings revealed hyperthyroidism with high levels of anti TSH antibodies. The patient was treated with methimazole 30 mg daily and b-adrenergic blocking agent with rapid improvement of symptoms and significant regression of gynecomastia in less than a month.

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EP157

Thyroid storm, a rare but life-threatening appearance of hyperthyroidism

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Thyrotoxicosis is characterised by the excess of thyroid hormones into blood. The most extreme appearance of it, is thyroid storm which is presented as an acute, severe, life-threatening, hypermetabolic state caused by the added quantities of thyroid hormones, causing adrenergic hyperactivity and abnormal periphery response of thyroid hormones. The incidence of thyroid storm is evaluated at 0.2/100000 in year. The mortality of untreated thyroid storm varies from 80–100% while treated one is 10–50%. The main cause of death is the multiorgan failure followed by cardiac failure, respiratory failure, arrhythmia, disseminated intravascular coagulation, hypoxic syndrome of brain and sepsis. Thyroid storm causes are related to endocrine disorders with primary or secondary origin. In rare cases it can be caused from exogenous pathology or drugs. The diagnosis is made based on Burch-Wartofsky score. The treatment is multidimensional and aims the most effective treatment possible of thyroid storm. In Endocrinology, Diabetes and Metabolic Diseases clinic in 'Mother Teresa' University Hospital Centre during the last year are hospitalised 5 patients, all females, with signs of thyroid storm crisis. All patients presented with fever, vomiting, abdominal pain and confusion. In two cases thyroid storm was precipitated by surgery, two cases from severe infection and in one patient by radioactive iodine therapy. Treatment was initiated immediately and fortunately we had zero mortality rate. Being a rare phenomenon and with a high mortality it is important to study the thyroid storm and its management.

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EP158

Indian endocrine surgery websites-comparable or not?

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Introduction
At present patients and relatives garner more knowledge through website rather than direct interaction with the Consultant physician. We aimed at assessing whether Indian website about Endocrine Surgery matched with their counterpart abroad.
Materials and methods
We identified two most searched Endocrine Surgery website world wide and 10 endocrine surgerywebsite maintained by trained Endocrine Surgeons (three years training leading to award of Superspeciality degree) from India. The website parameters and Number of hits, demographic data of website, rank and other parameters were assessed using professional website (www.Alexa.com). An Endocrine surgeon along with a technical website advisor rated the content, presentation and likesfrom a scale of 1 to 5. (1-minimum score and 5 maximum score).
Results
We analysed 10 Indian and 2 website from outside India. Fisher exact test was used to test the association between websites (India/Abroad) and individual variables. Results shows that there was no significant association Website(India/Abroad) and Thyroid facts, Parathyroid Facts, Adrenal, Pancreas, Photographs, videos, Publications, Landscape of website, Quality, Presentation of website, Number of views, Gender of person viewing thewebsite and age group of person ($P > 0.05$), while there was significant association with Post-operative advise as well as complications ($P < 0.05$).
Conclusion
Most parameters were comparable in both groups.But the complication rate was not available in many websites. Post operative advice was present in only few websites. The advantage of these website is that patient can gather much needed information and also save much of unneeded discussion with physician and also save on second consultation. Indian websites regarding endocrine surgery is comparable to other countries except the complications are not highlighted and post op advise not found.

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