CRANFIELD UNIVERSITY

MAHA MUSTAFA ALEID

UROGENITAL FUNCTION IN MORBIDLY OBESE MEN FOLLOWING BARIATRIC SURGERY

School of Aerospace, Transport and Manufacturing

Translational Medicine

PhD
Academic Year: 2011 - 2016

Cranfield Supervisor: Dr. Nicola White
External Supervisors: Prof. Selim Cellek, Mr. Asif Muneer, Mr David Ralph and Mr. Majid Hashemi

January 2016

CRANFIELD UNIVERSITY

School of Aerospace, Transport and Manufacturing
Translational Medicine

PhD

Academic Year 2011 - 2016

MAHA MUSTAFA ALEID

Urogenital function in morbidly obese men following bariatric surgery

Cranfield Supervisor: Dr. Nicola White
External Supervisors: Prof. Selim Cellek, Mr. Asif Muneer, Mr David Ralph and Mr. Majid Hashemi

January 2016

This thesis is submitted in partial fulfilment of the requirements for the degree of PhD

ABSTRACT

Introduction:

Obesity has been suggested to be one of the risk factors for erectile dysfunction (ED) and lower urinary tract symptoms (LUTS). Bariatric surgery has been used for the treatment of obesity and has been suggested to have a significant impact on obesity-related conditions such as diabetes mellitus, ED and LUTS. Previous studies have investigated the effect of bariatric surgery on erectile and urological function in obese men; however those studies used long-term time points post-operatively (more than 1 month). Since it is now known that bariatric surgery can potentially induce glycaemic improvement within one week independent of weight loss, this study aimed to investigate the short-term effect in order to test the hypothesis as to whether improvement in urogenital function after bariatric surgery is due to weight loss or whether it is due to glycaemic improvement.

Aim:

To evaluate the baseline characteristics of patients with erectile dysfunction and to determine the early effects of bariatric surgery on erectile and urological function in morbidly obese men.

Method:

This was a prospective study investigating the effect of BMI on urogenital function by conducting two separate clinical audits; the first audit was designed to investigate the baseline characteristics of patients with erectile dysfunction and determine if there were any correlations between urogenital function and obesity. The audit was set up and conducted over a nine month period between June 2014 and March 2015, involving 60 patients with any urological condition. The second audit was designed to investigate the effect of bariatric surgery on male patients' body mass index (BMI), urological symptoms, and sexual function. The audit was set up and conducted over a thirty month period between February 2013 to July 2015, involving 30 patients aged 30 years and above with a body mass index of 35 kg/m^2 and over undergoing bariatric surgery. Urogenital function was assessed in both audits using two validated

questionnaires: International Index of Erectile Function (IIEF) and International Prostate Symptom Score (IPSS). The second audit was completed before the surgery and four weeks, three months and six months after the surgery. The data were analysed using parametric and non-parametric tests for paired samples. The data were obtained from ongoing clinical audits at the UCL Hospitals. The study was approved by the Cranfield University Health Research Ethics Committee.

Results:

The analysis of 60 patients in the baseline characteristics audit indicates that 78.3% of the patients (n=47) suffered from being overweight and obese (BMI over 25 kg/m^2). 80% of patients had ED (IIEF score less than 25). There was no significant difference between the ED and NO-ED group in respect of their IPSS scores. A significant correlation was found between sexual desire, overall satisfaction and BMI ($p=0.01$) but no correlation was found between any of the IPSS domains and BMI. A significant positive correlation was found between testosterone and IIEF domains ($p<0.01$) except overall satisfaction ($p>0.05$). Although there was no significant correlation between testosterone and obesity ($BMI>30kg/m^2$), a significant correlation was found between free testosterone and overweightness ($25kg/m^2 \leq BMI <30kg/m^2$).

In the bariatric surgery audit, 18 patients reported ED (IIEF score <25) before the operation. BMI, IIEF, IPSS, fasting blood glucose and HbA1c all improved significantly starting at 1 month post-operatively and continued to improve throughout the study.

Conclusions:

The findings suggest that obesity could be an important risk factor for urogenital dysfunction in men. The results also highlight the role of testosterone in men with obesity on their urogenital function. Bariatric surgery leads to improvement in erectile and urinary function as well as glycaemic improvement within 1 month post-operatively. Since the surgery-induced weight loss occurred at an unexpectedly early time point, it was not possible to ascertain whether the

improvement in urogenital dysfunction was due to weight loss or glycaemic improvement. Further studies with even shorter time points and greater patient numbers are required to address this question.

Keywords:

Erectile dysfunction, obesity, bariatric surgery, International index of erectile function (IIEF), International prostatic symptom score (IPSS) and Lower urinary tract symptoms (LUTS).

ACKNOWLEDGEMENTS

First of all, I would like to express my sincere gratitude to my advisor Prof. Selim Cellek for the continuous support of my PhD and related research, for his patience, motivation, and immense knowledge. His guidance helped me all the time in research and writing of this thesis.

I would like to express my deepest gratitude to my advisor, Dr. Nicola White, for her excellent guidance, I could not have imagined having a better advisor and mentor for my PhD.

Besides my advisors, I would like to thank the rest of my external supervisors: Mr. Asif Muneer, Mr. David Ralph, and Mr. Majid Hashemi, for their insightful comments, encouragement, and for their eye openers which widened my research from various perspectives.

I would especially like to thank the surgeons, nurses, nurse assistants and dieticians in the Urology and bariatric clinics at the University College London Hospital. All of you have been there to support me when I collected data for my PhD.

My sincere thanks also goes out to King Faisal specialist hospital and research Centre; in particular, I am grateful to Dr. Sultan Alsudairy for enlightening me with the first glance of research and the Saudi cultural bureau in London-UK, who provided me the opportunity to continue my studies. Without their precious support it would not have been possible to achieve this PhD.

I would like to thank my husband, Dr Hamad Albahili. He was always there cheering me up and stood by me through the good times and bad. Words cannot describe how lucky I am to have him in my life. He has selflessly given more to me than I ever could have asked for. I love you, and look forward to our lifelong journey together.

A special thanks to my family. Words cannot express how grateful I am to my family for all of the sacrifices that you've made on my behalf. Your prayers for me were what sustained me thus far.

I dedicate this thesis to the memory of my beloved mother, Mrs Suaad Alsabti. It is your shining example that I try to emulate in all that I do.

Special thanks goes out to my father Mr. Mustafa I have been able to finish my PhD with his prayers, my two elder sisters Dr Weam and Mrs Ibtisam, and my two elder brothers Mr Mazin and Dr Hazim. They were always supporting me and encouraging me with their best wishes and prayers.

Finally, I would like to thank all my friends for all their support, advice, and believing in me, in particular, Mr. Faris Abomelha for his IT support.

Thank you God for everything

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF EQUATIONS

LIST OF ABBREVATIONS

AGE	Advanced glycation end-products
AHA/NHLBI	American Heart Association/National Heart, Lung and Blood Institute
AIDS	Acquired immune deficiency syndrome
ANOVA	Analysis of variance
AUA	American Urological Association
BACH	Boston area community health study
BMI	Body mass index
BMJ	British Medical Journal
BMSFI	Brief Male Sexual Function Inventory
BOMSS	British Obesity and Metabolic Surgery Society
BOO	Bladder outlet obstruction
BP	Blood pressure
BPD	Biliopancreatic diversion
BPE	Benign prostate enlargement
BPH	Benign prostatic hyperplasia
BSSM	British Society for Sexual Medicine
CAD	Coronary artery disease
CDC	Centre for Disease Control and Preservation
CDR	Clinical data repository
cGMP	Cyclic guanosine monophosphate
CNS	Central nervous system
COREC	Central Office for Research Ethics Committees
CUHREC	Cranfield University Health Research Ethics Committee
CVD	Cardiovascular disease
DIO	Diet- induced obesity
DM	Diabetes mellitus
DS	Duodenal switch
ED	Erectile dysfunction

ECG	Electrocardiogram
EF	Erectile function
EGP	Endogenous glucose production
FBG	Fasting blood glucose
FDA	Food and Drug Administration
ESR	Erythrocyte sedimentation rate
Free T4	Free thyroxine
FSH	Follicle stimulating hormone
eNOS	Endothelial nitric oxide synthase
EPIC	European prospective investigation into cancer and Nutrition
EpiLUTS	Epidemiology of LUTS study
EWL	Excess weight loss
GC	Guanylate cyclase
Glc6Pase	Glucose-6-phosphatase
GFR	Glomerular filtration rate
GTP	Guanosine-5'-triphosphate
HbA1c	Haemoglobin A1c
HCT	Haematocrit test
HDL	High-density lipoprotein
HFD	High fat diets
HOMA-IR	Homeostasis model assessment of insulin resistance
HPFS	Health Professionals Follow-up Study
ICS	International Continence Society
ICIQ-SF	International Consultation on Incontinence Questionnaire-Short Form
IDF	International Diabetes Federation
IIEF	International Index of Erectile Function
IP_3	Inositol triphosphate
IPSS	International Prostate Symptom Score
IR	Insulin resistance
IS	Intercourse satisfaction

IT	Information technology
IWQOL-L	Impact of Weight on Quality of Life - Lite
JIB	Jejunoileal bypass
LAGB	Laparoscopic adjustable gastric banding
LDL	Low density lipoprotein
LGB	Laparoscopic gastric banding
LH	Luteinizing hormone
LSG	Laparoscopic sleeve gastrectomy
LUTS	Lower urinary tract symptoms
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MDT	Multidisciplinary team
MetS	Metabolic syndrome
MPV	Mean platelet volume
MSHQ	Male Sexual Health Questionnaire
NBSR	National Bariatric Surgery Register
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIDDM	Non-insulin dependent diabetes mellitus
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
OF	Orgasmic function
OS	Overall satisfaction
OVB	Overactive bladder
PDE5	Phosphodiesterase type 5
PDE5-Is	PDE5-inhibitors
PEPCK	Phosphoenolpyruvate carboxykinase
PGE1	Prostaglandin E1
PKA	Protein kinase A
PLB	Phospholipase B

PLC	Phospholipase C
POLER	Prolong preoperative weight loss programme
PSA	Prostate specific antigen
PYY	Peptide tyrosine tyrosine
RDW	Red blood cell distribution width
ROCK	RhoA–Rho-kinase
RYGB	Roux Y gastric bypass
ISC	International Scientific Committee
SD	Sexual desire
SG	Sleeve gastrectomy
SHBG	Sex hormone binding globulin
T2DM	Type 2 diabetes mellitus
TSH	Thyroid stimulating hormone
UCL	University College London
UCLH	University College London Hospital
UI	Urinary incontinence
UK	United Kingdom
USA	United States of America
VBG	Vertical band gastroplasty
WHO	World Health Organization

1 INTRODUCTION

1.1 Obesity

1.1.1 Definition and classification

Obesity is a chronic disease defined as a high amount of body fat in relation to lean body mass resulting from high calorific intake that surpasses usage of energy (Wang *et al.* 2008a). Obesity has been classified (Table 1-1) according to the body mass index (BMI; Equation 1-1) which is the measurement of the mass in the human body, in kilograms, divided by height in meters squared.

Equation 1-1: Body mass index (Welbourn *et al.* 2014)

$$BMI = \frac{Weight\ (kg)}{Height^2\ (m^2)}$$

Table 1-1: Classification of body mass index (BMI) for obesity according to NICE guidelines (NICE 2014).

Types	BMI (kg/m^2)
Healthy weight	18.5-24.9
Overweight	25-29.9
Obesity type I	30-34.9
Obesity type II	35-39.9
Obesity type III	and more

The increase in obesity is a worldwide epidemic according to the World Health Organization (WHO), which estimates that more than 1.6 billion individuals are currently overweight and 400 million are obese (World Health Organisation 2000). Moreover, obesity has been linked to insulin resistance and type 2

diabetes mellitus (T2DM; (Wickremesekera *et al.* 2005) which can impact on the quality of life or can lead to mortality if left untreated (Fujimoto 2000).

1.1.2 Epidemiology of obesity

The worldwide epidemic of obesity and obesity related diseases such as T2DM continues to increase. Compared to the data from 1980, the overall prevalence in the world of individuals being overweight or obese has risen from 28.8% to 36.9% in men. Globally, every country is failing in its attempts to combat obesity (Ng *et al.* 2014) and, as such, many researchers have asserted that obesity is the characteristic disease of the 21st century (O'Brien 2010).

The United Kingdom is the 3rd most obese country in Western Europe after Iceland and Malta. In 2013, around 67% of men aged 20 years and over were overweight or obese with the incidence of obesity increasing since 1980 by 13% in that age group (Public Health England 2015).

The Public Health England (2010) revealed that in England in 2008, around 24% of men and 25% of women aged 16 or over were classified as obese, and 66% of men and 57% of women were overweight (NICE 2014). In the United States of America (USA) between 1960 and 1980, the percentage of individuals who were obese increased from 13.4% to 14.4%, and by 2000 the percentage doubled to 30.4% (Wang *et al.* 2008a, World Health Organisation 2000). In 2008, the percentage had increased to 33.8% and studies estimate that the percentage between 2010 and 2020 will be 37.4% for men and 44.2% for women (Wang *et al.* 2008a).

In the USA, the Centre for Disease Control and Prevention (CDC) found that the prevalence of obesity began to accelerate in the early 1980s. A 2008 report by Diabetes Australia (2008) found that over 77 million American adults are currently suffering from obesity, with a similar percentage of cases also being found in Australia, with roughly 3 million or 22% of adults suffering from the disease (O'Brien 2010).

1.1.3 Pathophysiology of obesity

The average middle-aged man and woman's body weight is made up of around 21% to 27% of fat. In the context of obesity, individuals consume more calories than they expend, and their appetite is not always satisfied or reduced by the rise in energy stores (Gurevich-Panigrahi *et al.* 2009). Furthermore, the adipose tissue and how much of it is produced are strictly regulated via hormonal and neural signals which are sent to the brain (Gurevich-Panigrahi *et al.* 2009). Therefore, energy balance is regulated by a complex system involving sensors of energy stores, found in the adipose tissue, as well as a mechanism to successfully send the information to vital control sites or the hypothalamus for successive integration, which determines energy outflow and food intake (Gurevich-Panigrahi *et al.* 2009, Lean 2000). Table 1-2 illustrates the symptoms and consequences of obesity.

Table 1-2: Symptoms and Consequences of Obesity (Lean 2000).

Physical symptoms	**Metabolic problems**
• Arthritis • Back pain • Breathlessness • Oedema, cellulitis • Stress incontinence • Sweating • Varicose veins	• Hypercoagulation • Hypertension • Ischaemic heart disease (IHD) and stroke • Non-insulin dependent diabetes mellitus (NIDDM) • Hyperlipidaemia
Anaesthetic and surgical hazards	**Endocrine problems**
• Hernia • Chest infections • Sleep apnoea • Wound dehiscence	• Hirsutism • Oestrogen-dependent cancers (breast, endometrium, prostate) • Oligomenorrhoea

Social Isolation

- Agoraphobia
- Discrimination
- Family, marital stress
- Unemployment

- infertility
- Menorrhagia

Psychological effects

- Tiredness
- Depression
- Low self-esteem
- Self-deception and distortion of thought

Genetic experiments performed on animal models have facilitated the understanding of the regulation of fat metabolism. For example, mice have been shown to become obese as a result of at least five identified genes being mutated: the "*obesity"* gene encoding leptin, the "*diabetes"* gene, *"fat"* genes, *"tubby"* and "*agouti yellow"* (Friedman *et al.* 1998). Homozygosity for mutant forms of obesity or diabetes genes produces mice that eat excessively and have low energy expenditure, they become obese and suffer from several metabolic abnormalities such as hyperglycaemia, hypothermia, hyperinsulinaemia, reduced thyroid hormone and decreased reproductive function (Gurevich-Panigrahi *et al.* 2009).

Leptin is a peptide hormone which is released predominantly from the adipose tissue and delivers signals to the brain based on the quantity of fat stores (Jackson 1999). Some obese patients are known to have mutations in both their leptin and leptin receptors (Jackson 1999). Given that normal leptin and obesity genes are observed in many obese individuals, the potential reasons for obesity have been suggested to include the alleles of several genes associated with regulating energy and metabolism, as well as environmental factors (Jackson 1999).

In obese individuals more calories are consumed than expended, which can be due to a reduction in physical activity, metabolic rate and thermogenesis which eventually decrease energy expenditure, leading to increased energy storage and obesity (Figure 1-1; (Gurevich-Panigrahi *et al.* 2009).

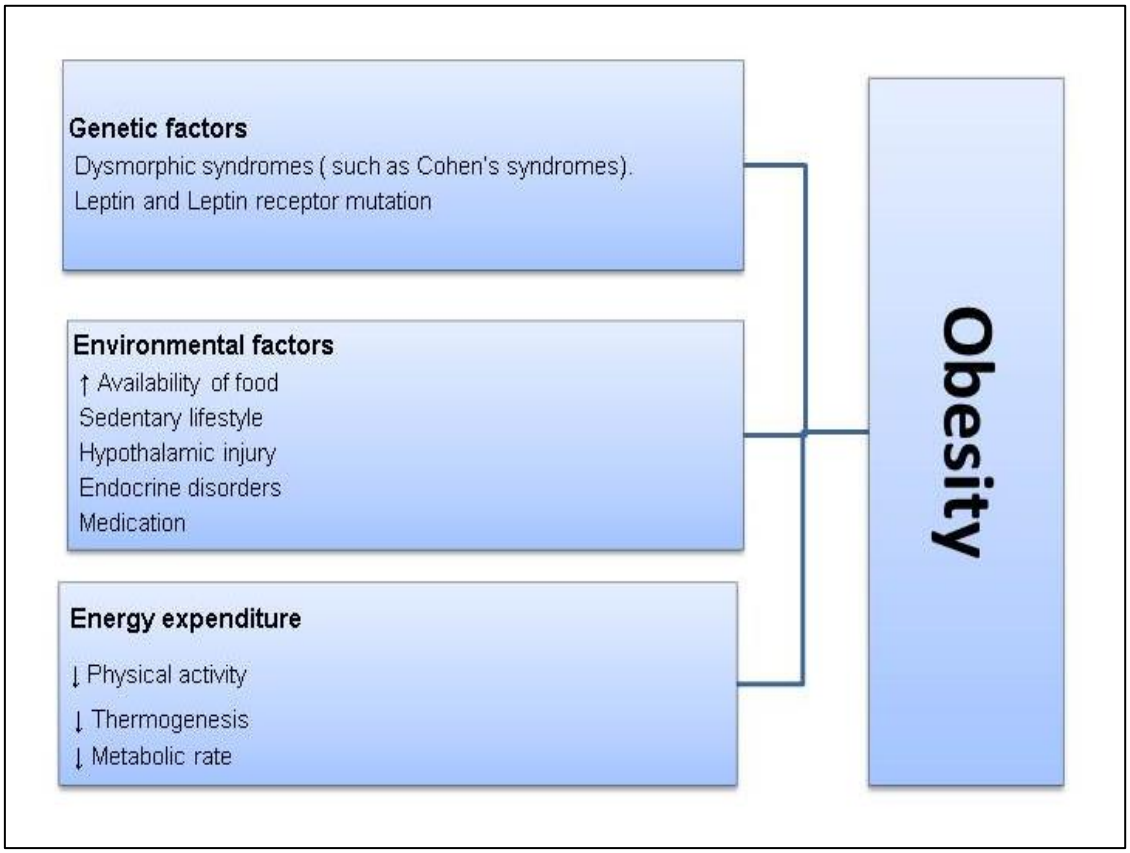


Figure 1-1: Energy balance and the aetiology of obesity (Gurevich-Panigrahi *et al.* 2009).
The relationship between energy expenditure and storage, and food intake determines energy balance. Obesity is perceived as a disorder that takes into account a myriad of factors caused by various genetic and environmental factors (Gurevich-Panigrahi *et al.* 2009).

1.1.4 Obesity and co-morbidities

Obesity, as has been previously described, increases the likelihood of developing so-called obesity related comorbidities. The most prevalent of these is T2DM, with around 382 million individuals estimated to be affected (Guariguata *et al.* 2014). Furthermore, there are two key epidemiological studies that strongly link increased weight and diabetes: the Male Health Professionals Follow-up Study (HPFS) who studied 51,000 male patients (Chan

et al. 1994) and the Nurses' Health Study which studied 112,000 female patients (Colditz *et al.* 1995) both demonstrated a significant increase in T2DM with weight gain. Moreover, the Nurses' Health Study (Colditz *et al.* 1995) shows that the likelihood of individuals developing T2DM who have a BMI of 25 is five times higher than that of an individual who has a BMI of 22. This increase is proportionate to BMI, with a BMI of 30 or more increasing likelihood of developing BMI 27-fold and a BMI of 35 or more increasing the likelihood 93-fold, when compared to a person with a BMI of 22.

Obesity has been suggested to lead to strokes, ischaemic heart disease, and diseases related to metabolic syndrome, such as polycystic ovary syndrome, obstructive sleep apnoea, dyslipidaemia and hypertension (Ning *et al.* 2010). It is also important to point out that the disease is suggested to increase the likelihood of cancer, especially colon, pancreatic, breast, renal and bladder cancers, among others (Calle *et al.* 2003). Furthermore, obesity has also been suggested as a risk factor for depression, and degenerative diseases of the knees and hips (Mokdad *et al.* 2003).

1.1.5 Treatment

1.1.5.1 Non-surgical treatment options

A number of non-surgical options are available for the treatment of obesity, such as lifestyle changes, for example reducing calorie intake, being more physically active and medical therapy (O'Brien 2010).

There are a number of different recommendations on weight management that have been suggested (Franz et al. 2007), including diet alone, diet and exercise, exercise alone, meal replacements[1], very-low-energy diets[2], weight-

[1] Meal replacements are drinks, bars, soups, etc. intended as a substitute for a solid food meal which were used for two or more meals per day and as an adjunct to a reduced-energy diet (Franz *et al.* 2007).

loss medications (e.g. orlistat[3]), and advice alone.

1.1.5.1.1 Lifestyle changes

The first line of treatment for obesity consists of two principal changes in lifestyle: a low calorie diet, and physical exercise (Papamargaritis *et al.* 2012). Studies have suggested that eating healthier foods and engaging in more physical activities is the safest way to lose weight (Bond *et al.* 2009, Gaesser 2013).

However, a conflicting study (Mauro *et al.* 2008) argues that many individuals lack the willpower or motivation to stick to a healthy diet, which in turn leads them back to their previous lifestyle that has contributed to their obesity. Indeed, 75% to 80% of individuals often regain weight after losing it, thus indicating that they do not stick to their regular diet plan after significant weight loss (Polivy *et al.* 2002). Therefore, they often turn to weight loss medications or as a last resort, to surgical methods such as bariatric surgery. A suggested clinical strategy to induce weight loss is shown in Figure 1-2.

---

[2] Very low energy diet is a diet of 800 kcal or less per day, usually in the form of a liquid diet (Franz *et al.* 2007).

[3] Orlistat (also known as tetrahydrolipstatin) is a drug designed to treat obesity. It is marketed as a prescription drug under the trade name Xenical (NHS Choices 2015a).

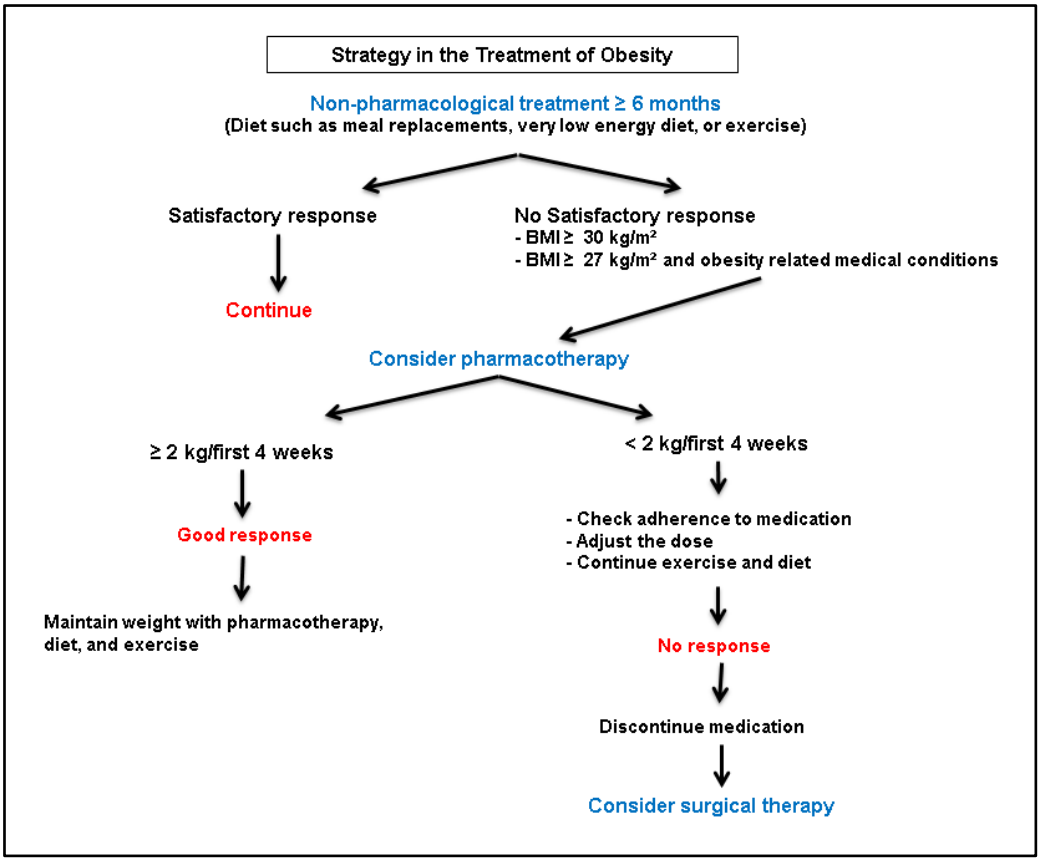


Figure 1-2: Various approaches to the treatment of obesity.
Obesity is a particularly challenging medical condition due to its complex aetiology. Non-pharmacological treatment such as exercise and healthy diet should continue if there is a satisfactory response. On the other hand, an unsatisfactory response would prompt alternative treatment such as pharmacotherapy. However, such treatment must only be carried out for patients whose BMI exceeds 30 and for those who have obesity-related medical conditions. After considering pharmacotherapy, in the event of those patients who do not lose a minimum of 2kg within the first 4 weeks of treatment, a reassessment and readjustment of their medication, exercise and dietary plans must be performed. The clinician must then consider stopping or at least replacing the patient's medication with another, in the event of the patient not responding well to the current medication. Finally, if there is no response to the newly prescribed medication, exercise and dietary plans, then surgical therapy is considered (Gurevich-Panigrahi *et al.* 2009).

1.1.5.1.2 Weight loss medications

Medications such as orlistat (Xenical, Alli) are designed to treat obesity by inhibiting gastric and pancreatic lipases (the enzymes that break down triglycerides in the intestine) thereby reducing fat absorption (Thomson PDR 2006). Patients who take orlistat lose on average an extra 2.9 kg (95%CL-3.2 to -2.5 kg) within a 12 month period (Li *et al.* 2005a)(Kang *et al.* 2012), as well as reducing the risk of T2DM and exhibiting reductions in their overall cholesterol. Side effects related to the mechanism of action of this group of drugs include

diarrhoea, faecal incontinence, oily spotting, flatulence, bloating, and dyspepsia (Ioannides-Demos *et al.* 2006, Padwal *et al.* 2003). Some cases of liver failure have also been reported (Thomson PDR 2006). Table 1-3 describes the pharmacologic options of obesity treatment.

Table 1-3: The pharmacologic options of obesity treatment (Gurevich-Panigrahi *et al.* 2009).

Groups	Example	Mechanism of action	Adverse effects
Appetite suppressors	Sibutramine *(Reductil)*®	Inhibits norepinephrine and serotonin reuptake in central nervous system (CNS)	Hypertension, tachycardia, dry mouth, insomnia, headache, constipation (Yanovski *et al.* 2003).
Inhibitors of fat absorption	Orlistat *(Xenical, Alli)*®	Binds gastrointestinal lipases	Gastrointestinal side effects, decreased absorption of fat-soluble vitamins such as vitamin A, D, E and K (Thomson PDR 2006).
Stimulators of thermogenesis (New and investigational drugs)	Rimonabant *(Acomplia)*®	Suppresses appetite, increases thermogenesis	Severe psychiatric mood related disorders (Akbas *et al.* 2009).

1.1.5.1.3 Efficacy of non-surgical methods

Based on a systematic review by Randall and colleagues (2014) which explored the effectiveness of non-surgical weight management interventions for obesity in the UK, the majority of the research articles identified a significant reduction in weight and/or BMI following engagement in a physical activity or diet-based intervention for both adult and child populations for a duration of twelve weeks and the largest reduction in weight was 9.8 kg recorded through a structured calorie controlled diet plan and management (Randall *et al.* 2014). However, this review is not explicit in detailing the optimisation of public health interventions since it only focused on UK-based articles ignoring many high quality articles that have been published elsewhere (Randall *et al.* 2014).

Another systematic review by Gloy and colleagues (2013), points out that non-surgical weight-loss interventions seem to produce conservative short-term

results but that these results are short lived, particularly in the morbidly obese (Gloy *et al.* 2013). This is known as “yo-yo syndrome” in which patients constantly gain and lose weight, and may end up developing severe long-term psychological and health problems (Amigo *et al.* 2007).

Numerous randomized controlled trials have shown that a modest weight loss of between 2 and 5 kg can be achieved in 12 months simply through lifestyle changes (O'Brien 2010). On the other hand, a systematic review by Franz and colleagues (2007) showed that weight-loss interventions involving attention to diet alone, diet and exercise, meal replacements, and weight-loss medications combined with diet, all with the exception of Sibutramine seem to produce encouraging results, but only in the short-term (Franz *et al.* 2007), as shown in Figure 1-3. Table 1-4 shows the advantages and disadvantages of lifestyle interventions versus pharmacotherapy interventions for weight loss.

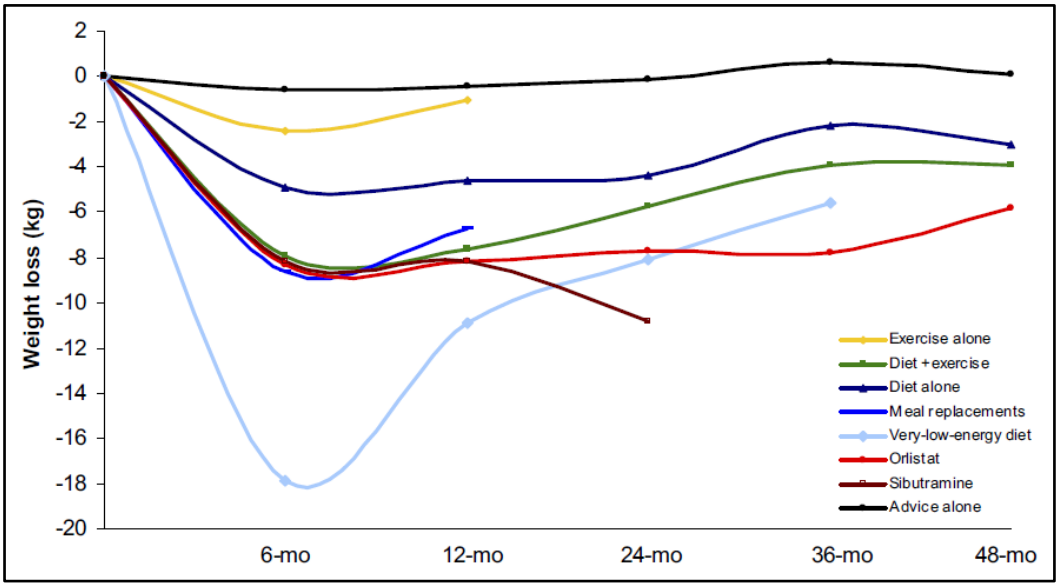


Figure 1-3: Average weight loss of subjects completing a weight management intervention for at least one year (Franz *et al.* 2007).
Data presents the average weight loss of all patients on each intervention at the specified time-point. The eight interventions studied were: exercise alone (yellow), diet and exercise (green), diet alone (dark blue), meal replacements (used for two or more meals per day; marine blue), very-low-energy diet (under 800 kcal per day; grey), Orlistat (in combination with lifestyle interventions; red), Sibutramine (in combination with lifestyle interventions; dark red) and advice alone (black). Weight loss was observed during the first six months of all interventions, and weight-loss reached plateaus after six months (Franz *et al.* 2007).

Table 1-4: Advantages and disadvantages lifestyle changes and weight loss medication (O'Brien 2010, Franz *et al.* 2007).

Non-surgical method	Advantages	Disadvantages	Weight Loss Range
Lifestyle changes (e.g. improved diet, regular exercise and psychological therapy)	• Safest way to lose weight • No adverse side-effects from weight loss medications • Better quality of life (Bond *et al.* 2009, Gaesser 2013)	• People often fail to stick to their diet plan and exercise regime • Most people end up losing weight and regaining it within 1-5 years after dieting • Most people end up turning to bariatric surgery as a result of failing to lose an adequate amount of weight (Franz *et al.* 2007).	Varies depending on whether people stick to their dietary plan (Franz *et al.* 2007).
Weight loss medication	• Simplest and quickest way to lose weight • No strict diet or rigorous exercise required • Easily accessible on the market. • There are various types of medications that tailor to patients' differing needs. • Orlistat in particular, has been shown to yield huge weight loss within a 12 month period, as well as reducing the risk of T2DM and exhibiting reductions in overall cholesterol (Franz *et al.* 2007, Papamargaritis *et al.* 2012, Kang *et al.* 2012).	• Can be expensive • Patients are often unaware of drug contents and risks, particularly those purchased online • Can cause a number of adverse side-effects, such as wooziness, nausea, and upset stomach. • Gastrointestinal side effects (e.g. diarrhoea, faecal incontinence, oily spotting, flatulence, bloating, and dyspepsia (Ioannides-Demos *et al.* 2006, Padwal *et al.* 2003).	2.9kg weight loss within the first 12 weeks (based on orlistat, and may differ among alternative drugs; (Franz *et al.* 2007).

1.1.5.2 Surgical treatment options (bariatric surgery)

The Greek roots of the word bariatric consist of *(bar)* mean weight, *(iatr)* meaning treatment and *(ic)* meaning pertaining to. Bariatric is defined as the division of medicine that deals with the causes, prevention, and treatment of obesity (The American Heritage® Stedman's Medical Dictionary 2014). Bariatric surgery therefore is a surgical procedure that is carried out to support individuals in losing weight, thus lowering the risk of death and severe obesity if combined with an improved lifestyle and better eating habits.

There are a number of surgical treatment options available, which include: endoscopic methods, for example, intra-gastric balloon, gastric banding, laparoscopic or open biliopancreatic diversion (BPD), Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (O'Brien 2010).

1.1.5.2.1 Indication of bariatric surgery

According to the National Institute for Health and Care Excellence (NICE) guidelines, patients are considered eligible for bariatric surgery if their BMI is 40 or more, or if they have a related condition such as diabetes and have a BMI of 35 or more. It is also recommended that all non-surgical actions are attempted prior to resorting to surgery (NICE 2014). Figure 1-4 describes the pathway of patients who are referred for bariatric surgical service according to the British healthcare system.

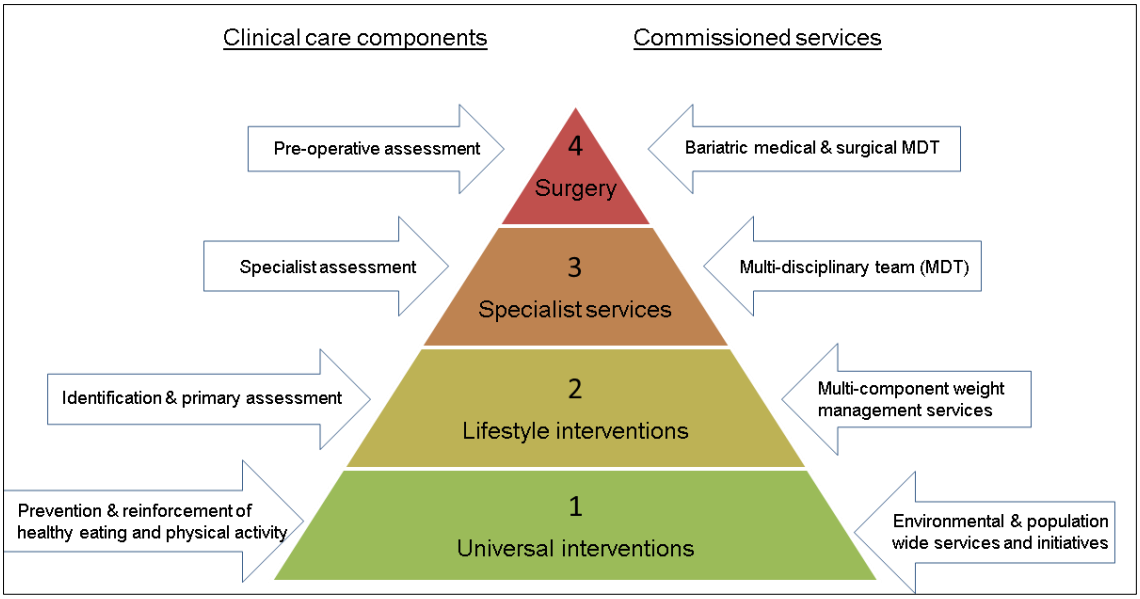


Figure 1-4: The process of weight assessment and management according to obesity surgery services of the NHS (Welbourn *et al.* 2014).
NICE guidance and BOMSS[4] standards describes the pathway of patients within the multi-disciplinary bariatric surgical service and states that patients who are referred for bariatric surgery will come from primary or secondary care specialist obesity services (Welbourn *et al.* 2014).

1.1.5.2.2 Evolution of bariatric surgery

In the early 1950s, the only bariatric surgery available was the jejunoileal bypass (JIB). Later, in the 1970s, gastric stapling surgeries such as Roux-en-Y gastric bypass (RYGB)[5] (Figure 1-6) and biliopancreatic diversion (BPD)[6] (Figure 1-7) started to emerge (Olbers *et al.* 2006).

Despite the initial success of JIB, several adverse events were directly related to the surgical procedure such as liver failure, hair loss, arthritis and vitamin depletion (Singh *et al.* 2009). By the 1980s, JIB was phased out following a

[4] BOMSS - British Obesity and Metabolic Surgery Society.
[5] RYGB is a variant of attaching the gastric mini-reservoir with the small bowel using a Roux-en-Y loop. Cesar Roux (1857-1934), a Swiss surgeon, was the first who suggested and promoted this variation of the anastomosis, to bypass the digestive segment (Popenţiu *et al.* 2011).
[6] BPD was originally described by *Scopinaro in 1979* as an alternative to jejunoileal bypass for severely obese patients (Scopinaro *et al.* 1979).

reported 91 deaths, as well as the surviving patients experiencing deleterious consequences from having the procedure (Singh *et al.* 2009, Griffen *et al.* 1983).

Recently, all types of bariatric surgery procedures have been able to achieve significant weight loss in the morbidly obese, but such procedures still do not appeal to some patients who suffer from obesity due to factors such as the risk of death and long term complications (O'Brien 2010).

The adoption of laparoscopic methods to perform advanced abdominal surgery, such as a gastric banding procedure, which has been widely used and developed over the past 15 years, has significantly improved safety, thereby encouraging patients to undergo these surgeries (O'Brien 2010). In Australia, for example, in 1993, only 400 bariatric surgeries were performed, while in 2008, that figure increased to over 14,000. According to Buchwald *et al*. (2009), there were an estimated 344,000 surgeries carried out globally in the same year (2008). Buchwald *et al*. also pointed out that the most common type of surgery was the Roux-en-Y gastric bypass, both open and laparoscopic, which represented 47% of the total number of bariatric operations.

The second most common surgery was gastric banding, which stood at 42% of the total number, followed by sleeve gastrectomy, which stood at 5%, and then BPD, at 2%. Moreover, in Europe, RYGB is on the rise, even though gastric banding is still the most common type of surgery (Buchwald *et al.* 2009). Indeed, according to the United Kingdom National Bariatric Surgery Registry (NBSR), RYGB was the most common form of bariatric surgery performed in the UK between 2011 and 2013 (Table 1-5; (Welbourn *et al.* 2014).

In the USA, gastric banding is now overtaking RYGB, while gastric banding in Australia is the preferred method of surgery, accounting for over 95% of bariatric surgeries carried out in the country (O'Brien 2010, Buchwald *et al.* 2009).

An important aspect that influences the choice of surgical methods and success rates in different countries is healthcare funding; for instance, the most common surgical procedure today is gastric banding, since it is the safest method of bariatric surgery. However, one of the most vital components of gastric banding is adjusting the band over time to satisfy one's appetite, thus it is important to have a follow-up program. In Australia the national healthcare scheme (Medicare) covers this follow up process and banding has come to be the most favoured approach in the country. On the other hand, Europe has limited funding to cover follow ups, thus complications arise in banding. Still further, Latin America, has no funding at all for aftercare, and thus there is little opportunity to receive banding (O'Brien 2010).

Table 1-5: Type of bariatric surgery performed between 2011 and 2013 according to the UK-NBSR (Welbourn *et al.* 2014).

Operation type	Number of surgeries
Roux-en-Y gastric bypass	9526
Gastric band	4075
Sleeve gastrectomy	3797
Gastric balloon	386
Duodenal switch	19
Duodenal switch and sleeve	12
Billio-pancreatic diversion	5

1.1.6 Types of bariatric surgery

Bariatric surgery is divided into two types, restrictive and malabsorptive. Restrictive surgery works by decreasing the quantity of food intake, an example of which is vertical band gastroplasty (VBG). This involves dividing the stomach into a small proximal pouch (<20 ml) and a more distal one (Dixon *et al.* 2012). While, malabsorptive surgery works by limiting the nutrient absorption by bypassing the duodenum and small intestine; the examples for this procedure are: biliopancreatic diversion with or without duodenal switch, and Roux-en-Y

gastric bypass; this procedure also has a restrictive component (Dixon *et al.* 2012).

1.1.6.1 Gastric band

In a laparoscopic adjustable gastric banding (LAGB), what is inserted around the stomach is an adjustable plastic or silicone ring, just underneath the gastro-oesophageal junction, thus forming a small pouch (Figure 1-5 (Dixon *et al.* 2012).

Gastric banding has been shown to be one of the most efficacious and cost effective types of bariatric surgery (O'Brien, 2010). The continued effect is achieved via the adjustability of the band; it is also reversible, allowing access to potential alternative therapeutic options in the future. Following this type of surgery long-term skilled aftercare is required, as well as surgical maintenance, with roughly 10% requiring revisional surgery, which is a surgery performed on patients who experienced complications from a previous bariatric surgery or did not attain significant weight loss from the initial surgery within the ten years succeeding surgery. Such post-surgical care significantly increases the cost of gastric banding.

Given the reduced level of risk associated with gastric banding compared to other surgical methods (e.g. risk of T2DM, heart attacks and strokes etc.; (O'Brien 2010, Dixon *et al.* 2012, Dixon *et al.* 2012). Research by Maggard *et al.* (2005) suggests that only 1 in 2000 or 1 in 3000 deaths rates occur in gastric banding, which is 10-15 times less than RYGB, for instance. In addition, O'Brien (2010) affirms that only roughly 10% of patients require a revisional procedure. Therefore, due to its gentle and effective nature, as well as the procedure not involving removing any part of the stomach like other surgical methods, gastric banding is the ideal procedure for those who wish to undergo a less risky procedure.

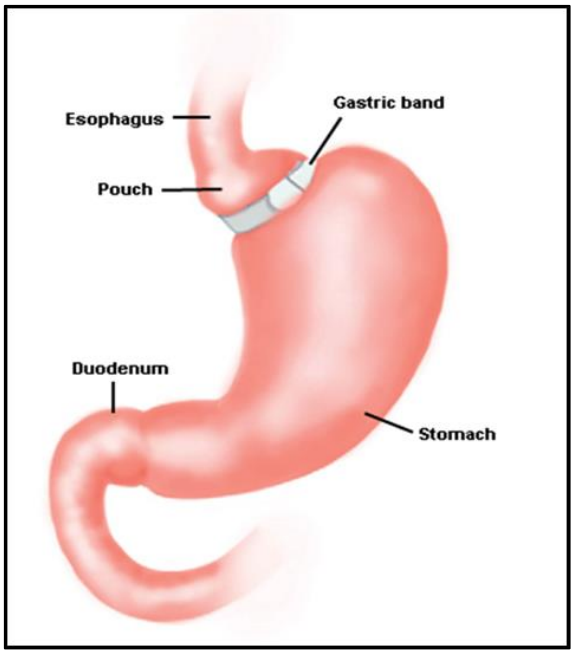


Figure 1-5: Gastric band (Dixon *et al.* 2012).
The gastric band is placed at the top of the stomach with no significant gastric pouch above. It is proposed that compression of vagal afferents within this area of gastric cardia mediate the satiety effect (O'Brien 2010).

1.1.6.2 Roux-en-Y gastric bypass

Since the early 1980s, one of the most effective bariatric surgery procedures known across the world has been the Roux-en-Y gastric bypass (RYGB; Dixon *et al*., 2012). During this procedure, the stomach is separated from the upper pouch (with a volume of roughly 15–30 mL), and the lower gastric remnant. Thereafter, by way of a gastro-jejunal anastomosis, the pouch is anastomosed to the jejunum in a RYGB manner (Papamargaritis *et al.* 2012). In other words, the procedure involves reducing the size of the stomach to a small pouch, thus encouraging the reduction of food intake during meals. The pouch is directly attached to the small intestine, which therefore lowers the amount of calories and fat that the patient can absorb from suitable foods they can eat for added weight loss (Tham *et al.* 2014); Figure 1-6).

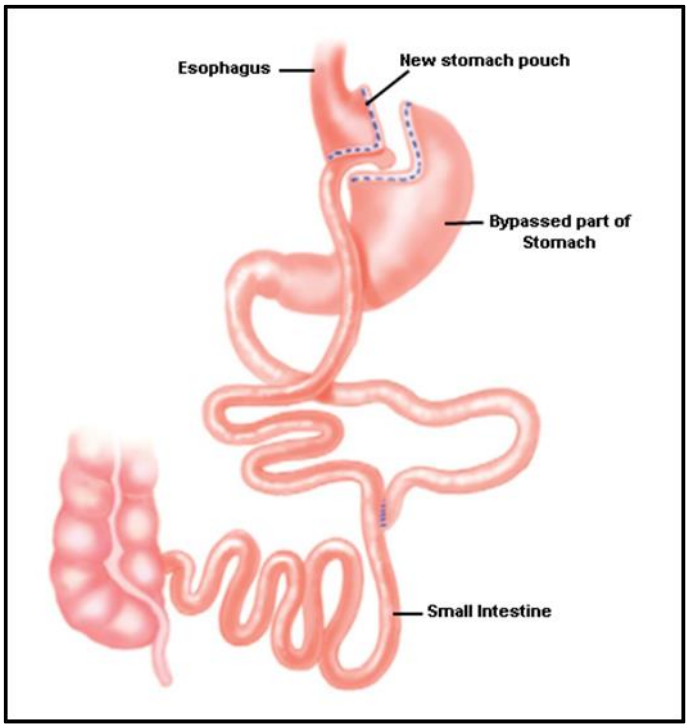


Figure 1-6: Roux-en-Y gastric bypass (RYGB; (Dixon *et al.* 2012).
The RYGB involved complete separation of a small section of upper stomach from the body of stomach, creation of a Roux-en-Y length of proximal jejunum which is anastomosed to the proximal gastric pouch. Intake is restricted by the small pouch, gastric emptying is restricted by the narrow gastrojejunostomy and food is diverted from the duodenum (O'Brien 2010).

RYGB is seen as the most effective way of achieving significant excess weight loss (EWL) within a short time period (Hall *et al.* 1990). The percentage of excess weight loss (%EWL) is a common metric for reporting weight loss after bariatric surgery. The %EWL can vary depending on the definitions of ideal body weight (IBW) used and the preoperative weight (Montero *et al.* 2011). EWL is the amount of existing extra weight that is lost in the body after an intervention (Equation 1-2).

However, such approaches like RYGB come with some limitations, for example, the pouch size cannot be adjusted nor is it reversible. Another downside is that over time, its effectiveness has been shown to wear off. A year after RYGB, EWL is around 60-70%, and subsequently this drops to 50% for those who attend the follow up after five years. According to Welbourn *et al*. (2014) of the UK National Bariatric Surgery Registry, between 55%-70% EWL can be

achieved through RYGB, whilst sleeve gastrectomy achieves only 55-60% EWL. Both of these are more effective than gastric banding which produces only 45-55% EWL. Therefore, these figures affirm why RYGB is the most effective procedure worldwide (Welbourn *et al.* 2014).

Equation 1-2: Percentage excess weight loss (% EWL; (Welbourn *et al.* 2014)

$$\%EWL = \frac{initial\ mass(kg) - current\ mass\ (kg)}{initial\ mass\ (kg) - [25\ (kg\ m^{-2}) \times height^2\ (m^2)]} \times 100$$

RYGB has been suggested to be effective in overcoming obesity related diseases such as T2DM, potentially through a post-prandial rise in the incretins such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). The mechanism of how bariatric surgery reverses diabetes will be discussed in further detail in section 1.1.7.

Since the likes of biliopancreatic diversion have shown similar outcomes to RYGB, such as reversing diabetes and achieving substantial weight loss (Flum *et al.* 2004), patients decide to undergo these types of surgeries to help overcome their obesity, despite the inherent risk of such surgeries (Flum *et al.* 2004).

1.1.6.3 Biliopancreatic diversion

Only a partial gastrectomy is required in biliopancreatic diversion (BPD), which leaves a gastric pouch with a volume of 400 ml. Then, to the nearest ileocaecal valve, the small bowel is joined to it (250 cm). After that, both the alimentary limb and the gastric pouch are joined together, thus creating a Roux–en–Y gastroenterostomy (Papamargaritis *et al.* 2012); Figure 1-7)

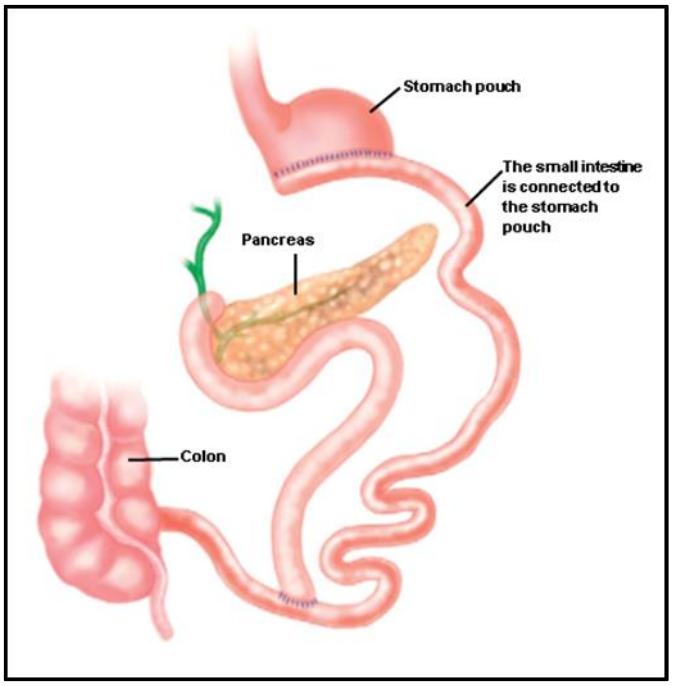


Figure 1-7: Biliopancreatic diversion (BPD; (Dixon *et al.* 2012).
The BPD is procedure comprises partial gastrectomy (about 50-60%) and gastroentero-anastomosis. The ileum is then divided 250 cm proximal to the ileocaecal valve and the distal end is anastomosed to the resected stomach. The proximal end of small bowel, which carries the biliary tract, is then sutured to the distal ileum at about 50 cm from the ileocaecal valve (Mingrone *et al.* 2009).

BPD has been proposed as the most metabolically severe choice of surgery, and has such has proven unpopular among surgeons and patients, despite the positive published outcomes. According to Anderson and co-workers (2013), the metabolic consequence of BPD is that patients can eat their everyday meals, but remain malnourished (Anderson *et al.* 2013); (Faintuch *et al.* 2004), besides developing common deficiencies, such as a deficiency of fat soluble vitamins, including vitamin B1, vitamin B12, and folate, iron-deficiency anaemia, hypocalcaemia, and protein calorie malnutrition (Aills *et al.* 2008).

It has been almost four decades since BPD was first made available (Scopinaro *et al.* 1979) and plays only a small role in modern bariatric surgery. Figures by Buchwald and Oien (2009) suggest that BPD makes up less than 2% of bariatric surgeries, despite significant weight loss results being achieved with

this procedure (75-80% EWL), thus it should be a second-line bariatric surgical choice (Buchwald *et al.* 2009).

1.1.6.4 Sleeve gastrectomy

A sleeve gastrectomy (SG) consists of transecting the stomach in a vertical direction, forming a gastric tube, and what is left is a pouch with a 150-200 mL volume. Thereafter, the left over stomach is removed (Figure 1-8; (Papamargaritis *et al.* 2012). The sleeve is the initial element of the duodenal switch procedure, which is a common alternative to BPD. Given that it is a simple and effective surgical procedure that requires no follow up, it has become one of the most popular single procedures in the world (O'Brien 2010).

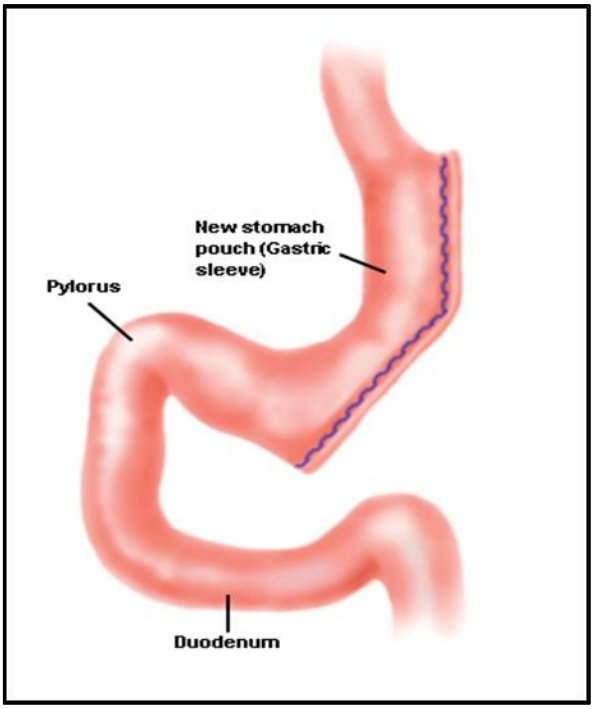


Figure 1-8: Sleeve gastrectomy (Dixon *et al.* 2012).
The stomach is transected vertically, creating a gastric tube and leaving a 150–200 mL pouch. The greater curve of the stomach is transected approximately 4–6 cm proximal to the pylorus and the remaining stomach is excised (Papamargaritis *et al.* 2012).

A 2009 systematic review of 36 studies exhibited an average weight loss of 55% within three years (Brethauer *et al.* 2009), however one study has reported a 40% weight regain within the five years post-operation (Weiner *et al.* 2007).

Furthermore, a study by the NBSR reaffirms these figures by pointing out that up to 55-60% EWL can be achieved by having sleeve gastrectomy surgery (Welbourn *et al.* 2010).

Moreover, it is often expected that the sleeve will not sustain weight loss due to the expansive nature of the stomach, and this would call for the completion of the duodenal switch (DS). DS yields malabsorptive and restrictive effects (O'Brien 2010). The malabsorptive effect is achieved by redirecting a large portion of the small intestine, making one common channel and two separate pathways, while the restrictive effect is achieved by taking out roughly 70% of the stomach along the greater curvature. However it should be noted that leakage can occur in less than 1% of cases and often lasts for a number of months, thereby producing further cost, morbidity and anxiety (O'Brien 2010).

1.1.6.5 Efficacy of types of bariatric surgery

Despite the positive effects of bariatric surgery, it is by no means the quickest solution for obesity. Bariatric surgery is a process that begins by carrying out a preliminary clinical evaluation and patient review, and after surgery, patient follow-up, which lasts roughly 3-4 weeks depending on the type of bariatric surgery (Shen *et al.* 2004). Table 1-6 summarises the advantages and disadvantages that have been reported between the most common types of bariatric surgery.

Furthermore, perioperative complications and, in worst case scenarios, death, are a possibility in all procedures. Thus, revisional surgery is common as preserving the right anatomy is essential for effectiveness. In spite of the previous issues, bariatric surgery can help to resolve the issue of obesity, since it can attain significant weight loss, better quality of life and health, as well as prolonged life expectancies (O'Brien 2010).

Table 1-6: Advantages and disadvantages several common types of bariatric surgery (Welbourn *et al.* 2014, O'Brien 2010, Buchwald *et al.* 2004)

Type of bariatric procedure	Advantages	Disadvantages	Excess weight loss (Welbourn *et al.* 2014).	Percentage of total number of bariatric procedures performed in UK (Welbourn *et al.* 2014).
Gastric band	First step for other procedures Safer, since the surgical procedure is low-risk. Fewer side effects than other operations. Fully reversible, since the stomach's anatomy is unaltered. Faster recovery times; it is a 30-45 minute procedure with very little scaring and patients are fully recovered within roughly one week (O'Brien 2010).	Patients can experience band slippage, where the band slides up and down the stomach from its starting position. Stomach enlargement Band migration; this happens when the gastric band progressively wears through the stomach wall. The band can cause discomfort, thereby forcing patients to have the band removed. Nutritional deficiencies; iron, calcium, and vitamin B12 being among the most common. Acid reflux symptoms as a result of the gastric band being placed too tight (O'Brien 2010).	Approximately **45-55%**	**23.2%**
Roux-en-Y gastric bypass	Effective for patients with a higher BMI as more excess weight loss can be attained via this procedure. Helps to reduce the risk of T2DM and can induce hormonal changes, thus the need for diabetic medication is reduced, or in some cases, no medication is required at all. Helps to overcome obesity related issues, such as high cholesterol and	Even though it is possible to reverse this procedure in a technical sense, such cases are rare, thus leaving very little options. Complications are more serious compared to other procedures; the worst case being death. Patients can suffer from nutritional deficiency because of the reduced absorption of nutrients and vitamins (O'Brien 2010).	Approximately **55-70%**	**53.8%**

Type of bariatric procedure	Advantages	Disadvantages	Excess weight loss (Welbourn *et al.* 2014).	Percentage of total number of bariatric procedures performed in UK (Welbourn *et al.* 2014).
	blood pressure, among others. No need for continuous adjustments, which are needed in other procedures such as gastric banding (O'Brien 2010)			
Biliopancreatic diversion	The amount of food eaten is not restricted. Patients are able to maintain weight loss. Roughly 95% of patients will completely reverse their diabetes within around two years (Buchwald *et al.* 2004).	Surgical complications are more likely compared to other procedures. Nutritional deficiencies such as deficiencies in iron, calcium, vitamin A and D and protein. 60% chance of developing gallstones due to rapid weight loss. Dumping syndrome which occurs in the course of eating high amounts of fat, sugar or alcohol, or large amounts of food, which causes nausea, vomiting, diarrhoea, sweating, faintness, weakness and increased heart rate (Buchwald *et al.* 2004).	Approximately **75-80%**	**N/A** [7]
Sleeve gastrectomy	It reduces the volume of the stomach, thus making the patient feel full faster; the part of the stomach that produces ghrelin, which is responsible for the sensation of hunger, is completely removed, thus eliminating prolonged	More risk of insufficient weight loss Patients may regain weight compared to band or bypass surgeries. The procedure is irreversible, since particular parts of the stomach are	Approximately **55-60%**	**21.5%**

[7] No data was reported for the prevalence of this operation as a proportion of the total number of surgeries performed; however, this operation falls under the category of other, which accounts for approximately 1.5% of total bariatric surgeries performed between the years 2011 (Welbourn *et al.* 2014).

Type of bariatric procedure	Advantages	Disadvantages	Excess weight loss (Welbourn *et al.* 2014).	Percentage of total number of bariatric procedures performed in UK (Welbourn *et al.* 2014).
	hunger. The stomach will function as normal, thus patients' can still eat their everyday foods, but in reduced portions. Patients will not suffer from dumping syndrome, since the pyloric part of the stomach remains intact. Reduced operative times in the hospital. No foreign bodies are placed in the stomach as in band surgeries (O'Brien 2010).	removed (Buchwald *et al.* 2004).		

1.1.7 Mechanisms of weight loss and metabolic improvement following bariatric surgery

The proposed mechanisms for weight loss following bariatric surgery can be divided into three main categories: 1) malabsorption, in which weight loss is due to a decreased absorption of nutrients and particularly fat in the intestines, 2) restriction, in which weight loss is due to decreased nutrient absorption in the stomach as well as decreased food intake due to reduced stomach size and 3) hormonal, in which a change in hormones released from the gut and fat tissue resulting in change in absorption of fat, satiety, food intake and food preference is the cause of weight loss.

Gastric bypass procedures, for example, BPD were originally thought to increase calorie malabsorption since the signs of decreased fat absorption such as increased faecal fat, diarrhoea and an increase in the occurrence of hypoalbuminaemia (a lower than normal level of albumin in the blood) were observed following BPD (Cornicelli *et al.* 2010).

RYGB was primarily intended to combine two mechanisms: malabsorption and restriction (Papamargaritis *et al.* 2012). This procedure has been suggested to cause malabsorption due to pancreatic and biliary secretions that mix with the food in short segments of the small intestine (Proczko-Markuszewska *et al.* 2011). Some researchers have described normal levels of albumin and faecal fat, while other researchers have observed only small increases in faecal fat levels following RYGB procedure (Papamargaritis *et al.* 2013). Hence, the malabsorption after RYGB has been proposed to depend on the length of the intestine and food choices (Papamargaritis *et al.* 2012).

Some bariatric procedures are intended to reduce stomach size such as RYGB, SG and LAGB (Papamargaritis *et al.* 2012). Early gastric distension occurrence due to the smaller size of the stomach leads to a decrease in the size of the meals taken and to early satiety (Papamargaritis *et al.* 2012, Tadross *et al.* 2009, Le Roux *et al.* 2006, Stylopoulos *et al.* 2009).

Moreover, most of the bariatric researchers in LAGB propose that gastric restriction is not the main physiological mechanism for weight loss (Papamargaritis *et al.* 2012). Another theory that can help to explain body weight loss, blood glucose balance and body energy is the gut hormones and their effect. The main gut hormones involved in these processes are: glucagon like peptide-1 (GLP-1), peptide YY (PYY) and ghrelin (Papamargaritis *et al.* 2012, Pournaras *et al.* 2010).

1.1.7.1 Glucagon like Peptide-1

Glucagon like Peptide-1 (GLP-1) is produced by L-cells which are mainly found in the ileum, and secreted by the gastrointestinal tract within minutes of food intake, causing glucose dependent secretion of insulin (Papamargaritis *et al.* 2012, Basso *et al.* 2011). Bariatric surgery has been shown to enhance postprandial GLP-1 secretion which is associated with an increase in insulin release from pancreatic beta cells while suppressing glucagon release from pancreatic alpha cells (Karra *et al.* 2010). GLP-1 also promotes satiety both through a direct inhibitory effect on gastric emptying and a stimulatory effect on the satiety centre in the hypothalamus. It is thought that the increased speed by which undigested nutrients are delivered to the small intestine after bariatric surgery increases the release of GLP-1 in response to a meal. This increase is thought to be a partial mechanism that contributes to weight loss (Karra *et al.* 2010).

1.1.7.2 Peptide YY

Peptide YY (PYY) is a 36-amino acid peptide produced by the L-cells of the distal small intestine and colon which is released into the circulation after food ingestion together with GLP-1 (Karra *et al.* 2010). PYY also inhibits gastric and pancreatic secretion. PYY has similar functions to GLP-1, as it slows gastric emptying, stimulates satiety centrally, and regulates appetite and body weight (Karra *et al.* 2010, Fenske *et al.* 2012). Similarly to GLP-1, the delivery of undigested nutrients to the intestine after bariatric surgery occurs more rapidly,

increasing secretion of PYY which may contribute to weight loss (Karra *et al.* 2010).

1.1.7.3 Ghrelin

Ghrelin is a 28 amino acid peptide produced by the X/A-like cells of the fundus and the body of the stomach (Papamargaritis *et al.* 2012, Karra *et al.* 2010, Fenske *et al.* 2012). Ghrelin has an important role in the stimulation of insulin regulatory hormones such as glucagon and C-peptide (Porcellati *et al.* 2003), inhibiting the insulin-sensitising hormone adiponectin and suppressing insulin secretion (Papamargaritis *et al.* 2012, Karra *et al.* 2010). Increasing the level of ghrelin causes an increase in hunger and its suppression occurs just minutes after food intake. However, the level of ghrelin increases with diet-induced weight loss, which may be an obstacle behind long-term weight loss. Bariatric surgeries decrease ghrelin levels which could be advantageous in controlling weight loss (Karra *et al.* 2010).

1.1.7.4 Adipose tissue

Leptin and ghrelin are two hormones that have been recognized to have a major influence on energy balance. Leptin is a mediator of long-term regulation of energy balance, suppressing food intake and thereby inducing weight loss.

Ghrelin on the other hand is a fast-acting hormone, seemingly playing a role in increasing hunger (Klok *et al.* 2007), which is known to be higher in obese patients, but it decreases after bariatric surgery, independent of weight loss (Drucker *et al.* 2006). Leptin, on the contrary to ghrelin, is a cell-signalling hormone that helps to regulate body weight, food intake and appetite, as well as modulating the size of the body's adipose tissues (Wortley *et al.* 2004).

Adiponectin is a protein that is involved in the regulation of glucose levels and fatty acid breakdown. Obese patients present lower levels of this hormone which plays a role in insulin resistance. It increases after bariatric surgery, independent of weight loss (Drucker *et al.* 2006, Gan *et al.* 2007).

1.1.7.5 Change in food preference

Some human studies published support the idea that patients' experience changes in eating behaviour from high to low fat foods after bariatric surgery (Papamargaritis *et al.* 2012, Olbers *et al.* 2006, Dixon *et al.* 2012, Favretti *et al.* 2002). Moreover, a rodent study also showed the same effect after a bariatric procedure (Suzuki *et al.* 2011). The authors suggest that the eating behaviour is affected by two factors; internal signals, for example, hormonal or neural, and external signals, such as food amount and social conditions (Rolls 2012).

Furthermore, Le Roux reported in 2012 that one of the mechanisms for weight loss after bariatric surgery might be an effect on food preference. These could be the effect of post-ingestion and taste perceptions (Papamargaritis *et al.* 2012). However, one of the possible causes of weight reduction and changes in food preferences might be dumping syndrome due to quick gastric emptying and the increased secretion of gut hormones. Dumping syndrome is a series of symptoms, consisting of abdominal discomfort, weakness, and diarrhoea or quick bowel evacuation, which occurs straight after meals in those patients who have had gastric surgery (Papamargaritis *et al.* 2013). There are two phases of dumping syndrome that progress after a bariatric surgery: early dumping initiates 15-30 minutes after eating, with symptoms like nausea, vomiting, diarrhoea and fatigue (Tack *et al.* 2009). Late dumping occurs one to three hours after, with symptoms such as sweating, dizziness and weakness (Tack *et al.* 2009).

According to Papamargaritis and co-workers (2012), patients who undergo RYGB present a decreased preference for sweet food (Papamargaritis *et al.* 2012). Olbers and co-workers (2006) report that taste preference is changed after RYGB in both animals and humans (Olbers *et al.* 2006). One year after RYGB, patients reported consuming fewer sweet foods and making more healthy choices like fruits and vegetables (Tam *et al.* 2011).

1.1.7.6 Change in appetite

Some patients have reported changes in appetite, increased satiety and decreased hunger a few days after bariatric surgery (Le Roux *et al.* 2006, Dixon *et al.* 2005). In 2006, Le Roux and his group proposed that the probable mechanisms for changes in hunger and satiety, such as decreased food intake and the ability to maintain weight loss for longer after bariatric procedures, are due to the changes in the postprandial levels of GLP-1 and PYY that induce satiety, before any major weight loss (Basso *et al.* 2011).

1.1.8 Effects of bariatric surgery on diabetes

There have been direct and strong links shown between obesity and T2DM through both preclinical and clinical studies (Torquati *et al.* 2005). The majority of patients who are diagnosed with T2DM are overweight, with 50% obese and 9% morbidly obese (Dixon *et al.* 2005). Consequently, weight loss is possibly the most powerful treatment for T2DM: both surgical (Proczko-Markuszewska *et al.* 2011, Pournaras *et al.* 2010), or non-surgical weight loss (Chakaroun *et al.* 2012), have resulted in a significant percentage of patients with T2DM achieving glycaemic control and entering remission (Gan *et al.* 2007, Lee *et al.* 2012).

Bariatric surgery has been shown to cause remission in T2DM (Buchwald *et al.* 2004). Indeed, the first report of the improvement of diabetes after gastrectomy was more than 50 years ago (Table 1-7) (Vidal *et al.* 2008, Rizzello *et al.* 2010).

In 1995, there were changes described in glycaemic control after gastric bypass surgery in morbidly obese patients with diabetes (Pories *et al.* 1995). The effects of bariatric surgery on T2DM have been described in two systematic reviews (Buchwald *et al.* 2004, Maggard *et al.* 2005). Buchwald and Maggard reported a range of 64–100% improvement in T2DM and there was a direct relationship between weight loss and remission (Buchwald *et al.* 2004, Maggard *et al.* 2005). Weight loss and diabetes resolution were shown in patients undergoing biliopancreatic diversion/duodenal switch, gastric bypass, and

banding procedures (Buchwald *et al.* 2004). Insulin levels dropped significantly postoperatively; as did haemoglobin A1c (HbA1c) and fasting glucose values (Buchwald *et al.* 2009).

However, the most striking observation was that the improvement in glycaemic control occurred within days of surgery, before any significant weight loss had been achieved, and this therefore suggested that the mechanism is independent of weight loss (Buchwald *et al.* 2009, Pories *et al.* 1995).

The effect of bariatric surgery on T2DM is believed to be, at least in part, through a decrease in hepatic and peripheral insulin resistance (Pournaras *et al.* 2010, Gan *et al.* 2007). Several studies have demonstrated a drop in insulin resistance as quickly as six days after bariatric surgery (Wickremesekera *et al.* 2005). Remarkably, this acute change in insulin resistance has been reported to occur many weeks before weight loss is observed (Wickremesekera *et al.* 2005, Pournaras *et al.* 2010). Although the exact mechanism explaining how bariatric surgery can alter insulin resistance so quickly has not been elucidated, several hypotheses have been proposed. These include alteration in gastrointestinal peptides (i.e. GLP-1), in inflammatory response or in change in appetite and food preference (Pournaras *et al.* 2010).

Although a good diet and an adequate amount of exercise are vital towards treating T2DM, bariatric surgery has recently been suggested as an alternative therapeutic approach for T2DM (Dixon *et al.* 2012, Stylopoulos *et al.* 2009, Schauer *et al.* 2003). As a result, bariatric surgery has now been labelled as a "*metabolic surgical procedure*" or "*metabolic surgery*" (Rubino *et al.* 2010b). Table 1-7 describes a number of studies that have observed an improvement in blood glucose levels as well as insulin resistance within a short period following bariatric surgery. There are currently several competing hypotheses that offer explanations of how glycaemic improvement might occur before weight loss, following bariatric surgery: the hindgut hypothesis, the foregut hypothesis, the inflammation hypothesis and the gluconeogenesis hypothesis, all of which are discussed below.

1.1.8.1 Hindgut hypothesis (changes in insulin secretions)

The main site for the absorption of nutrients following digestion and for maintenance of the balance of fluids in the gastrointestinal system is the small intestine, which consists of three parts: the duodenum, the first segment after the stomach (25 cm length), the jejunum, the middle segment after the duodenum (100 -110 cm length) and the ileum, the lower segment of the small intestine after the jejunum (150 -160 cm length; (Papamargaritis *et al.* 2012). The food is redirected after the surgery, and partly digested food is delivered to the distal gut. The shorter gastrointestinal tract results in an increase in insulin secretions and gut hormones such as GLP-1 and PYY (Pournaras *et al.* 2010). This leads to improved glycaemic control (the effect of food on an individual's blood glucose level) in the short-term (within days) and to weight loss in the long-term (within months) (Mingrone *et al.* 2009).

1.1.8.2 Foregut hypothesis (changes in hepatic insulin resistance)

Bypass surgeries affect the proximal part of the small intestine, which decreases the secretion of insulin and encourages insulin resistance through as yet unknown gastrointestinal factors (Pories *et al.* 2001). The remission in T2DM is due to the increase in secretion or effect of insulin and reduction of anti-incretins (Rubino *et al.* 2010b). After bypass surgery, the rapid delivery of nutrients to the lower intestine (the duodenum) increases stimulation of L-cells, which results in increased secretion of hormones such as GLP-1 that improve insulin release and action, thus resulting in a decrease in blood glucose (Rubino *et al.* 2010b). However, this may have a contradictory effect, as the duodenum tries to correct the anti-incretin reduction, which results in the reduction of insulin secretion and production, resulting in a higher risk of T2DM (Garrido-Sanchez *et al.* 2012). In rodents, the improvements in T2DM have been shown to be due to reduced hepatic glucose production (Papamargaritis *et al.* 2012).

Table 1-7: Summary of evidence for the effect of bariatric surgery on diabetes.

Reference	Surgery type	Improvement in insulin resistance	Time of improvement in insulin resistance
(Basso *et al.* 2011)	Sleeve gastrectomy	Restoration of the first phase of insulin secretion and improved insulin sensitivity in diabetic obese patients immediately after SG, prior to any food passage through the gastrointestinal tract and prior to any weight loss. Appears to be associated with GLP-1, ghrelin, and PYY hormonal alterations of likely gastric origin and is not down to meal nor weight related changes.	3 days, but not significant
(Rizzello *et al.* 2010)	Sleeve gastrectomy	Reduction in serum glucose and insulin concentration, as well as the homeostasis model assessment of insulin resistance (HOMA IR)[8] value.	5 days
(Wickremesekera *et al.* 2005)	Roux-en-Y gastric bypass	The modification in insulin resistance observed after RYGB, which helps to overcome T2DM occurs within 6 days of the procedure, prior to any substantial weight loss being observed.	6 days
(Isbell *et al.* 2010)	Roux-en-Y gastric bypass	Signs of insulin sensitivity improving are observed 6 days after the RYGB procedure without any significant weight loss. Within 1 week after the RYGB, prior to any observable weight loss, insulin sensitivity (HOMA-IR) had improved by 25%.	6 days

[8] HOMA IR is defined as the product of fasting plasma insulin and glucose divided by 22.5 and is a tool used to estimate insulin sensitivity from a single sample (Matthews *et al.* 1985).

Reference	Surgery type	Improvement in insulin resistance	Time of improvement in insulin resistance
		2-10 weeks after the RYGB, recurring stability in fasting levels of GLP-1 is detected.	
(Pournaras *et al.* 2010)	Gastric bypass and gastric banding	T2DM is improved by undergoing a gastric bypass procedure, and in the best case scenario, the patient is put in a state of remission, regardless of weight loss. It remains unexplained how within the first hours after the procedure, insulin resistance improves, although insulin production usually rises within the same week, which could be justified by the improved postprandial GLP-1 responses.	7 days
(Garrido-Sanchez *et al.* 2012)	Gastric bypass and biliopancreatic diversion	Unlike those procedures that include the duodenum (i.e., SG), surgical procedures that exclude the duodenum (i.e., BPD) show abrupt modifications in the extent of insulin resistance in those patients who are morbidly obese.	15 days
(Mingrone *et al.* 2012)	Gastric bypass and biliopancreatic diversion	Weight loss dose not significantly predict diabetes remission within 2 years or improvements in glycaemia after 1-3 months.	1 month
(Vidal *et al.* 2007)	Laparoscopic SG, laparoscopic Roux-en-Y gastric bypass	Laparoscopic SG and RYGB caused a similar rate of T2DM resolution 4 months after the procedure.	4 months
(Reis *et al.* 2010)	Gastric bypass	This procedure resulted in improved weight loss and better erectile function, as well as increased total testosterone (TT), follicle-stimulating hormones (FSH), free testosterone (FT) and prolactin (PRL) levels.	4 months
(Torquati *et al.*	Roux-en-Y gastric bypass	Most patients stopped taking all antidiabetic medications including insulin, six months after surgery. After the RYGB, there is a premature occurrence of improved glucose metabolism, and this is not totally associated with weight loss.	6 months

Reference	Surgery type	Improvement in insulin resistance	Time of improvement in insulin resistance
2005)			
(Vidal *et al.* 2008)	Sleeve gastrectomy	1 year after the procedure, both SG and RYGB are equally as effective in encouraging the remission of T2DM.	12 months

1.1.8.3 Anti-incretin hypothesis

As discussed in section 1.1.7, incretins are gastrointestinal peptides whose secretions are activated by the passage of food through the small intestine (Sjöholm 2009). GLP-1 lowers glucose by decreasing gastric emptying, restoring insulin sensitivity, and decreasing glucagon secretion, which may result in a reduction in the production of hepatic glucose (Basso *et al.* 2011). The initial stimulation of L-cells after bariatric surgery may cause increased production of GLP-1 and improved insulin secretion (Rizzello *et al.* 2010).

In addition to incretins, other hormones might affect the glucose balance after bariatric surgery, including ghrelin, PYY, leptin and adiponectin (Papamargaritis *et al.* 2012). This may be explained by an increase in anti-incretin, which could disturb the incretin/anti-incretin balance. Furthermore, diabetic patients who have had a gastric bypass may show inhibition of the excess release of anti-incretins, but this hypothesis has not been confirmed (Rubino *et al.* 2010b).

1.1.8.4 Inflammation hypothesis

Another hypothesis that has been presented is the so-called inflammation hypothesis. The first organ that interacts with infectious agents or food-borne toxins is the gastrointestinal tract (Rubino *et al.* 2010b). The micro-biota of the gut can affect energy metabolism, obesity and T2DM (Rubino *et al.* 2010a). Inflammation in the adipose tissue has been shown to be one of the major factors in the regulation of hepatic insulin sensitivity (Troy *et al.* 2008). In 2011, Tam and his group linked inflammation in the GI tract with a high fat diet (HFD) and obesity. This link is further supported by research confirming that germ-free mice have less body fat and are resistant to diet-induced obesity (DIO) and that DIO is related to changes in gut micro-biota and increased gut inflammation (Tam *et al.* 2011).

1.1.8.5 Gluconeogenesis hypothesis

Intestinal gluconeogenesis is the *de novo* production and release of glucose by the small intestine. The main enzymes of gluconeogenesis are glucose-6-

phosphatase (Glc6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) (Figure 1-9; (Troy *et al.* 2008). Moreover, the small intestine can be a significant supplier of glucose production when the liver is deficient. Intestinal gluconeogenesis encourages glucose infusion into the portal vein.

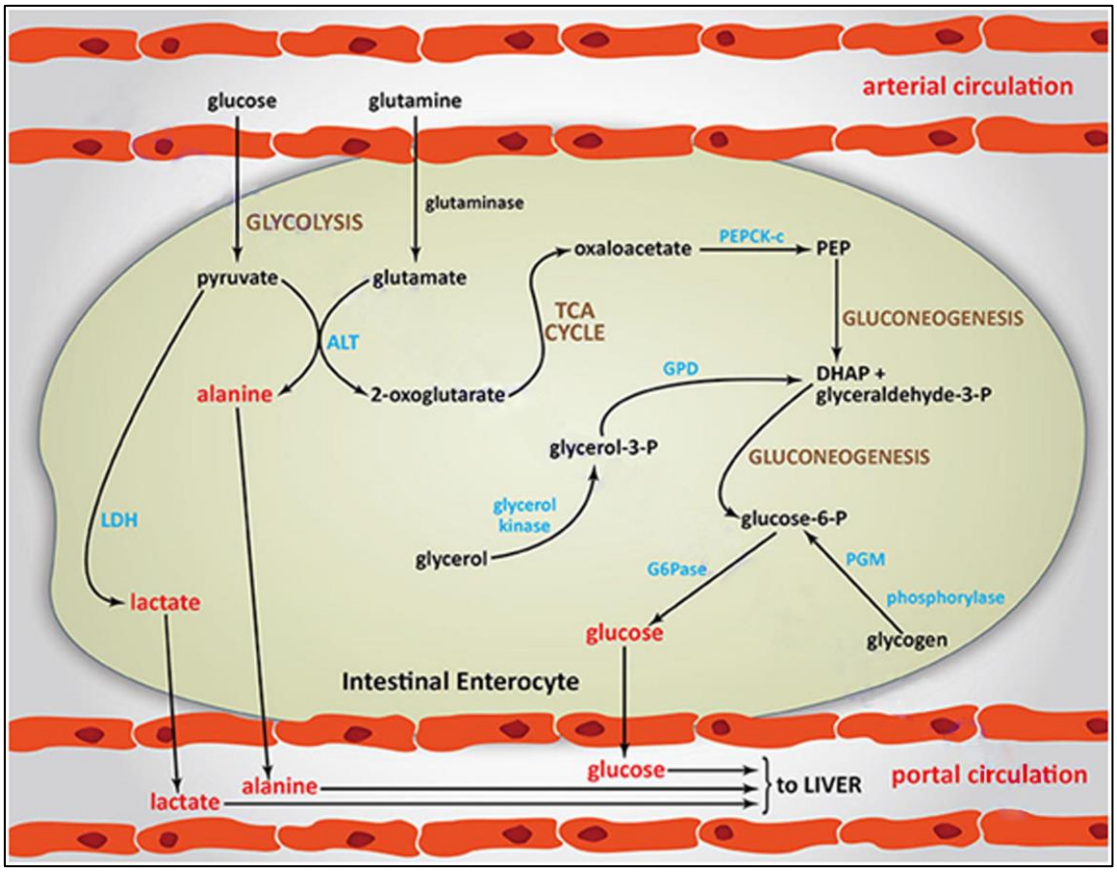


Figure 1-9: Intestinal Gluconeogenesis Pathway (The medical biochemistry page 2015).
Glucose and glutamine reach intestinal enterocytes from the arterial blood supply. The glutamine' carbon atoms are a major substrate for intestinal gluconeogenesis, being catalysed by glutaminase and alanine transaminase (ALT) resulting 2-oxoglutarete (α-ketoglutarate) that is transformed to oxaloacetate (OAA) and then to phosphoenolpyruvate (PEP). PEP is then diverted into the gluconeogenic pathway. Glucose can be oxidized to pyruvate through glycolysis and then the carbon atoms of pyruvate can be reduced to lactate or transaminated to alanine, both of which can function as major gluconeogenic substrate in the liver following delivery through portal circulation (The medical biochemistry page 2015).

Protein-rich diets are shown to reduce hunger and induce the expression of G6Pase, PEPCK-c, and glutaminase in the intestine after food intake in both humans and animal models (Mithieux 2012). The gut releases glucose into the portal blood supply following the intake of a protein-rich diet and the level of

glucose release from the gut is sufficient to account for the level of reduction in food intake. This glucose which results from intestinal gluconeogenesis, does not increase overall endogenous glucose production (EGP), this is due to the liver compensating by reducing its own level of gluconeogenesis while increasing glycogen storage. Animal studies demonstrate that portal sensing of intestinal gluconeogenesis is a key mechanism in the satiety effect induced by dietary protein (Mingrone *et al.* 2012, Mithieux 2012). When mice are fed a protein-rich, carbohydrate-free diet they do not show a decrease in their level of food intake and show a loss of satiety induction when portal vein afferent nerve (nerves send signals from body locations to the brain) connections are chemically or surgically destroyed (Mithieux 2012).

Hence, a gastric bypass could possibly increase intestinal gluconeogenesis (Troy *et al.* 2008) and may also cause an enhancement of hepatic insulin sensitivity, in theory due to decreased hepatic gluconeogenesis, without having an effect on peripheral insulin sensitivity (Mingrone *et al.* 2009).

1.2 Urogenital dysfunction

The term urogenital refers to both urinary and genital organs. The male urogenital system consists of several parts, which include the testes, epididymis, vas deferens, ejaculatory ducts, urethra, penis, prostate and accessory glands (Figure 1-10) (Virtual Medical Centre 2015).

The male sexual organ is the penis and its internal structure consists of the tunica albuginea, the corpora cavernosa, the urethra, two main arteries; and several veins and nerves (Courtenay 2002).

The corpora cavernosa are two chambers that fill most of the penis. The chambers are filled with a spongy erectile tissue that, during an erection, fills with blood, expands and becomes rigid.

A membrane called the tunica albuginea surrounds the corpora cavernosa which helps maintain the erection by keeping blood in the penis. The urethra is the tube which runs down the underside of the penis, under the corpora

cavernosa and connects the urinary bladder to the meatus, which is located at the glans (penis head) (Courtenay 2002). The prostate is a small gland located in the pelvis and surrounds the urethra and plays an important role in the production of semen and in ejaculation (Figure 1-10) (Virtual Medical Centre 2015, Courtenay 2002).

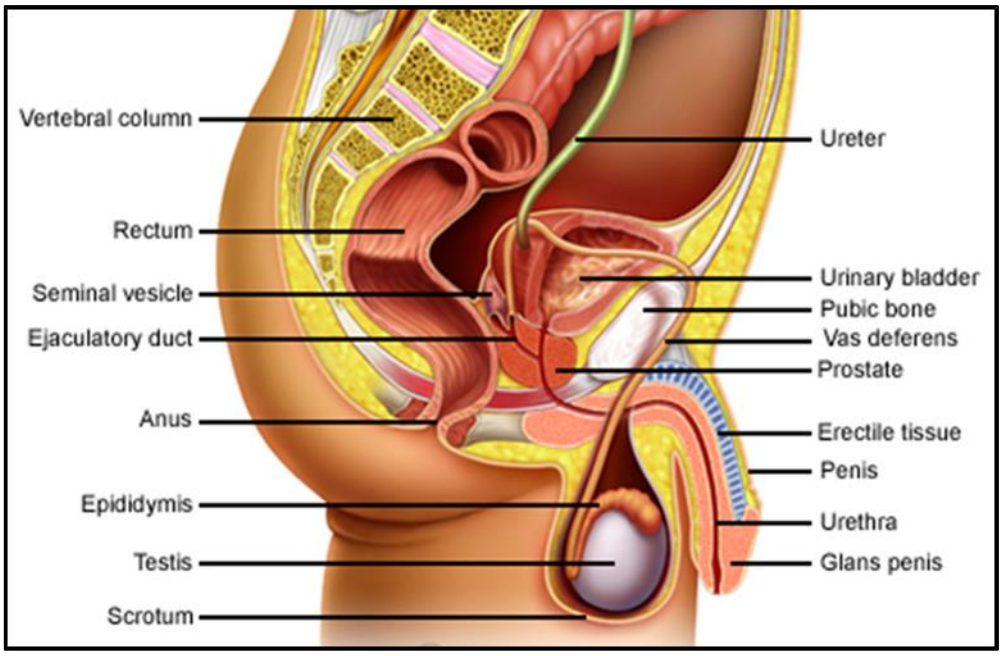


Figure 1-10: Male urogenital system anatomy (Virtual Medical Centre 2015)**.** The male urogenital system consists of several parts, which include the testes, epididymis, vas deferens, ejaculatory ducts, urethra, penis, prostate and accessory glands (Virtual Medical Centre 2015).

1.2.1 Definition of erectile dysfunction (ED)

Erectile dysfunction (ED) is defined according to the National Institute of Health Consensus Development Panel on Impotence as the consistent inability to obtain or maintain an erection for satisfactory sexual intercourse (National Institutes of Health 1993). ED affects the quality of life and life satisfaction, not only of the patient but also his partner, causing loss of self-confidence and depression (Bushmakin *et al.* 2014). Erection is a complex neurovascular event consisting of the relaxation of the trabecular smooth muscles, arterial dilatation and activation of the corporeal veno-occlusive mechanism (Wespes *et al.* 2002).

1.2.2 Epidemiology of erectile dysfunction

ED is a common medical disorder, which was coined by a National Institute of Health consensus panel in 1993, and mainly affects middle-aged men aged over 40 (Braun *et al.* 2000). Current studies show a 1-10% prevalence of ED in men under 40, and this prevalence increases with age; there is 2-9% prevalence in men in the 40-49 age group, and it increases to 20-40% in the 60-69 age group (Scopinaro *et al.* 1979, Bose *et al.* 2009, Dallal *et al.* 2008). In addition, there is a 50-100% prevalence in men aged over 70 (Braun *et al.* 2000). By 2025, the expected number of ED cases worldwide is expected to reach 322 million (Aytaç *et al.* 1999). A more recent study by Schwartz and Kloner (2011) claims that over 150 million men are currently suffering from ED, particularly middle-aged men over the age of 40 (Schwartz *et al.* 2011). In addition, Kalejaiye and Persad (2014) expect that the prevalence of ED will continue to rise as the population ages (Kalejaiye *et al.* 2014), and thus will more than likely meet Aytac's projected figures by 2025 (Aytaç *et al.* 1999).

It is clear that ED is a major health problem today, especially for the ageing population. A number of studies have found that ED is linked to diabetes, depression, hypertension, hyperlipidaemia, metabolic syndrome, and lower urinary tract symptoms (LUTS) (Shamloul *et al.* 2013). Furthermore, several studies have linked ED with cardiovascular disease (CVD) (Chung *et al.* 2011, Inman *et al.* 2009, Clark *et al.* 2007) as well as stroke, and all-cause mortality (Dong *et al.* 2011). Several studies (Dong *et al.* 2011, Cheng *et al.* 2007, Rosen *et al.* 2005) have also found that particular environmental and lifestyle factors, such as a lack of physical activity, obesity and smoking, all contribute towards ED. It has also been suggested that modifying one's lifestyle habits through dietary reform and engaging in more exercise, decreases the risk of ED (Esposito *et al.* 2004).

ED can also be a consequence of urogenital surgery. In 2003, 225,000 men were diagnosed with prostate cancer in the US alone, and out of these, 45% underwent radical prostatectomy surgery to remove the prostate gland. A major

disadvantage of this surgery is that most men will suffer from either permanent or temporary erectile dysfunction due to physical injury to the cavernous nerves during the surgery (Nandipati *et al.* 2006).

In addition to radical prostatectomy, postsurgical ED can be caused by radical cystectomy; urinary diversion (in the case of bladder cancer), and colorectal cancer surgery. Not only may there be a loss of erection, but damage to cavernous tissue can also cause a reduction in penile size in both length and circumference. Such changes are likely to become apparent in the first few months after the surgery (Kirby *et al.* 2014). Furthermore, there is a 16-86% variance in the recovery of potency following radical prostatectomy. Even though radical changes in surgical technique seem to be hopeful, there are still high rates of ED currently being reported (Shamloul *et al.* 2013).

1.2.3 Physiology of penile erection

Within the central nervous system, sexual stimuli (tactile, visual, olfactory, and imaginative) are processed and integrated. Certain autonomic and somatic pathways are then activated inside the central and peripheral nervous systems, thus leading to a penile erection; this is the result of both the penis's cavernosal and vascular smooth muscle becoming relaxed (Nunes *et al.* 2012). In contrast, a flaccid or detumescent penis consists of a heightened smooth muscle tone, and thus the tone of the penile smooth muscle is the key factor of erectile function. Furthermore, a rise in arterial inflow is achieved through the vascular smooth muscle becoming relaxed in the blood vessels supplying the penis, and through concurrent relaxation of the cavernosal smooth muscle. When combined with the decreased outflow via the contraction of striated ischiocavernosus muscles and the compression of subtunical venules, the intracavernosal blood pressure exceeds the systemic blood pressure, thus leading to a rigid erection (Nunes *et al.* 2012, Lue *et al.* 2004).

Therefore, the key event in penile erection is the relaxation of vascular and cavernosal smooth muscle. The key signalling molecule involved in penile smooth muscle relaxation is nitric oxide (NO), which is released from the

nitregic nerves and endothelial cells (Figure 1-11) (Lue *et al.* 2004). NO levels in the blood vessels and corpus cavernosum increase as sexual stimulus activates certain parts of the central nervous system and autonomic nerves. NO diffuses rapidly to neighbouring smooth muscle cells and activates intracellular soluble guanylate cyclase enzymes which synthesise cyclic guanosine monophosphate (cGMP) from guanosine-5-triphosphate (GTP). Elevated intracellular cGMP concentrations lead to a reduction of intracellular calcium concentrations resulting in vascular and cavernosal smooth muscle relaxation. Intracellular cGMP concentrations in the smooth muscle cells are tightly regulated by an enzyme called phosphodiesterase type 5 (PDE5) which hydrolyses cGMP to inactive 5'GMP. PDE5 inhibitors achieve enhanced penile erection by enhancing smooth muscle relaxation by slowing down the breakdown of cGMP levels (Sáenz de Tejada *et al.* 2004).

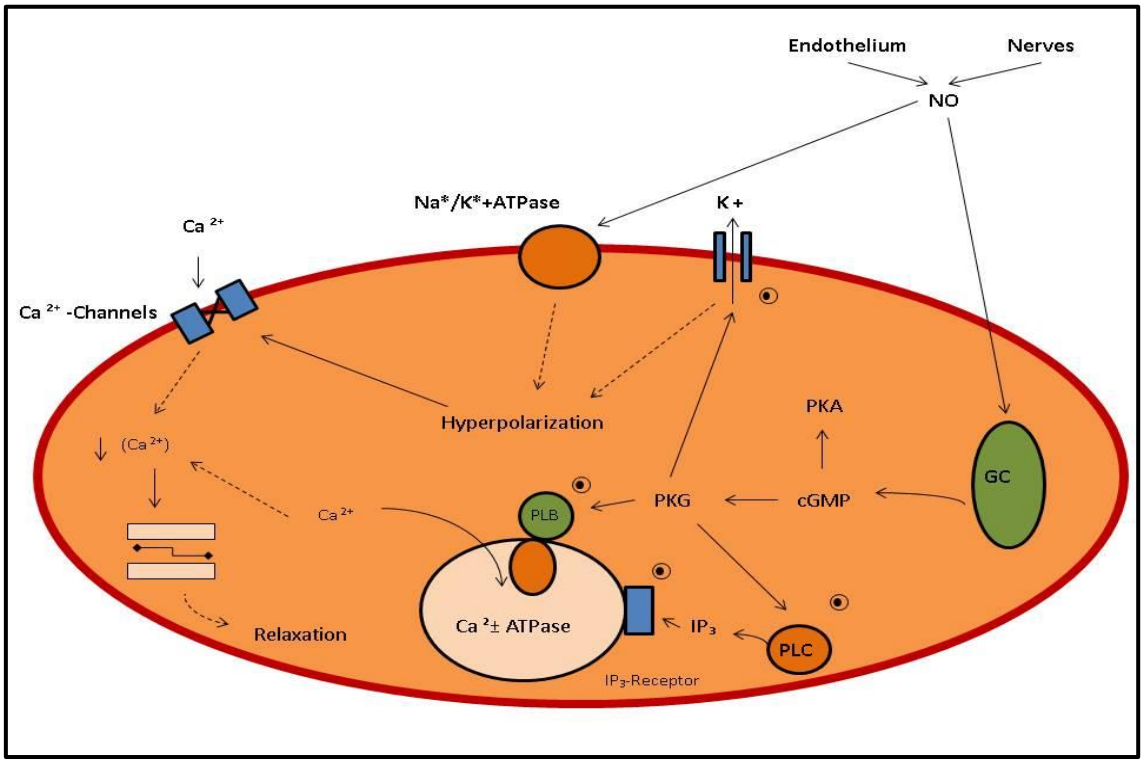


Figure 1-11: Molecular mechanism of penile smooth muscle relaxation (Sáenz de Tejada *et al.* 2004).
Legend: GC – guanylate cyclase; IP_3 – inositol triphosphate; PKA – protein kinase A; cGMP – cyclic guanosine monophosphate; PLB – phospholipase B; PLC – phospholipase C; NO – nitric Oxide (Sáenz de Tejada *et al.* 2004).

1.2.4 Pathophysiology of erectile dysfunction

Normal sexual activity is a bio-psychosocial process that involves the psychological, vascular, endocrine, and neurological systems (Shamloul *et al.* 2013). The physiological process of penile erection is a multifaceted process including the peripheral nervous system, CNS and hormonal and vascular systems (Ulrich *et al.* 2001). Any irregularities in these systems, either from disease or medication, will have an influence on erectile function (Fedele 2005).

The pathophysiology of ED can be divided into three mechanisms:

1) Psychogenic erectile dysfunction is defined as the persistent inability to achieve or maintain a satisfactory erection for sexual performance due to psychological or interpersonal factors (Rosen 2001). Earlier, psychogenic dysfunction was presumed to be the most common type, with 90% of impotent men thought to suffer from this condition (Dean *et al.* 2005). Sexual behaviour and penile erection are controlled by the hypothalamus, the limbic system, and the cerebral cortex. Therefore, stimulatory or inhibitory messages can be relayed to the spinal erection centres to facilitate or inhibit an erection (Dean *et al.* 2005).
2) Endothelial factor: because corporeal smooth muscle controls the vascular event leading to an erection, change of smooth muscle content and ultrastructure can affect erectile response (Dean *et al.* 2005). Diseases like diabetes and hypercholesterolemia have been shown to alter the endothelium-mediated relaxation of the cavernous muscle and impair erection (Dean *et al.* 2005).
3) Neurogenic factor: It has been estimated that 10% to 19% of ED is of neurogenic origin (Dean *et al.* 2005). Even though the presence of neurologic dysfunctions does not eliminate other causes, confirming that ED is neurogenic in origin can be challenging. Since an erection is a neurovascular process, disorders affecting the brain, spinal cord, cavernous and pudendal nerves can induce ED (Dean *et al.* 2005).

However, during radical prostatectomy, which is a procedure required when the patient needs all or part of the prostate gland removed, injury can occur to the cavernosal nerve which may lead to erectile dysfunction but also to urinary incontinence. The recovery of erectile function is highly unlikely, although not entirely impossible (Nandipati *et al.* 2006, Chung *et al.* 2013). Nerve sparing prostatectomy is a technique that has been developed in an attempt to reduce erectile dysfunction following radical prostatectomy (Nandipati *et al.* 2006). There are two bundles of nerves which run parallel to the prostate, and these nerves assist in controlling erections. The surgeon carefully removes prostate tissue away from the nerve bundles without damaging them during a nerve sparing prostatectomy, as removing the prostate without causing harm to the nerves means it is far more likely for the patient to be able to have erections post-surgery; however, nerve sparing surgery increases the risk of some cancer cells not being removed (Garcia *et al.* 2014). Nerve sparing surgery is only suitable for patients with prostate cancers in the very early stages, and the cancer must be located entirely inside the prostate. Despite the majority of the nerves being preserved in the surgical procedure, some temporary ED usually occurs, however with the nerve-sparing technique; particularly bilateral nerve-sparing, permanent ED is less likely compared to non-nerve sparing surgery, with recovery usually taking place within the first year or two after the procedure (Garcia *et al.* 2014).

In sexual medicine, the concept of “Penile Rehabilitation” is relatively new, which involves medical and therapeutic treatment with the aim of restoring penile health and function before, during or after surgery, illness, trauma, or even lack of use. Penile rehabilitation is important for aiding men in regaining satisfactory sexual function. PDE5 inhibitors such as sildenafil, tadalafil or vardenafil are often used to treat ED post-surgery, (Kirby *et al.* 2014).

In addition, the preoperative use of PDE5 inhibitors may help in protecting blood vessels and autonomic nerves (Gontero *et al.* 2004a, Gontero *et al.* 2004b). Moreover, some studies have shown that such medical treatments can in fact increase the amount of smooth muscle in the penis (Corbin 2004, Li 2015).

1.2.5 Diagnosis of erectile dysfunction

There are several questionnaires that are widely used to diagnose urogenital dysfunction such as: The Male Sexual Health Questionnaire (MSHQ) which assesses the sexual function and satisfaction in older men with urogenital symptoms of LUTS and sexual dysfunction (Rosen *et al.* 2004). Brief Male Sexual Function Inventory (BMSFI) is a measure of sexual function in males (O'Leary *et al.* 1995). The International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) is a four-item, disease-specific questionnaire that assesses the symptoms and quality of life for patients with urinary incontinence (Gotoh *et al.* 2009). The International Index of Erectile Function (IIEF; (Yule *et al.* 2011) and International Prostate Symptom Score (IPSS; (Plante *et al.* 1996) are tools used to evaluate the sexual and urological functions in males.

The International Index of Erectile Function (IIEF) was designed and developed specifically for the assessment of male sexual function (Rosen 1999). The IIEF is simple, psychometrically sound and has been extensively validated. It is self-administered and it has been demonstrated to have good sensitivity and specificity for detecting treatment-related changes in patients with erectile dysfunction (Rosen *et al.* 2004).

The International Index of Erectile Function (IIEF) is a questionnaire that consists of 15 questions with multiple choice answers. IIEF was established in 1996–1997 and has been used in several clinical trials including in populations of diabetic men (Yule *et al.* 2011).

The IIEF questionnaire (Appendix A) consists of different domains: erectile function (6 questions); orgasmic function (2 questions); sexual desire (2 questions); intercourse satisfaction (3 questions) and overall satisfaction (2 questions; (Rosen 1999). Each question is scored on a scale of 0-5 (see Appendix A; (Rosen *et al.* 1997).

Responses are recorded on a Likert-type scale[9] with response choices over a 5 or 6 point scale for questions 1-10 and 11-15 respectively. The lower anchor for the 6 point Likert-type scale is 0 while the highest rating is 5. The 5 point Likert-type scale ranges from 1 to 5 with 1 representing the lower anchor.

The questions are not weighted and total scores range from 5 to 75. The domain scores are computed by summing the scores for each individual question in each domain. The domain scores have the following ranges: erectile function (1-30), orgasmic function (0-10), sexual desire (2-10), intercourse satisfaction (0-15) and overall satisfaction (2-10).

On the erectile function sub-scale, lower scores indicate *worse* erectile dysfunction, while on the remaining sub-scales higher scores indicate *less* dysfunction. All questions have to be completed.

The IIEF assessment has two key limitations in assessing sexual dysfunction in males: very limited assessment of partner relationships and only a superficial assessment of psychosexual background. Therefore, this questionnaire must be seen as a means of support for comprehensive sexual examination and history (Rosen *et al.* 1997) including questions about erectile problems that have had an impact on the patient's sex life during the previous four weeks prior to his appointment. In Rosen's study patients were also asked to describe their erectile function according to questions 1, 2, 3, 4, 5 and 15 (Rosen *et al.* 1997). The maximum score of erectile function (EF) domain is 30, and any score lower than 25 suggest impaired EF. An optimal cut-off score of 25 or less has been used for the diagnosis of ED (Cappelleri *et al.* 1999) and, in accordance with Cappelleri's study, the evaluation of erectile function as a domain of IIEF has been divided into five categories according to severity: No ED (EF score from

[9] Likert-type scale is one of various different rating scales that have been developed to measure attitudes directly (i.e. the person knows their attitude is being studied). Examples of the multiple choices in the Likert scale are as follows: strongly agree/ agree/ undecided/ disagree/ strongly disagree (Wilson *et al.* 2000).

26 to 30); mild ED (EF score from 22 to 25); mild to moderate ED (EF score from 17 to 21); moderate ED (EF score from 11 to 16), and severe ED (EF score 6 to 10; (Cappelleri *et al.* 1999).

1.2.6 Treatment of erectile dysfunction

The principal step in treatment of ED is taking a detailed history of medical, sexual and psychosocial conditions (Esposito *et al.* 2004). Medical therapy with phosphodiesterase type 5 (PDE5) inhibitors is the first line of treatment (Costabile *et al.* 2003), and these medications are highly acceptable for patients and easy to administer, because of their efficacy and low side effects (Hatzimouratidis *et al.* 2009, Kubin *et al.* 2003). Unfortunately, the response rate to PDE5 inhibitors is lower in diabetic men than in non-diabetic (Goldstraw *et al.* 2007). In about 30-40% of diabetic patients, PDE5 inhibitor treatment is not successful due to autonomic neuropathy and peripheral vasculopathy (Goldstraw *et al.* 2007, Sarwer *et al.* 2012).

Further treatments consist of psychosexual therapy such as sex education and interpersonal therapy for relationship problems (Rosen 1999); shifts in lifestyle to being more healthy and active by increasing physical activity; weight reduction, quitting smoking (Horasanli *et al.* 2008), and testosterone supplementation.

Second line therapies include intracavernosal injections, intraurethral injections and vacuum constrictive devices (Shamloul *et al.* 2013). However, vacuum erection devices and transurethral injection of Prostaglandin E1 (PGE1) are not commonly used either because of urethral infections following the use of PGE1 and because of the difficulty of using vacuum devices (Esposito *et al.* 2004, Hatzimouratidis *et al.* 2009).

When ED management is unsuccessful, a penile prosthesis (a device that is implanted in place of cavernosal bodies and produces an erection that allows the patient to have a normal sexual intercourse) is recommended as a third line of therapy (Shamloul *et al.* 2013). However, as soon as the patient has

undergone the penile prosthesis procedure, it becomes impossible to achieve smooth muscle relaxation, since the corporal tissue has been removed. The penile prosthesis has two key forms: semi-rigid and inflatable prosthesis. Semi-rigid prostheses are often simple to implant and are more durable compared to inflatable prostheses, although they are unable to create a complete erection. Additionally, it is often difficult to fully cover the prosthesis after surgery. The inflatable prosthesis often has two or three parts, such as two penile cylinders and, in the case of inflatable prostheses, a scrotal pump (Shamloul *et al.* 2013). A treatment algorithm for ED is shown in Figure 1-12.

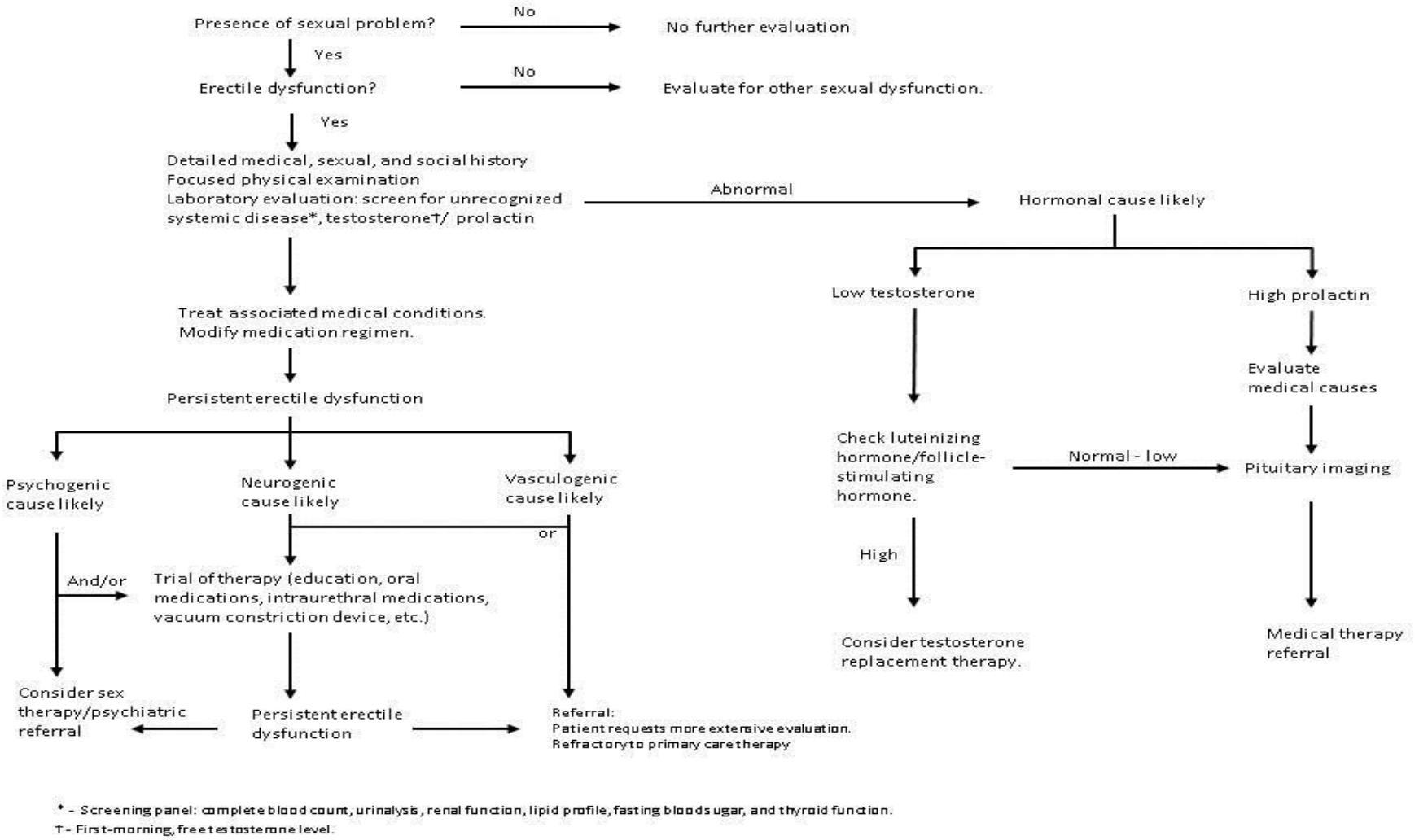


Figure 1-12: Treatment algorithm for erectile dysfunction (Miller 2000).

1.3 Lower urinary tract symptoms

1.3.1 Anatomy of urinary function

The lower urinary tract consists of the urinary bladder and the urethra (Figure 1-13). The urethra has both smooth and striated muscle.

The bladder is a triangle-shaped, hollow organ which is situated in the lower abdomen. Ligaments hold it in its place as well as it is attached to other organs and the pelvic bones (Andersson *et al.* 2004).

The bladder is lined by a mucous membrane and covered on its outer aspect partly by peritoneal serosa and partly by fascia. Its muscular wall is formed of smooth muscle cells, which comprise the detrusor muscle (Andersson *et al.* 2004). The cells of the outer and inner layers have a tendency to be oriented longitudinally and those of the middle layer circularly. The bundles of muscle cells of variable size are enclosed by connective tissue rich in collagen (Andersson *et al.* 2004).

The smooth muscle cells of the main bundles may occur in sets of small functional units, or fascicles, and the orientation and interaction between smooth muscle cells in the bladder are important for the behaviour of the bladder and the activity of the cells (Drake *et al.* 2001).

The prostate is a gland located between the bladder and the penis (Figure 1-10) (Seftel *et al.* 2008). The urethra goes through the center of the prostate, from the bladder to the penis, letting urine and semen flow out of the body. The function of the prostate is to secrete an alkaline fluid that nourishes and protects sperm during ejaculation. There are some medical conditions that can have an effect on this gland such as prostatitis (inflammation of the prostate), prostate cancer and enlarged prostate (benign prostatic hypertrophy (BPH). The principal consequence of these conditions is an increased difficulty in urination (Parsons 2010).

The enlargement of the prostate is a very common condition associated with ageing and the mechanism behind it is not known (Rosen *et al.* 2014). An enlarged prostate can put pressure on the urethra, which can affect urination in various ways, including a difficulty to start or to stop urinating, a weak flow of urine, straining, an inability to fully empty the bladder, prolonged dribbling after urinating and an increased frequency of urination (Parsons 2010); Figure 1-13).

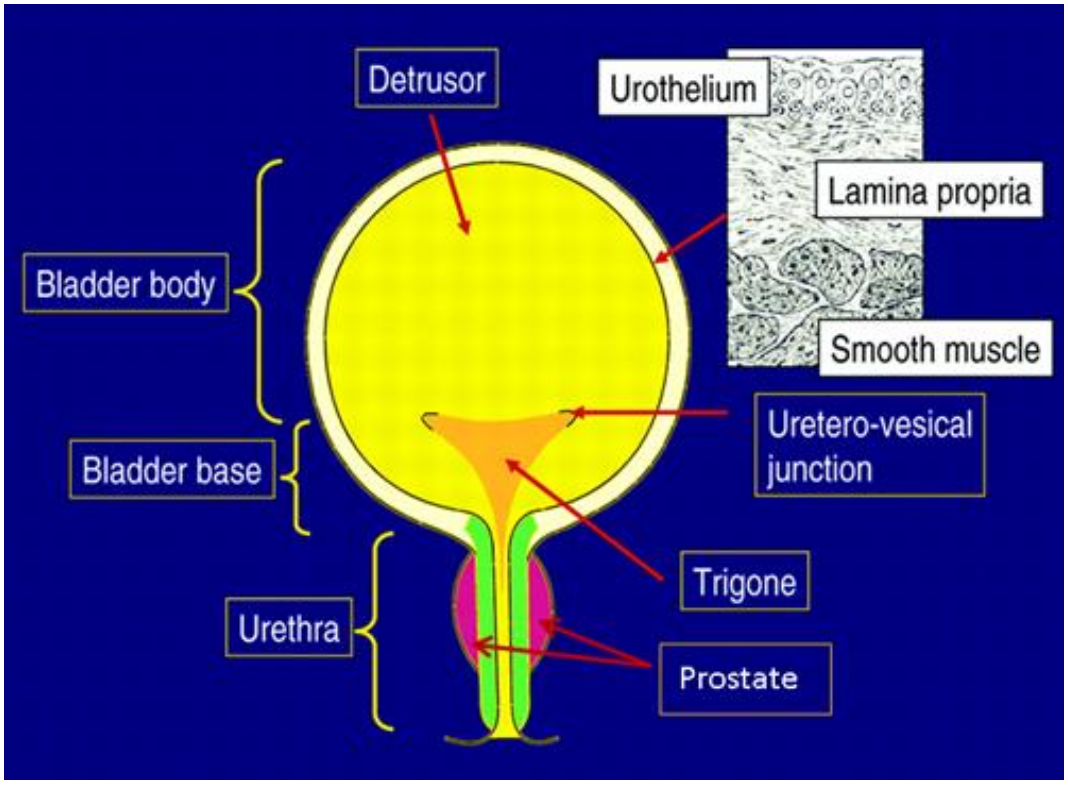


Figure 1-13: Diagram of the bladder. Adapted from (Andersson *et al.* 2004)**.**
The bladder can be divided into two main components: the bladder body, which is located above the urethral orifices, and the base, consisting of the trigone, urethrovesical junction, deep detrusor, and the anterior bladder wall. The urethra contains both smooth and striated muscles and the bladder is a hollow smooth muscle organ lined by a mucous membrane and covered on its outer aspect partly by peritoneal serosa and partly by fascia (Andersson *et al.* 2004).

1.3.2 Symptoms and signs of lower urinary tract symptoms

Lower urinary tract symptoms (LUTS), according to NICE, include voiding symptoms (straining, weak/intermittent urinary stream, incomplete emptying, hesitancy, and terminal dribbling); post-micturition symptoms (post-micturition

dribbling), and storage symptoms (urgency, frequency, urgency incontinence and nocturia; (NICE 2015). LUTS can be caused by abnormalities in the prostate and its functionality, as well as anomalies in the bladder/sphincter and urethra. In addition, post-micturition symptoms are one of the most common among LUTS, and can be very uncomfortable for the patient (Verhamme *et al.* 2003).

For men, benign prostate enlargement (BPE) is the most common cause that often blocks the bladder outlet (Bibel 2012). This occurs when the number of cells in the prostate increase due to a condition known as benign prostatic hyperplasia (BPH). Other conditions that cause LUTS include urinary tract infections, prostate cancer and neurological diseases, among others. Even though LUTS do not necessarily lead to severe illness they can, however, impact the quality of life for men, and might indicate underlying pathologies of the urogenital tract (Kirby *et al.* 2013) .

Additionally, most studies showed that obesity increases the risk of BPH (Giovannucci *et al.* 1994, Kristal *et al.* 2007), but not all (Burke *et al.* 2006, Fritschi *et al.* 2007). Increasing physical activity has been linked to a decreased risk of BPH surgery, while obesity is strongly associated with a lack of physical activity (Parsons 2010, Parsons *et al.* 2013).
The physiological mechanisms of obesity's influnce on BPH still needs to be described and the independent influence the sex steroid hormones on BPH is also unclear (Parsons *et al.* 2013). The adipose tissue might stimulated the aromatization of circulating testosterone into oestrogen leading to changes in the balance between testosterone and oestrogen in the prostate tissue which may contribute in BPH pathogenesis (Parsons *et al.* 2013).

However, Glasser *et al*. (2007) and Sexton *et al*. (2009) argue that storage LUTS are more bothersome and prevalent among men than voiding and post-micturition LUTS, and tend to be associated with primary bladder dysfunction, which might be secondary to BPE, or may become apparent due to other factors which may affect the bladder's physiology (Roosen *et al.* 2009).

Therefore, it is vital for clinicians to consider all potential reasons for LUTS before treatment, such as issues with fluid intake and medical conditions, such as heart failure and diabetes, as well as urological conditions such as an overactive bladder. Nevertheless, BPE is the most common cause of LUTS in men, which is due to BPH (Parsons 2010). Moreover, (NICE 2015) explains that BPH becomes more prevalent as men age and roughly 25-50% of males who suffer from BPH also suffer from LUTS.

For the ageing male population, LUTS is a huge burden (Kirby *et al.* 2013). For example, a cohort study of 80,774 males showed that men over the age of 40 are 15-60% more likely to experience bothersome LUTS than men under 40 which is a sizable group that may require treatment (NICE 2015). Even though the figures vary in each study due to the different definitions given and study methodology, LUTS is highly prevalent and these figures are set to continue rising due to increases in life expectancy and thus, of the elderly population (NICE 2015, Kirby *et al.* 2013).

1.3.3 Epidemiology of urinary tract symptoms

As men age, the severity of LUTS becomes more prevalent, and this progressive rise in the number of ageing men has also resulted in a further prevalence in social economic burden, besides the severity of LUTS (Engström *et al.* 2005). The direct cost of this burden is in prescription medications, medical visits, diagnostics and sadness. A high score for sadness was reported by 29% of men with LUTS, compared with 10% of men with no LUTS. Smokers with LUTS had a greater risk of obtaining a high score for sadness than smokers with no LUTS (Engström *et al.* 2005).

Jackson (1999) previously discovered that the relationship between increased prevalence of LUTS and age is limited to symptoms such as urgency, weak stream and nocturia, and that other symptoms are prevalent across different age groups. Despite the fairly low prevalence of nocturia, frequency, urge incontinence and nocturnal incontinence, these symptoms can be highly bothersome for those people who experience them (Abrams *et al.* 2003).

Moreover, a Taiwanese epidemiological study found that roughly 15% of the male population had reported that their quality of life had reduced due to their LUTS (Kuo 2007).

1.3.4 Epidemiological studies in urinary tract symptoms

The International Continence Society (ICS) measured the inconvenience of men's LUTS via a questionnaire study, which studied 1,271 male patients across 12 countries who were presenting at urology clinics (Llorente 2010). The study found a high prevalence (90-94%) in voiding symptoms like increased hesitancy, intermittency, and stream compared to storage symptoms, like frequency, nocturia and urgency (66-71%), although the latter appear to be the most bothersome. On the other hand, the European Prospective Investigation into Cancer and Nutrition (EPIC) survey was carried out in five different countries (Canada, Germany, Italy, Sweden, and the United Kingdom), and was a computer assisted telephone survey that was both population-based and cross-sectional (Irwin *et al.* 2006). It was discovered that both genders exhibit a similar prevalence of LUTS, with 66.6% of women and 62.5% of men reporting at least one symptom. Meanwhile, storage symptoms were more prevalent in women (59.2%) compared to men (51.3%), while voiding symptoms were more prevalent in men (27.5%) compared to women (19.5%), and both sexes exhibited a similar prevalence in post-micturition symptoms (14.2% in women and 16.9% in men).

Similarly, the Boston Area Community Health (BACH) survey also reported a prevalence of LUTS among both sexes (Kupelian *et al.* 2006), which supports the provision of vital information on both the use of medication and quality of life. Moreover, the study concluded that as people age, the prevalence of LUTS increases, which is concordant with the ICS conclusions. Meanwhile, the Epidemiology of LUTS (EpiLUTS) study was performed in the US, UK and Sweden via the internet, and was a population-based, cross-sectional survey (Coyne *et al.* 2009). There were two symptom frequency thresholds that helped to define the prevalence of LUTS: "at least sometimes", with 72.3% prevalence

in men and 76.3% prevalence in women, and “at least often”, with 47.9% prevalence in men and 52.5% prevalence in women.

What these four epidemiological studies indicate is that the prevalence of LUTS is not determined by gender or race, despite voiding symptoms appearing to be more prevalent in men, and storage symptoms appearing to be more prevalent in women (Llorente 2010). In addition, LUTS has been linked to various chronic diseases, and such observations may help to shed some light on the pathophysiology of LUTS (Llorente 2010).

1.3.5 Pathophysiology of urinary tract symptoms

Given the multifactorial nature of LUTS, its pathophysiology not well characterised. Usually, men’s LUTS are due to bladder outlet obstruction (BOO), caused by an enlarged prostate, primarily benign prostatic hyperplasia (BPH) (Kuo 2000). However, current studies have yet to discover any significant relationship between LUTS and bladder outlet obstruction (Kuo 2007).

The pathophysiology of LUTS can be attributed to bladder dysfunction. Some men have both LUTS and storage dysfunction, which comprises of complex emptying and bladder storage symptoms. In the past, the treatment of LUTS focused more on bladder outlet obstruction (BOO) and emptying symptoms. Recent studies have indicated that the urinary bladder’s sensory innervation is important in storage, besides emptying LUTS (Kuo 2007).

Bladder dysfunction that affects emptying or storage of urine is also referred to as voiding dysfunction which describes the aberrations in emptying or filling the bladder (Sarwer *et al.* 2012). The primary cause of bladder dysfunction is diabetes, and more than half of men and women with diabetes suffer from bladder dysfunction. Although the disorder is not usually fatal, it can be linked to severe weakening symptoms, diabetic cystopathy (increased post-void residual urine volume, poor contractility, and reduced bladder sensation) being the most common (Goldstraw *et al.* 2007). The prevalence of diabetic bladder dysfunction is unconnected to the gender or age of the patient and rises with

the occurrence and duration of diabetes (Goldman *et al.* 1999, Kaplan *et al.* 1995). Bladder dysfunction due to diabetes (or diabetic bladder dysfunction) may be the result of hyperglycaemia, urothelial dysfunction and also changes in the function of neurons (Yoshimura *et al.* 2005). This neurologic defect has been associated with axonal damage and demyelination at several sites in the nervous system, caused by high levels of glucose (Fedele 2005). Moreover, urothelial cells release a variety of mediators such as nitric oxide (NO), prostanoids and ATP (Birder *et al.* 2002) and an increase in the release of ATP, for instance, may lead to different abnormalities with diabetic bladder dysfunction (Birder *et al.* 2002).

These neurological abnormalities related to bladder dysfunction are associated with nitrergic fibres which are responsible for bladder contraction during urination as well as sympathetic efferent fibres which control the internal sphincter and afferent sensory fibres which modulate transmission of the sensation of bladder fullness (Fedele 2005).

1.3.6 Diagnosis and treatment of urinary tract symptoms

Diagnosis of LUTS involves patients completing a questionnaire known as the International Prostate Symptom Score (IPSS; Table 1-8), which helps to measure the symptoms of the condition, together with a physical examination. The IPSS was approved by the World Health Organization International Committee and used since the early 1990s (Plante *et al.* 1996). It is the most widely used self-administered questionnaire for pre-diagnosing patients with BPH (Plante *et al.* 1996).

The IPSS is based on seven questions about urinary symptoms and one question regarding quality of life. Each question relating to urinary symptoms permits the patient to choose one out of six answers representing the increasing severity of a particular symptom. The responses are based on a Likert scale from 0 to 5 where 0 represents “Not at all” and 5 represents “Almost always”. The total score can range from 0 to 35 (asymptomatic to very symptomatic), (Table 1-8).

Table 1-8: IPSS Questionnaire Scores (Plante *et al.* 1996).

Questions	Symptom
1	Incomplete emptying
2	Frequency
3	Intermittency
4	Urgency
5	Weak Stream
6	Straining
7	Nocturia

The American Urological Association (AUA) Symptom Index presently classifies the symptoms from the first seven questions as follows: mild (symptom score ≤ 7), moderate (symptom score range 8-19) and severe (symptom score range 20-35; see Appendix A).

The last question focuses on the quality of life of the patient and the International Scientific Committee (ISC), with the support of the WHO recommends the answers to this question to range from “delighted” to “terrible” or 0 to 6 (Plante *et al.* 1996, Barry *et al.* 1992).

As soon as the severity of LUTS has been discovered and diagnosed via the IPSS, it is vital that an acceptable management programme is established by the physician and patient. Men who have mild to average LUTS that does not cause any complications or is not bothersome, must be managed conservatively within primary care, alongside a range of additional factors including lifestyle advice, for instance, adjusting or reducing fluid intake, no caffeine intake, alcohol, or artificial sweeteners; exercises, for instance, pelvic floor muscle and bladder training exercises; containment products, for instance, pads/collection devices, and frequent monitoring (Oelke *et al.* 2012).

It is vital that pharmacotherapy is provided to men who have bothersome LUTS, in cases where conservative management options are unsuitable or unsuccessful (Abrams *et al.* 2003, Oelke *et al.* 2012). Furthermore, considering comorbidities, as well as ongoing treatments prior to selecting drug treatments for LUTS, is also important. Men who have moderate to severe LUTS have a number of pharmacological treatment options available to them, which include 5 α-reductase inhibitors, antimuscarinics, monotherapy with α-blockers, vasopressin analogues, or a combination of the above treatments in particular clinical circumstances (Oelke *et al.* 2012).

1.3.6.1 Monotherapy

The first-line of treatment for men who suffer from bothersome LUTS and request treatment should be α-blockers (Oelke *et al.* 2012). These drugs also have a quick reaction time, and thus should only be used on an irregular basis for those patients that require no long-term treatment. Oelke and co-workers (2012) have explained that all α-blockers in suitable doses will be similarly effective, regardless of the prostate specific antigen (PSA) level or prostate size, despite these drugs not having any impact on prostate size (McConnell *et al.* 2003).

Particular drugs, such as doxazosin and terazosin, call for initial dose titration, while others, such as alfuzosin, silodosin and tamsulosin, do not. Men who have an enlarged prostate and moderate to severe LUTS, and are likely to be at a greater risk of their disease progressing, may be given 5 α-reductase inhibitors such as dutasteride and finasteride if the prostate volume is more than 40 ml or if the PSA level is greater than 1.4 ng/mL (Roehrborn *et al.* 1999).

Fesoterodine, tolterodine and solifenacin are antimuscarinics, which are used to manage men's storage symptoms (Oelke *et al.* 2012). Even though most patients who took part in the clinical trials of these agents were women, these studies show that men who have storage symptoms saw similar side effects and benefits after using antimuscarinics. Therefore, these drugs are an effective first-line treatment for men who suffer from bothersome storage LUTS, and a

second-line treatment for men who have used alternative medications that have failed. However, for men who have BOO, prescribing antimuscarinics should be avoided given the risk of urinary retention (Badlani *et al.* 2008), which therefore necessitates awareness of safety and efficacy profiles of the drugs used (Jones *et al.* 2010).

Oral agents, such as vasopressin analogues and loop diuretics, which reduce urine production during night time hours, may be provided to men who suffer from nocturnal polyuria (so long as other medical conditions are ruled out, such as diabetes, polydipsia, or intake of diuretics during night time hours). Prior to sleeping, the vasopressin analogue desmopressin is taken once per day, and there is a need for careful dose titration (starting on lower dosages of the medication and gradually increasing levels in each session) (Oelke *et al.* 2012).

1.3.6.2 Combination therapy

Monotherapy may not be adequate to control all LUTS for particular patients, in these cases combination therapy using two or more monotherapies is used. Combination treatment is seen as more efficacious than monotherapy, although it is important that additional costs and adverse effects are weighed against better efficacy (Oelke *et al.* 2012). A reduced urinary flow, alongside high risk BPH progression, and an enlarged prostate are often common symptoms of bothersome moderate to severe LUTS in men (Roehrborn *et al.* 1999). Therefore, combining an α-blocker and a 5 α-reductase inhibitor may form the ideal solution to reducing these common symptoms. The 5 α-reductase inhibitor delays or prevents the disease from progressing, while the α-blocker swiftly relieves the bothersome LUTS. It is also important to consider combining both an α-blocker with an antimuscarinic for those men who suffer from moderate to severe LUTS, alongside existing storage symptoms, if monotherapy is unsuccessful (Oelke *et al.* 2012).

1.3.6.3 Associated medications

The use of other medications, such as cold and influenza medications that contain phenylpropanolamine and diphenhydramine, can adversely impact the safety and efficacy of antimuscarinics. As previously suggested, it is important for physicians to question patients regarding over the counter medication and current prescriptions, as well as reminding patients to seek advice prior to starting new medication. Furthermore, it is important to keep on top of recommended exercise and lifestyle reforms, as well as adjusting or reducing fluid intake as well as intake of caffeine, alcohol, and artificial sweeteners (Oelke *et al.* 2012).

1.3.7 Link between erectile dysfunction and urinary tract symptoms

In spite of the vast literature supporting the relationship between ED and LUTS, it appears that in both primary and secondary care, there is limited awareness of this relationship, and this reflects the lack of available treatments (Kirby *et al.* 2013) and suitable diagnostic tools (Seftel *et al.* 2008). For instance, Kirby and co-workers (2013) asserted that in an audit of 100 UK patients who suffered from LUTS, there were less than 10% of doctors who enquired about ED, and over 80% of those patients were not offered any therapy at all, although 91% of ED sufferers who were given no treatment wanted medical assistance.

A survey of the services that inform doctors about treating patients in the UK, indicates that despite the potential connection being mentioned, there was still no reference of co-diagnosis being provided to patients. For example WebMentor, which is a clinical IT system, contains no mention of sexual function or ED in LUTS information for GPs, as well as no reference to LUTS in ED information (Kirby *et al.* 2013). Likewise, in the current NICE - LUTS guidelines, despite the reference to ED, again, there are no productive recommendations on how to enquire about and manage a patient's ED related problems, such as providing better access to care for their physical and emotional conditions (NICE 2015). There are a number of factors that may prevent physicians asking their patients about sexual function, such as limited

time, lack of knowledge and embarrassment around sexual health; although the most significant reason for such failure regarding ED in LUTS is the unfamiliarity with the relationship between the two conditions (Kirby *et al.* 2013).

1.3.7.1 Studies suggesting a link between ED and LUTS

1.3.7.1.1 Epidemiological evidence

In spite of the differences in design, there are a number of large studies that have used effective multivariate analyses and provide strong evidence linking ED and LUTS (Kirby *et al.* 2013). Table 1-9 summarises the epidemiological evidence from the studies that have been carried out highlighting the relationship between ED and LUTS.

Table 1-9: Examples of epidemiological evidence for the association between ED and LUTS

Reference	Country/Continent	Sample Number	Applicable results for the relationship between ED and LUTS
(Blanker *et al.* 2001)	Holland	3,924	Patients with ED found they had urinary issues; risk of ED is higher in moderate to severe LUTS sufferers compared to cardiac and smoking symptoms.
(Demir *et al.* 2009)	Turkey	190	Patients with severe LUTS had a significantly lower erectile function and greater prevalence of ED compared to those who had moderate LUTS.
(Li *et al.* 2005b)	Asia	1,155	There were increases in both sexual disorders and severity of LUTS with age. ED was highly prevalent in older age groups who had severe LUTS (54-84%). Overall, 91% of men had moderate to severe LUTS.
(Mehraban *et al.* 2008)	Iran	357	68.2% of patients who suffer from LUTS displayed sexual dysfunction, and all cases were age related.
(Ozayar *et al.* 2008)	Turkey	453	36% of men were found to have ED with moderate LUTS and 94% of men with severe LUTS had ED.
(Shiri *et al.* 2007)	Finland	1,683	Men who had moderate to severe ED showed a higher relative risk of LUTS compared to those who did not suffer from ED.
(Tsao *et al.* 2008)	Taiwan	398	The prevalence of moderate to severe ED and LUTS had a strong relationship, especially in the 60-69 age group
(Vallancien *et al.* 2003)	Europe	1,274	There was a strong connection between ED and age, BMI and LUTS, among other factors, and those patients who suffered from severe LUTS were more likely to have ED.
(Wang *et al.* 2008b)	China	245	A relationship was discovered between ED and severity of LUTS, with almost 96% of patients with severe LUTS reporting ED.

1.3.7.1.2 Preclinical evidence

There have been a number of reviews based on the mechanisms that underlie the relationship between LUTS and ED (Shiri *et al.* 2007, Gacci *et al.* 2011). These reviews provide preclinical data and a clear theoretical background to the mechanisms that are already being used in clinical practice, including, changes in the NO-cGMP pathway, autonomic hyperactivity, pelvic atherosclerosis, and RhoA–Rho-kinase (ROCK) signalling (Andersson *et al.* 2011). Further supporting factors, like sex steroid ratio imbalance and chronic inflammation could also be important (Penna *et al.* 2009, Corona *et al.* 2010). Knowledge of pathways that link these mechanisms should aid in better understanding the pathophysiology of both conditions (Gacci *et al.* 2011). Recently it has been proposed that neurovascular dysfunction could be the underlying common cause for both BPH/LUTS and ED (Cellek *et al.* 2014).

1.3.7.2 Risk factors associated with ED and LUTS

As described previously, several risk factors are associated with erectile dysfunction, including, age, obesity, sedentary physical lifestyle and poor psychological health, smoking (cigarettes and marijuana), poor glycaemic control, certain medications such as antihypertensives, and occurrence of other diabetic complications such as neuropathy (Shamloul *et al.* 2013). Furthermore, other risk factors include cardiovascular disease (CVD), depression, insomnia, and T2DM, among other psychiatric/psychological disorders (Shamloul *et al.* 2013).

A recent study by Hyde *et al*. (2012) that studied 3,000 elderly men (75 to 95 years old), found that factors such as coronary artery disease (CAD), depression, diabetes, insomnia and prostate disorders had a strong association with ED related issues in these elderly men. The study also found that ED diagnosis could be predictive of coronary artery disease (CAD), with a reduced CAD risk time, that is to say, the time period in which CAD is likely to occur, of two to five years. Therefore, spotting ED, especially in men under the age of 60

and those who suffer from diabetes, can result in early diagnosis of CAD (Miner *et al.* 2012).

On the other hand, there are a number of risk factors that are related to men's LUTS, which include CVD, obesity, BPE, diabetes, inflammation and age, among others, all of which have been pointed out in a number of recent studies (Lee *et al.* 2012, Shamloul *et al.* 2013, Parsons 2010). A recent study has shown that using statins might suspend LUTS by five to seven years, from developing the condition through the reduction of moderate to severe LUTS, BPE and inflammation (St Sauver *et al.* 2011). Furthermore, ED and LUTS have also been found to be related to metabolic syndrome (Hammarsten *et al.* 2011), with waist circumference being heavily linked to various prostate related problems. Lee et al. (2012) also found that an increased waist circumference is further related to a higher prevalence of T2DM, obesity and CAD, besides ED related issues and ejaculatory dysfunction.

Kirby *et al.* (2013) further suggested that patients have to meet certain risk criteria or risk factors to be affected by ED related issues. A combination of the current definitions by the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF) have established the following conditions (Zimmet *et al.* 2011): Blood pressure (BP) of 130/85 mmHg or more, elevated waist circumference (males: greater than 94cm), fasting glucose of 5.6 mmol/l or more (> 100 mg/dl), high-density lipoprotein (HDL) under 1.03 mmol/l (< 40 mg/dl; men) and triglycerides of 1.7 mmol/l or more (> 50 mg/dl) (Kirby *et al.* 2013).

1.4 Obesity and urogenital dysfunction

Obesity appears to have an adverse effect on urogenital function, especially on men with comorbidities such as diabetes and hypertension, which increase sexual dysfunction (Kuruba *et al.* 2007). There have also been several studies on the relationship between male sexual dysfunction and morbid obesity; however those studies have used modest and inconsistent methods to assess the impact of weight loss on other conditions (Dallal *et al.* 2008).

Obesity has also been associated with erectile dysfunction, and the mechanisms behind this are probably multifactorial (O'Brien 2010, Sarwer *et al.* 2012). However, some of the studies propose that obesity induced ED may be reversed when obesity is treated (Dallal *et al.* 2008).

1.4.1 Clinical correlation between obesity and urogenital dysfunction

1.4.1.1 Studies on obesity and sexual function

Dallal and colleagues (2008) examined 97 men with an average age of 48 and average BMI of 51 who went through gastric bypass surgery. The brief male sexual function inventory (BMSFI) was given out to examine the sexual function of the patients twice before surgery (between 30 and 90 days prior to surgery) and after surgery (6 months after) (Dallal *et al.* 2008). The BMSFI is a measure of sexual function in males. It involves 11 questions that cover five aspects: sexual drive (2 questions), erectile function (3 questions), ejaculatory function (2 questions), sexual problem assessment (3 questions), and sexual satisfaction (1 question) (O'Brien 2010).

The objective of this study was to measure sexual function in morbidly obese men before and after significant weight loss achieved by gastric bypass (Dallal *et al.* 2008). The finding was that obesity is an extremely difficult disease to treat and bariatric surgery despite its inherent risks has been shown to improve quality of life and comorbidities (Dallal *et al.* 2008). Dallal and colleagues also suggested that changes in glucose metabolism or the presence of cardiovascular disease may not be the main cause of obesity associate erectile dysfunction (Dallal *et al.* 2008).

Ranasinghe and colleagues (2011) examined, in a retrospective study the effects of weight loss following laparoscopic gastric band surgery (LGB) on urinary and sexual function in patients with a mean BMI of 47.3 (Ranasinghe *et al.* 2011). Between 2001 and 2009, three questionnaires were mailed to 653 females (160 responded) and 145 males (36 responded), after exclusion criteria were applied (due to some of the patients either having had surgery or being on

medication for urinary or sexual function), 142 females and 34 males were included in this study (Ranasinghe *et al.* 2011). The questionnaires that were used were the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), the IPSS and the IIEF. According to the Ranasinghe study, there was no improvement in the IIEF score for sexual function in men after the weight loss surgery (Ranasinghe *et al.* 2011).

Reis and colleagues (2010) measured erectile function and hormonal changes after significant weight loss either surgically or non-surgically in morbidly obese males (Reis *et al.* 2010). This study was a prospective randomised controlled trial where they studied 20 morbidly obese men for 24 months and divided them into two groups: Group A (intervention) included 10 patients who went through life style adjustments (exercise and diet) for four months and then a gastric bypass. Group B (control) included another 10 patients who were examined on a weekly basis who did not receive any lifestyle or surgical intervention.

All patients performed the IIEF-5 questionnaire and blood chemistry values were taken for serum oestradiol, prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormones (FSH), and free and total testosterone (FT and TT; (Reis *et al.* 2010).

Reis and colleagues suggested that weight loss after gastric bypass (group A) improves erectile function and hormonal activity in morbidly obese men to a greater extent than with a non-surgical method (group B) to reduce weight. Erectile dysfunction is considered to be a reversible complication of obesity (Reis *et al.* 2010). A strong association was found between body weight and erectile function, with morbidly obese men showing the same degree of sexual dysfunction as non-obese men 20 years older (Kolotkin *et al.* 2003). Men represent about 20% of patients who go through bariatric surgery (Dallal *et al.* 2008).

In addition, some of the causes of peripheral vascular disease are insulin resistance and obesity, due to atherosclerosis and endothelial dysfunction (Borges *et al.* 2009). Both are recognised as risk factors for erectile dysfunction

(Demir *et al.* 2006). After weight loss there is an improvement in sexual function because of improvement in insulin resistance (Esposito *et al.* 2004). Since bariatric surgery improves insulin resistance through weight reduction, erectile dysfunction was expected to improve after bariatric surgery (Wickremesekera *et al.* 2005). However, the improvement in erectile function after bariatric surgery is not clear cut (Ranasinghe *et al.* 2011).

In contrast, other studies (Dallal *et al.* 2008) and (di Frega *et al.* 2005) show six patients who went through gastric bypass and developed erectile dysfunction. It was suggested that the reason was zinc deficiency due to malabsorption of nutrients after gastric bypass surgery. Males showed no significant improvement in urinary incontinence (UI) with surgically induced weight loss (Ranasinghe *et al.* 2011). Furthermore, while erectile function did not improve after LGB, it trended towards worsening with time (Ranasinghe *et al.* 2011).

Esposito and colleagues measured, through randomised controlled trials, the effect of lifestyle changes on erectile dysfunction in 110 obese men (BMI >30 kg/m^2) who had erectile dysfunction and did not have comorbidities such as diabetes or hypertension. On a very low calorie diet, they showed improvement in erectile function, assessed by IIEF. This improvement was independent of weight reduction (Esposito *et al.* 2004).

1.4.1.2 Studies on obesity and urological function

The occurrence and development of urological diseases depends on several factors, including obesity (Mydlo 2004), which has been shown to be a risk factor for stress and mixed urinary incontinence (Kuruba *et al.* 2007) and diabetes (Ranasinghe *et al.* 2011). Moreover, Lee and colleagues have reported that increased waist circumference is associated with worsened voiding function and pelvic dysfunction (Lee *et al.* 2012).

Kuruba *et al* (2007) prospectively collected data from 201 patients between 2004 and 2006 that underwent bariatric surgery. Urinary incontinence was improved in 82% of patients after surgery (Kuruba *et al.* 2007). Similarly, Burgio

et al (2007) showed that urinary function improved between three and four months after LGB (Burgio *et al.* 2007). However, both studies were on female patients.

In contrast, Ranasinghe and colleagues (2011) examined, in a retrospective study, the effects of weight loss following laparoscopic gastric banding surgery (LGB) on urinary incontinence in both male and female patients. However, no improvement in urinary function, despite weight loss after LGB, was observed in males (Ranasinghe *et al.* 2011).

1.4.2 Proposed mechanisms linking obesity to urogenital dysfunction

As noted in various studies, obesity has been strongly linked with the development of ED (Traish *et al.* 2009).

Demir et al. (2009) have shown that 96.5% of obese males who suffer from metabolic syndrome (MetS) had ED. Furthermore, comparable studies found that 43% of men suffering from ED also had MetS, and the severity of ED worsened with MetS (Bansal *et al.* 2005). It is interesting to note that insulin resistance (IR) also had a significant impact on the severity of ED. Therefore, ED signifies a significant risk factor and could potentially be a clear indicator of IR and MetS, both of which can result in the risk of CVD. Moreover, men who had moderate to severe ED also had the most severe cases of MetS (22-70%).

Whether obesity is related to ED independently, or through cardiovascular risk factors, obese men are more than likely to suffer from ED, which impacts on their sexual life. (Andersen *et al.* 2008) explored the association between ED and obesity in men who were aged between 20 and 45, and found that obesity is directly related to ED in younger males. Furthermore, another study found that men with a BMI greater than 28.7 are 30% more at risk of ED, compared to those with a typical BMI of 25 (Kuo 2007, Bacon *et al.* 2003).

The association between ED and obesity can be explained by the increased levels of various pro-inflammatory cytokines in obese people (Traish *et al.*

2009). However, these authors admit that obesity might be directly associated with the aetiology of ED, and they discovered that obese males, irrespective of their BMI, besides leading inactive lifestyles, were at a far greater risk of developing ED. Although the health risks associated with obesity are more common among people with extreme abdominal obesity, which can cause dysfunction by releasing pro-inflammatory cytokines, the potential relationship between obesity and ED requires further investigation (Esposito *et al.* 2004, Després 2006).

However, another study (Esposito *et al.* 2004) found that men who were given advice about the ways in which they can effectively lose weight and achieve weight loss of 10% or higher by lowering their calorie intake and increasing their physical activity, had improved ED compared to controls. Therefore, this is good advice for men who suffer from ED, since obesity is clearly associated with ED, and weight loss alone can show signs of improvement (Bacon *et al.* 2003). However, (Teloken *et al.* 2006) points out those previous studies have failed to clearly demonstrate that “obesity is a risk factor for ED” and thus they call for more research to be carried out to clarify this association.

Androgen deficiency, which is a medical condition where the body has reduced levels of male hormones, has been found to be associated with insulin resistance (IR) and T2DM, and thus contributes towards ED (Ginsberg *et al.* 2000, Cersosimo *et al.* 2006). Also, Corona *et al*. (2009) point out that obesity is directly related to lower androgen levels in men who suffer from ED, and that obesity related comorbidities, particularly hypertension, are considered significant causes of arteriogenic obesity-related ED. On the other hand, it also seems that central obesity in particular has a strong relationship with the reduction in circulating androgen levels. Even though androgens are vital to typical erectile function, a healthy lifestyle, reducing calorie intake, and increasing exercise, are all factors that contribute towards improved erectile function in men who suffer from ED (Traish *et al.* 2009).

Despite the above studies focussing on the strong relationship between obesity and ED, additional research is required to affirm whether individual symptoms of

MetS, such as hypertension, have a strong relationship with ED. In a study by (Zohdy *et al.* 2007), 158 obese men were tested and correlated MetS and androgen deficiency with ED. The results show that men with higher BMIs had increased hypogonadism and ED. In contrast, men who were given testosterone therapy for their androgen deficiency showed significant improvement in their erectile function (Yassin *et al.* 2006, Kurbatov *et al.* 2008).

The relationship between obesity and ED has also been shown to include another mechanism whereby obesity might contribute to infertility in both men and women (Hammoud *et al.* 2006). In a study by (Feldman *et al.* 2000), 79% of men who reported symptoms of ED were in fact not only obese, but suffered from cardiovascular problems, and infertility. Furthermore, research has pointed out that the association between obesity and ED can be partly justified through increased levels of various pro-inflammatory cytokines in obese people (Esposito *et al.* 2004, Després 2006, Esposito *et al.* 2005). These signs of inflammation have a strong connection with endothelial dysfunction, which is directly related to ED through the nitric oxide pathway. Therefore, it is unclear whether this relationship is because of an independent effect or because of CVD risk factors that are common to both ED and obesity (Hammoud *et al.* 2006). Furthermore, other risk factors leading to cardiovascular disease, such as diabetes, smoking, dyslipidaemia and hypertension, all have a strong epidemiological connection with ED. (Seftel 2006) found that hypoandrogenism is the main contributor towards sexual dysfunction in males suffering from obesity. Moreover, irrespective of whether obesity is related to ED independently or through CVD risk factors or hypoandrogenism, men who suffer from obesity are highly likely to develop ED, especially if they are above the age of 40, which will impact on their fertility and sexual life (Hammoud *et al.* 2006).

(Esposito *et al.* 2005) and (Esposito *et al.* 2006) studied 55 obese and 55 non-obese males and the impacts of weight loss programs on ED over a two year period. They found that 31% of males did see improvement in ED as a result of weight loss, irrespective of age. Therefore, despite the scepticism of such programs failing to deliver weight loss for its user, they do seem effective for

obese males suffering from ED (Traish *et al.* 2009). Additionally, many studies have pointed out that obesity might be an important independent risk factor for ED (Esposito *et al.* 2004, Traish *et al.* 2009, Hammoud *et al.* 2006), and thus weight loss programs, among other remedial mechanisms are required to help reduce this prevalent risk.

On reflection, with the ever increasing prevalence of inactive lifestyles and dietary reforms, obesity is now the most significant cause of adverse health outcomes, which include CVD, infertility, MetS and ED, among other conditions (Hammoud *et al.* 2006). Therefore, healthy lifestyle choices are essential in order to overcome or at least reduce the risk of developing these conditions, thus leading to a better quality of life. (Esposito *et al.* 2006) have shown that a "Mediterranean Diet", which is a diet in which foods such as vegetables, fruits, nuts, beans, cereal grains, olive oil and fish are eaten on a daily basis, can significantly improve men's health. The results from the study further indicate that ED improved in men suffering from MetS on this diet, thereby increasing erectile function, particularly in older men (Traish *et al.* 2009, Esposito *et al.* 2006).

Even though ED may be seen as an indicator for MetS, as previously mentioned, the association between these two conditions is difficult to determine, since the mechanisms of MetS symptoms like hypertension, are also clearly important in the aetiology of ED. (Riedner *et al.* 2006) also discovered that various assessment parameters associated with central obesity can also be used to estimate the likelihood of developing ED.

1.4.3 Effect of bariatric surgery on urogenital function

1.4.3.1 Animal models

Various studies using diabetic rat models, and especially T2DM models, show that vasodilatory signalling is damaged through a reduction in neuronal NOS (nNOS) content/activity, impaired endothelial NOS (eNOS) activity, cavernosal hypercontractility, oxidative stress, androgen deficiency and neuronal

dysfunction, amongst other factors. Together, these alterations are considered potential mechanisms that underlie the development of ED (Jesmin *et al.* 2003, Hidalgo-Tamola *et al.* 2009).

In a study by Choi and co-workers (2014), a T2DM rat model was assessed in which they investigated the impact of duodenojejunal bypass surgery on glucose homeostasis. In the control group that was kept on a standard diet with 15% fat, a reduced glucose homeostasis was observed, resulting in both microvascular and structural damage (Zhiqing *et al.* 2014). Furthermore, there were reduced levels of eNOS and nNOS expression, while there was an increase in Rho kinase expression in rats suffering from diabetes that were given the sham operation, as opposed to those rats who were given bariatric surgery, thereby resulting in vascular dysfunction and cavernosal smooth muscle atrophy. As a result of these structural modifications, ED was improved in the bariatric surgery group, (Choi *et al.* 2014). Glucose homeostasis recovery was also detected, which resulted in metabolic and biochemical restoration, a reduction in the level of Rho kinase expression, and an increased level of eNOS and nNOS expression. This microvascular structural restoration resulted in macrostructural recovery, thereby leading to functional recovery.

Apoptosis and DNA and intracellular damage, which result in fibrosis in the corpus cavernosum has been shown to be caused by reactive oxygen radicals. Choi *et al*. (2014) found that rats who underwent the bariatric procedure exhibited reduced 8-OHdG levels, which is a clear sign of DNA oxidative stress, demonstrating that such procedures may reduce oxidative stress related to T2DM in the penile corpus cavernosum (Choi *et al.* 2014). Further changes were also observed in the penile corpus cavernosal structure in both the control and bariatric surgery groups. T2DM resulted in a reduction in smooth muscle and definitive cavernosal fibrosis in the control group, while rats had a higher amount of smooth muscle fibres in the cavernosal tissue in the bariatric surgery group (Oberbach *et al.* 2014). Therefore, such procedures can possibly reduce cavernosal fibrosis in diabetes. Moreover, these results show that bariatric surgery also enhances glucose homeostasis accompanied by biochemical

factors, thus resulting in both functional and structural improvements in the corpus cavernosum and leading to better erectile function (Palleschi *et al.* 2015, Luke *et al.* 2015).

1.4.3.2 Clinical studies

Several studies evaluating sexual function after bariatric surgery have been published to date, as described in section 1.4.1.1 (Reis *et al.* 2010, Dallal *et al.* 2008, Esposito *et al.* 2004, Ranasinghe *et al.* 2011).

Dallal and colleagues reported an improvement in sexual function at two years after gastric bypass surgery, using the Brief Male Sexual Function Inventory (BMSFI; (Dallal *et al.* 2008). Moreover, Hammoud and colleagues (2009) showed an improvement in sexual function after gastric bypass surgery, by using the Impact of Weight on Quality of Life (IWQOL-L) questionnaire (Hammoud *et al.* 2009). Reis and colleagues (2010) also showed an improvement in sexual function in men who underwent gastric bypass surgery, using the short version of the IIEF questionnaire (IIEF-5; (Reis *et al.* 2010). Finally, Mora and colleagues (2013) showed an improvement in sexual function in 39 men that underwent gastric sleeve surgery, using the full version of the IIEF questionnaire (IIEF) before and at one year after surgery (Mora *et al.* 2013).

In contrast, Ranasinghe and colleagues (2011) failed to demonstrate a significant change in the score of each of the 5 IIEF sexual domains in patients who underwent the adjustable gastric banding procedure and were evaluated at three years post-surgery (Ranasinghe *et al.* 2011).

The disagreement between the Dallal, Reis and Mora studies and the Ranasinghe study might be due to the variations in the tools used in the studies, such as the biomedical tests, the questionnaires, period of the study, and the number of participants that took part in the study (Reis *et al.* 2010, Dallal *et al.* 2008, Mora *et al.* 2013). Also, there is possible influence from the study design and the medical centre type: primary, secondary or tertiary and the number of

medical centres participating (single or multi-centre). Overall, the evidence for improvement of erectile function in males after bariatric surgery is debatable. The results do not show a statistically significant improvement in sexual function. On the contrary, there was a worsening of erectile function (EF), orgasmic function (OF), sexual desire (SD), intercourse satisfaction (IS), overall satisfaction (OS) and IIEF total score after bariatric surgery (Reis *et al.* 2010, Dallal *et al.* 2008, Ranasinghe *et al.* 2011, Mora *et al.* 2013). However, Dallal and colleagues (2008) demonstrated significant improvement in all aspects of the Brief Male Sexual Function Inventory (BMSFI; $p< 0.0005$ in all aspects; (Dallal *et al.* 2008, Mora *et al.* 2013).

Ranasinghe and colleagues (2011) found no improvement in IIEF total score ($p= 0.70$) despite a significant weight loss ($p<0.0001$) after gastric band (Ranasinghe *et al.* 2011). Thus, the initial findings from this study do not support that bariatric surgery is associated with the improvement of sexual function in morbidly obese men in the short term. Nevertheless, the total numbers of patients with true sexual dysfunction in the study were low and so were the numbers of patients with severe sexual dysfunction in each domain. The lack of a control group in the study prevents the assessment of the prevalence of impaired sexual function in patients who did not undergo bariatric surgery over time.

Numerous studies evaluating urological function after bariatric surgery have been published recently (Palleschi *et al.* 2015, Luke *et al.* 2015, Schouten *et al.* 2013). Luke and co-workers (2015) evaluated the effects of bariatric surgery on lower urinary tract symptoms (LUTS); patients undergoing bariatric surgery with LUTS were assessed using the IPSS and weight, serum glucose, insulin and prostate-specific antigen (PSA) levels were also noted. The study suggested there was an improvement in LUTS after weight loss but there was no correlation between the improvement in LUTS and the time course or degree of weight loss. Also the study suggests that the improvement in symptoms is linked to the improvement in insulin resistance (Luke *et al.* 2015).

Palleschi *et al* (2015) suggest that overactive bladder (OAB) syndrome may improve in morbidly obese patients who were treated by laparoscopic sleeve gastrectomy (LSG) (Palleschi *et al.* 2015).

Schouten *et al* (2013) evaluated the prevalence of perioperative urinary incontinence and bladder retention after laparoscopic gastric bypass surgery in sixty morbidly obese female patients. The study concludes there were no differences between the patients with and without postoperative incontinence in relation to age, body mass index and presence of diabetes mellitus (Schouten *et al.* 2013).

1.5 Study rationale, aims and objectives

1.5.1 Rationale

Within the past decade, obesity has become a significant health issue in the UK. In spite of this, the number of people with obesity continues to rise. In 2008, roughly 34% of the UK population was obese, which is up from less than 20% a decade ago (NHS Information Centre 2014), thus making the UK the fifth most obese country in the developed world. Indeed, McQuigg *et al.* (2005) concluded that weight management interventions should be a public health priority to alleviate the burden of disease in the general population (McQuigg *et al.* 2005). Furthermore, the effect of obesity on the National Health Service (NHS) is a concern of the Department of Health, and it is estimated that the disease currently costs the NHS over £4bn each year (NICE 2014). Obesity-related morbidity and mortality has a significant impact on individuals' quality of life with associated risks such as cancer and cardiovascular disease and places a large burden on the NHS (Randall *et al.* 2014). Furthermore, obesity has known links to hypertension, diabetes, cardiovascular disease and urogenital dysfunction, all of which have a substantial impact on health services (Ranasinghe *et al.* 2011). Lower urinary tract symptoms, diabetes mellitus, obesity, inactive lifestyle and hypertension are all risk factors for erectile dysfunction (ED) which is a strong predictor for cardiovascular and coronary artery diseases due the multifactorial aetiology of the disease that interacts with many organs to complete the

erection process (Shamloul *et al.* 2013). As a result of this multifactorial aetiology it may be hard to define the factors involved in developing ED. Although the baseline characteristics of patients with ED are well characterised, the effect of obesity, in particular, on the incidence of ED has not been clarified (Mydlo 2004).

Therefore, the aim of the first audit was to assess the effect of BMI on urogenital function using the IPSS in men over 18 and to collate and analyse other baseline characteristics such as age, smoking status and medical history. This is the first assessment of the baseline characteristics of patients with ED at University College London Hospital (UCLH).

Moreover, bariatric surgery is one of the treatment options that is able to provide significant weight loss, prolonged life expectancy, and improve a number of co-morbidities of obesity, like hypertension, T2DM and urogenital dysfunction. Furthermore, there are limited studies into the relationship between obesity and male urogenital function, since there have only been a few studies that have been published studying patients who suffer from morbid obesity, or a BMI of 40 or above. For those reasons, this study has been driven by the desire to understand the ways in which bariatric surgery may have an impact on sexual and urological dysfunction in men.

Specifically, the short-term effect of bariatric surgery on erectile and urological function is under studied. As mentioned in this chapter, the effect of bariatric surgery on blood glucose can precede the effect on body weight. Accordingly, the effect of bariatric surgery on erectile and urological function prior to weight loss has not been studied. This is particularly interesting as this gives an opportunity to assess whether the improvement in erectile and urological function is due to glycaemic improvement or due to weight loss and its associated effects.

The aim of this project is therefore to study the short term (four weeks post-operation) and longer term (three and six months post-operation) effects of bariatric surgery on the urological and erectile function of men with morbid

obesity as seen in Figure 1-14. It is hypothesised that there could be two possible outcomes:

First outcome; if the recovery of erectile function occurs early (i.e. before weight loss; as depicted with a red broken line in (Figure 1-14)) in parallel with normalised blood glucose, this proposes that the improvement of blood glucose has more impact than body weight on pathophysiology of urogenital dysfunction.

Second outcome; if the recovery of EF occurs later (i.e. in parallel to weight loss; as depicted with a broken black line in (Figure 1-14)), this suggests that body weight is as important as, if not more than, the normalisation of blood glucose.

The effect of bariatric surgery on erectile function (Reis *et al.* 2010) has been studied in obese men with T2DM but none of those studies have investigated the effect in the short term (i.e. before weight loss occurs).

Currently, the effect of bariatric surgery on bladder function is unknown. Therefore, this study will be the first to investigate the short term effects on the urogenital function which will permit interrogation of the link between insulin resistance and urogenital dysfunction in men with morbid obesity during the early post-operative stages, so as to fill the gap in the literature.

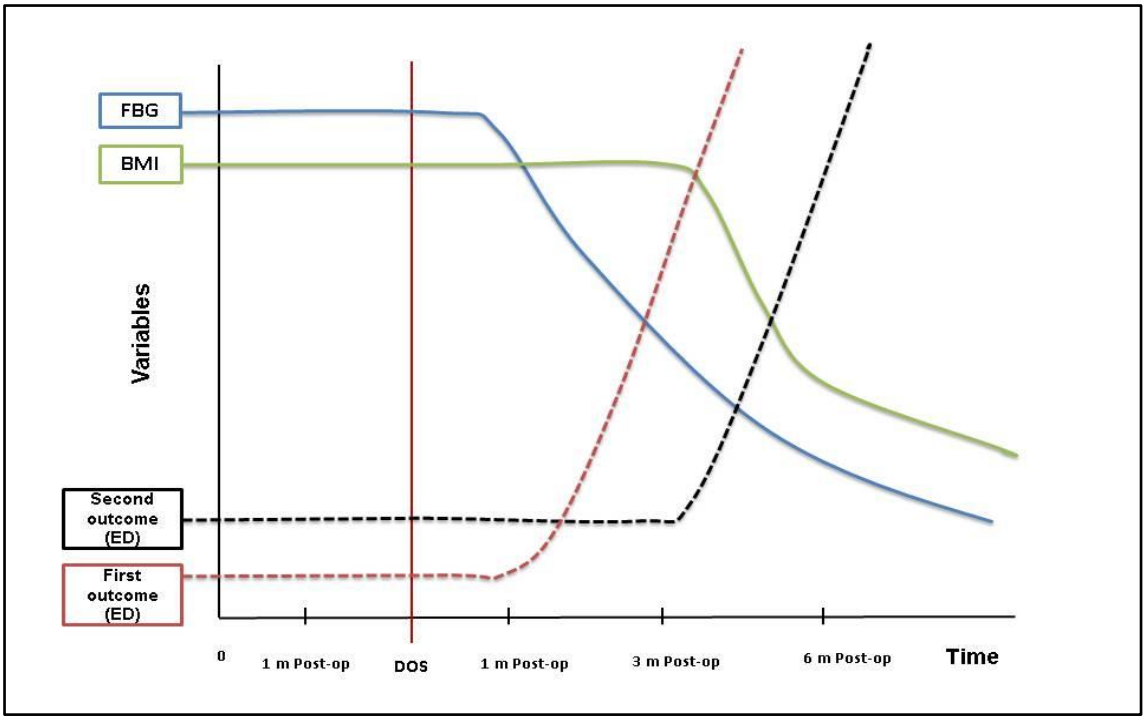


Figure 1-14: Study rationale scheme.
Blue solid line (FBG); the expected changes in blood glucose level (Pournaras *et al.* 2010). Green solid line (BMI); the expected changes in body weight (Nijamkin *et al.* 2012). Red solid line (DOS); indicates day of the bariatric surgery. Red broken line indicates the first outcome (reversible ED); expected reversal of ED in parallel with normalisation of blood glucose. Black broken line indicates the second outcome (irreversible ED); expected reversal of ED in parallel with weight loss.
1m pre op: one-month pre-operation; DOS: day of surgery; 1m post-op: one month post-operation; 3m post op: three months post-operation; 6m post op: six months post-operation.

1.5.2 Aims and objectives

The overall aim of the proposed research is to evaluate the baseline characteristics of patients with erectile dysfunction and to determine the impact of bariatric surgery on erectile and urological function in morbidly obese men by conducting two separate clinical audits and analysing the audit data at different time points.

1.5.2.1 Objectives

1. To conduct an initial audit to investigate the baseline characteristics of men over 18 years of age and attending the urological clinic at UCLH using IIEF and IPSS questionnaires.

2. Perform an audit to explore the effect of BMI on urogenital function in men over 18 years of age and attending the urological clinic at UCLH using IIEF and IPSS questionnaires.
3. To collate and analyse other baseline characteristics such as age, smoking status, and medical history.
4. To conduct a second audit to investigate the effect of bariatric surgery on the urogenital function and BMI of morbidly obese men over 30 years of age and BMI of 35 and over.
5. To analyse the urogenital function and biomarker data acquired in the second audit to assess the effect of bariatric surgery on urogenital function and recommend further work based on these analyses.

2 METHODS

The following chapter sets out the details of the research methodology undertaken to support this thesis. It describes the approach and the primary purpose of the two clinical audits performed. Details are given of each of the processes required for the use of two questionnaires: the international index of erectile function, or IIEF (Rosen *et al.* 1997) and the international prostate symptom score, or IPSS (Plante *et al.* 1996). Ethical considerations are provided in sections 2.1.4 and 2.2.4. The necessary statistical analyses used to address the study questions are explained in sections 2.1.5 and 2.2.5. All documentation relating to this process, including patient information sheets and approval letters can be found in Appendix B.

2.1 Audit of baseline characteristics of urogenital function

According to the National Institute for Health and Care Excellence (NICE) and the Healthcare Commission, clinical audits can be described as a quality improvement process which aims to improve patient care and outcomes by carrying out a systematic review of care according to specific criteria and the subsequent adjustment to the previous process that is carried out (Copeland 2005).

Performing a good audit requires both time and sufficient funding, whether the audit is prospective or retrospective.

Time is assigned by most NHS trusts to implement the presentation of audits and allow room for discussion. Importantly, the sample chosen for the audit should be sufficiently small to allow for rapid data acquisition, but big enough to ensure that the data is representative (Copeland 2005).

2.1.1 Baseline characteristics audit design

The baseline characteristics audit was designed as a prospective cohort study, set up to investigate the effect of BMI on urological function and its role in the management of urological diseases, in response to predicted trends in health

care and gaps identified in the existing literature. A cohort study classically examines multiple health effects from an exposure; subjects are defined according to their exposure levels and followed for disease occurrence (Weiss *et al.* 2014). The baseline characteristics audit was organised around two research questions: (1) “what are the baseline characteristics of patients with erectile dysfunction?” (2) “are there any effects of obesity on urological conditions?”

The audit was set up and conducted over a nine month period between June 2014 and March 2015, involving patients with any urological condition, in attendance at the urology clinic at University College London Hospitals (UCLH).

The study was conducted using a multidimensional scale for assessment of erectile dysfunction the IIEF (Rosen *et al.* 1997), and the IPSS (Plante *et al.* 1996). Additional information was acquired from patients’ records using the UCLH database.

2.1.2 Baseline characteristics audit setting

This audit was carried out at the urology department, surgical specialities, UCLH in accordance with the requirements of the research governance frameworks. The audit complied with all reporting requirements, systems and duties of action put in place by the trust.

2.1.3 Patient recruitment

The patients participating in the baseline characteristics audit were recruited at the UCLH Urology clinics for either treatment of ED or other urological conditions such as infertility (controls).

2.1.3.1 Study population

UCLH delivers first class general and specialist services to both local patients and those from throughout the UK and abroad. The hospital has 665 inpatient beds and 12 operating theatres. The hospital is located on Euston Road in the

Fitzrovia area of the London Borough of Camden. The hospital provides acute services to the local populations of Camden, Islington, Barnet, Enfield, Haringey and Westminster. Over 950,000 outpatients, over 125,000 accident and emergency attendances and over 156,000 patients are admitted each year (University College London Hospitals, NHS Foundation Trust, 2015). From the patients who have been listed to attend the urological clinic at the UCLH, there is a high proportion aged above 45, and the patient sample in this audit reflects this point.

2.1.3.2 Recruitment of participants

All patients who have been or are newly diagnosed with erectile dysfunction or transferred from GP practices with other urological problems were selected using the clinical data repository (CDR) at the UCLH. Those patients who met the inclusion and exclusion criteria have been included in the audit.

Inclusion criteria:

- Patients were required to be listed for attending one of the urological clinics at UCLH.
- Patients were also required to be able to read, speak and understand English due to the non-availability of interpreters throughout the audit period.
- Patients were required to be between 18 and 75 years old.

Exclusion criteria:

- Patients were excluded if they were considered by the clinician to be too unwell to take part in filling in the questionnaires.
- Patients were excluded if they had another serious illness such as a neurodegenerative disease or cancer.

- Any patients who were younger than 18 and older than 75 were excluded.

In order to safeguard patient confidentiality, Mr Asif Muneer and Mr David Ralph were responsible for the recruitment process to comply with the research governance framework at UCLH NHS Trust. The prospectively collected data from those patients who attended the urology clinics for ED from June 2014 to March 2015 were analysed. During this period, sixty patients met the inclusion and exclusion criteria and were asked to complete the two questionnaires voluntarily.

2.1.3.3 The patient recruitment process and data collection

The NHS network and clinical data repository (CDR) system database was accessed via one of the NHS computers at the urology department, UCLH in order to identify patients who met the audit inclusion and exclusion criteria. A list of patients who met the inclusion and exclusion criteria was then given to the surgeons (Mr. Asif Muneer and Mr. David Ralph) who made the final selection according to the audit inclusion and exclusion criteria and accordingly recruited the patients, and then gave the NHS patient ID number of the recruited patients to the researcher.

In the Urology Clinic, the researcher accessed the patient information using one of the NHS computers and created a unique identifier for the recruited patients (BC001, BC002, BC003…)[10]. The surgeons or fellows who recruited the patients gave the patients the two questionnaires (see Appendix A) and information sheet (see Appendix B) and undertook the biochemistry and haematology requests as per standard of care.

Due to the requirements for patient confidentiality, the participating urologist and not the researcher, invited the patients to participate in the audit and

[10] BC stands for baseline characteristics.

administered the questionnaires**.** The researcher then received the completed anonymous questionnaires directly from the urologists. The patients were asked not to put their names or any other personal information on the questionnaires to ensure the study was totally anonymised. The only data that were transferred to Cranfield University were two completed questionnaires (IIEF and IPSS) as well as age, body mass index (BMI), smoking status, medical history and blood chemistry values. No subject identifiable data were transferred.

The researcher created an Excel spreadsheet which links the unique identifier (assigned by the researcher) to the NHS patient ID that complies with the honorary audit assistant authority. The file that links the NHS patient ID and researcher's unique identifier was kept in the NHS system at all times. No other copy was created. This file has never been taken out of the NHS system. Another spreadsheet was stored on the researcher's laptop where each patient had a unique identifier, along with the results of the questionnaires and clinical data. Neither the NHS patient ID nor any other personally identifiable data were kept in this file/folder. This file was kept on the researcher's laptop which is password protected. The folder and file have their own passwords. Moreover the file is encrypted using 128 advance encryption standard as recommended (UCL Library Services 2015).

Hard copies (paper) of all questionnaires were locked away at Cranfield University. The data collection process followed UCL/UCLH standards under the NHS data protection policy (UCL Library Services 2015).

2.1.3.4 Assessment of baseline blood chemistry and haematology

A complete blood profile test, requested by one of the audit team, was used to assess participants' overall blood chemistry. Venous blood was drawn from the study participants following UCLH guidelines by an experienced member of staff (Table 2-1) (Appendix A).

Table 2-1: List of items that were investigated in the blood test.

Biochemistry tests	Haematology tests
Fasting blood glucose	White cells count
HbA1c	Red cell count
Prolactin	Haemoglobin
Testosterone [a]	HCT (Haematocrit test)
Free testosterone [b]	MCV (Mean corpuscular volume)
Bioavailable testosterone [b]	MCH (Mean corpuscular haemoglobin)
FSH (Follicle stimulating hormone)	MCHC (Mean corpuscular haemoglobin concentration)
TSH (Thyroid stimulating hormone)	RDW (Red blood cell distribution width)
FT4 (Free T4)	Platelet count
Alkaline phosphate	MPV (Mean platelet volume)
Alkaline transaminase	Neutrophils
Total bilirubin	Lymphocytes
Albumin	Monocytes
LH (Luteinising hormone)	Eosinophil
Sodium	Basophils
Potassium	
Creatinine	
ESR (Erythrocyte sedimentation rate)	
Urea	
Estimated GFR (Glomerular filtration rate)	
Cholesterol	
Triglyceride	
HDL (High density lipoprotein)	
LDL (Low density lipoprotein)	
Cholesterol: HDL ratio	
SHBG (Sex hormone binding globulin)[a]	

[a] Additional tests (not part of the UCLH routine) requested by the surgeon.
[b] Parameters calculate separately using albumin, SHBG and testosterone serum values (de Ronde *et al.* 2006).

2.1.4 Ethical considerations

Ethical approval to conduct this audit was obtained from Cranfield University Health Research Ethics Committee (CUHREC; Appendix B) in June 2014. The relevant documents were then submitted to the urology department at the UCLH NHS Foundation Trust in June 2014. The audit was then approved by the audit leads for surgical specialties and Gastrointestinal Specialties. The researcher was then able to undertake the role of an honorary audit assistant within the urology department, surgical specialties, UCLH.

The patient information sheet explained the aims of the audit and what was being asked of the patient, and stated clearly that participation in the audit was voluntary and would not affect the patient's medical care in any way. Patients were only asked to fill in the two questionnaires once they had met with the surgeon, and read and understood the information sheet (Appendix B).

2.1.5 Statistics

The research design and statistical analysis were carried out by the researcher with the statistical support from the statistics department, UCL Institute of Child Health And Great Ormond Street Hospital for Children NHS Trust.

Statistical analysis was performed by using the statistical package SPSS version 22 (SPSS Inc., Chicago, IL, USA) for Windows, to perform exploratory data analysis and produce descriptive statistics.

Normality was tested using the skewness and kurtosis test[11], the values for these parameters should be zero in an ideal normal distribution with values between -1 and +1 indicating a normal distribution (Groeneveld *et al.* 1984).

The data were also visually inspected through observation of the frequency distribution (histogram): when a histogram's shape approximates a bell-curve it suggests that the data follows a normal distribution (Ghasemi *et al.* 2012) (Figure 2-1).

The data not normally distributed when skewed to any side; positive skew when the right tail is longer, negative skew when the left tail is longer (Groeneveld *et al.* 1984).

[11]Skewness is the measurement of symmetry while kurtosis is the measurement of "peakedness" of the data (Groeneveld *et al.* 1984).

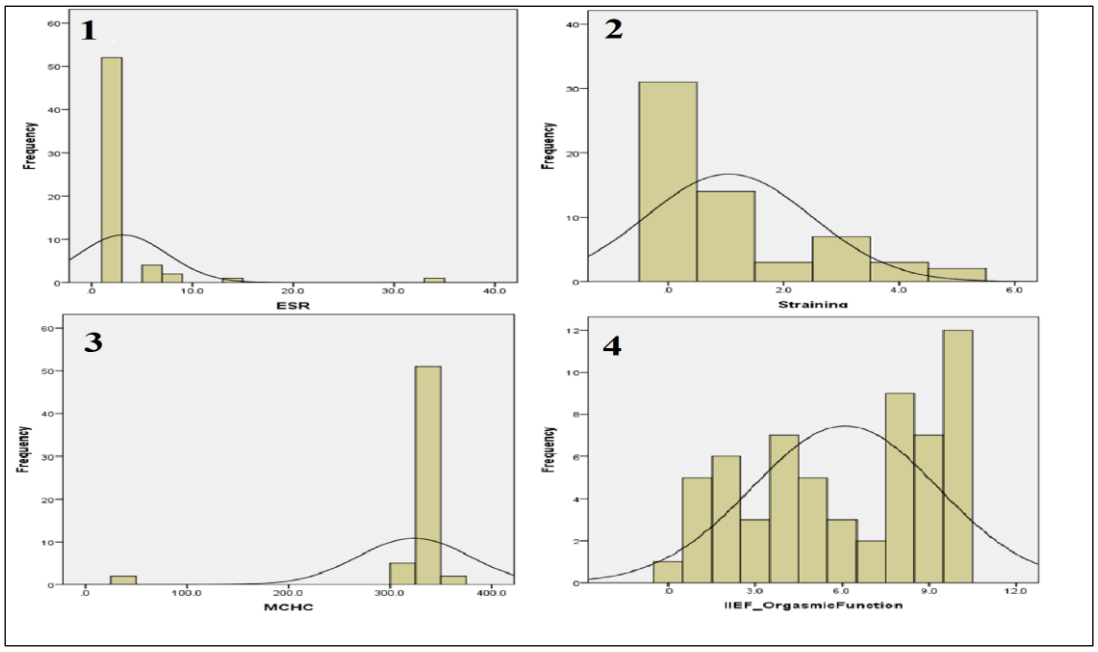


Figure 2-1: Examples of testing normality by histogram.
The data in charts (1, 2) were positively skewed (the right tail is longer of both charts), most of the distribution is concentrated on the left of the figure and chart (3) the data have a strong negative skew (the left tail is longer) most of the distribution is concentrated on the right of the figure and chart (4) the data is slightly positively skewed but considered as normally distributed.

The normally distributed data have been expressed as the mean ± standard deviation. Parametric tests were also used, such as two samples independent t-test to compare the means of two groups. Welch's t-test[12] (or unequal variances t-test) was used to test the hypothesis that two populations have equal means but unequal variances and unequal sample sizes (Ruxton 2006). While, chi-squared test (X^2) was used to calculate the variances of the presence of the medical conditions; Fisher's exact test was used for the same purpose but when the sample size of the variances were smaller than seven patients per medical condition (Petrie *et al.* 2013) and the level of significance was $p<0.05$ (Altman

[12] Welch's t-test (or unequal variances t-test) are two-sample tests of difference, in populations that have equal means. Welch's t-test is an adaptation of Student's t-test, and is more reliable when the two samples have unequal variances and unequal sample sizes (Ruxton 2006).

1990). Pearson correlation coefficient was used to investigate any association between the normally distributed variables (Petrie *et al.* 2013).

Not normally distributed data have been expressed as the median and the interquartile range (IQR)[13] also called middle fifty. The non-parametric tests were used to explore the differences in blood test values between the ED group and NO-ED group, Mann Whitney U test[14] was used to perform this calculation and the level of the significance was $p<0.05$ (Altman 1990). Spearman's correlations[15] were utilised to assess the predictors of sexual and urological functions. The correlation analysis was performed using the IIEF and IPSS scores as dependent variables, and age, BMI, comorbidities and blood tests as independent variables.

[13] IQR is the measurement of variability, based on dividing a data set into quartiles. Quartiles divide a rank-ordered data set into four equal parts. The values that divide each part are called the first, second, and third quartiles; and they are denoted by Q1, Q2, and Q3, respectively (Kokoska *et al.* 2000).

[14] Mann–Whitney *U* test is a nonparametric test that is used for two samples that come from the same population but one population is likely to have larger values than the other whereas t-test can only be applied on normal distributions (Petrie *et al.* 2013).

[15] Spearman's rank correlation coefficient or Spearman's (rho) is a nonparametric measurement of the statistical dependence between two variables and is defined as the Pearson correlation coefficient between ranked variables (Corder *et al.* 2014).

2.2 Bariatric surgery audit

The bariatric surgery audit was conducted as a prospective planned audit for surgical specialities at University College London hospitals, NHS foundation trust, in collaboration with the urology and the bariatric surgery units.

The UCLH bariatric centre for weight management and metabolic surgery centre was opened in July 2007 and is now a major obesity and bariatric centre in the United Kingdom. The centre offers comprehensive medical and surgical services for the treatment of adolescents and adults with obesity. The service has a multidisciplinary approach, including three specialist consultant surgeons, two consultant physicians, psychiatrists, psychologists, clinical nurse specialists, and dieticians. Anaesthetic support is provided by a team of five bariatric anaesthetists (NHS- Services 2015). The centre sees about 700 new patients per year and operates on around 360 of these patients (NHS- Services 2015). Morbidly obese male patients scheduled to undergo bariatric surgery were approached before the operation by the bariatric nurse at the specialist clinic and were invited to take part in the audit. The audit was carried out by the centre for weight loss, metabolic and endocrine surgery, surgical specialities, UCLH. The participants were recruited by Mr Majid Hashemi, bariatric surgery fellows and the bariatric nurse specialist. The audit complied with all reporting requirements, systems and duties of action put in place by the UCLH- NHS Trust.

Patients were required to be listed for attending a bariatric clinic with one of the following surgeons at UCLH; Mr Majid Hashemi, Mr Marco Adamo, Mr Andrew Jenkinson, Prof Nicolas Finer and Mr Mohamed Elkalaawy.

2.2.1 Inclusion and exclusion criteria

Inclusion criteria:

- Patients were required to be listed for bariatric surgery at UCLH.

- Patients were also required to be able to read, speak and understand English due to the non-availability of interpreters throughout the audit period.

- Patients were required to be aged 30 years or older.

Exclusion criteria:

- Patients were excluded if they were considered by the clinician to be too unwell to take part in filling in the questionnaires.

- Patients were excluded if they had another serious illness such as a neurodegenerative disease or cancer.

- Patients younger than 30 and older than 75 were excluded.

Participants were given questionnaires and had their weight and height measured and were referred for basic blood tests by a member of the research team one month before surgery as well as one, three and six months after the surgery.

2.2.2 Patient recruitment process and data collection:

Patients who met inclusion and exclusion criteria listed above were selected using the clinical data repository (CDR) system at UCLH. A list of patients who matched the inclusion and exclusion criteria was then given to the surgical team. In order to protect patient confidentiality and abide by ethical considerations, Mr Majid Hashemi or one of the bariatric surgery team, and not the researcher recruited the patients. However, all responsibilities and roles of the honorary audit assistant were undertaken by the researcher to comply with the research governance framework of the UCLH NHS trust. The data were collected from February 2013 to July 2015.

In order to safeguard patient confidentiality, the surgeon or nurse specialist, and not the researcher, invited the patients by giving out the questionnaires (Appendix A). The researcher then received the completed anonymous

questionnaires directly from the surgeon, surgical fellow or bariatric nurse specialist. The patients were asked not to put their names or any other personal information on the questionnaires and the audit was therefore totally anonymised. The only data that were transferred to Cranfield University were two completed questionnaires (IIEF, IPSS), as well as age, BMI, medical history and blood chemistry values. No subject identifiable data were transferred.

When a patient agreed to take part in the audit, the researcher gave the patient a unique identifier number (001, 002, 003…). This identifier number was written at the top of the questionnaires before they were given to the patient. The researcher created a file that linked the unique identifier number to the NHS identifier number. No copies were made of this file and the file has never left UCLH system in order to comply with the UCL's information security policy (UCL Library Services 2015).

The data from the anonymised questionnaires and blood tests were collected on a spreadsheet by the researcher. This file was kept on the laptop which was double password protected. The folder and file had their own passwords. Moreover, the file is encrypted using 128 advance encryption standard as recommended by the NHS (UCL Library Services 2015). Hard copies (paper) of all questionnaires were kept in a locked cupboard at Cranfield University. The data collection process followed UCL/UCLH standards under the NHS data protection policy (UCL Library Services 2015).

2.2.3 Bariatric surgery audit design

The audit was designed as a prospective cohort study which was set up to investigate the impact of bariatric surgery on patients' sexual and urological function. It was conducted between February 2013 and July 2015 with male patients who underwent surgery and follow-up for gastric bypass, sleeve gastrectomy or gastric band at UCLH.

Audit patients were divided in to three groups according to their sexual activity.

The first group was the erectile dysfunction group (ED), patients were considered to have ED if the IIEF-EF score was below 25.

The second group was the non-erectile dysfunction group (NO-ED); patients were defined as not having ED when their EF score was equal to, or greater than 25.

The third group was the control group, consisting of patients who were listed for surgery, but whose surgery was abandoned during the operation due to the discovery of a large cirrhotic liver and a poor response to standard liver shrinkage. It was therefore deemed unsafe to proceed with the operation. As a result of the abandoned surgery, these patients enrolled in the POLER programme (prolonged preoperative weight loss programme), and were then listed for a second attempt at surgery. The patients were restricted to 1100 calories per day: 95 g protein, 100 g carbohydrates and 20 g fat from semi skimmed milk fortified with milk powder, Fybogel (medication to relieve constipation), multivitamins and fluid with at least one salty drink a day.

The audit aimed to determine the effect of bariatric surgery on male patients' body mass index (BMI), urological symptoms, and sexual function.

2.2.3.1 Assessments

2.2.3.1.1 Initial assessments (one stop assessment clinic)

The first assessment took approximately 4 hours. The patient was assessed by the dietician, clinical nurse specialist and surgeon; the patient may also have been seen by a physician at this visit. The patients were asked a number of questions about medical history, weight loss history and eating habits. They were also provided with information to help them choose the operation which best suited their expectations, lifestyle, eating habits, medical condition and physical anatomy. The average time elapsed between the first assessment appointment and the day of the surgery was around 8 months; the minimum time taken was 3 months. During this period additional studies may have been required, such as sleep studies (i.e. to screen for obstructive sleep apnoea);

psychological assessment (i.e. some patients were seen by the psychologist for more personalised support) or physician support (i.e. some patients were required to undergo a medical review).

After the first assessment patients' cases were discussed at the multidisciplinary team (MDT) meeting and patients were informed of the team's decision regarding surgery after this meeting by mail (Figure 2-2).

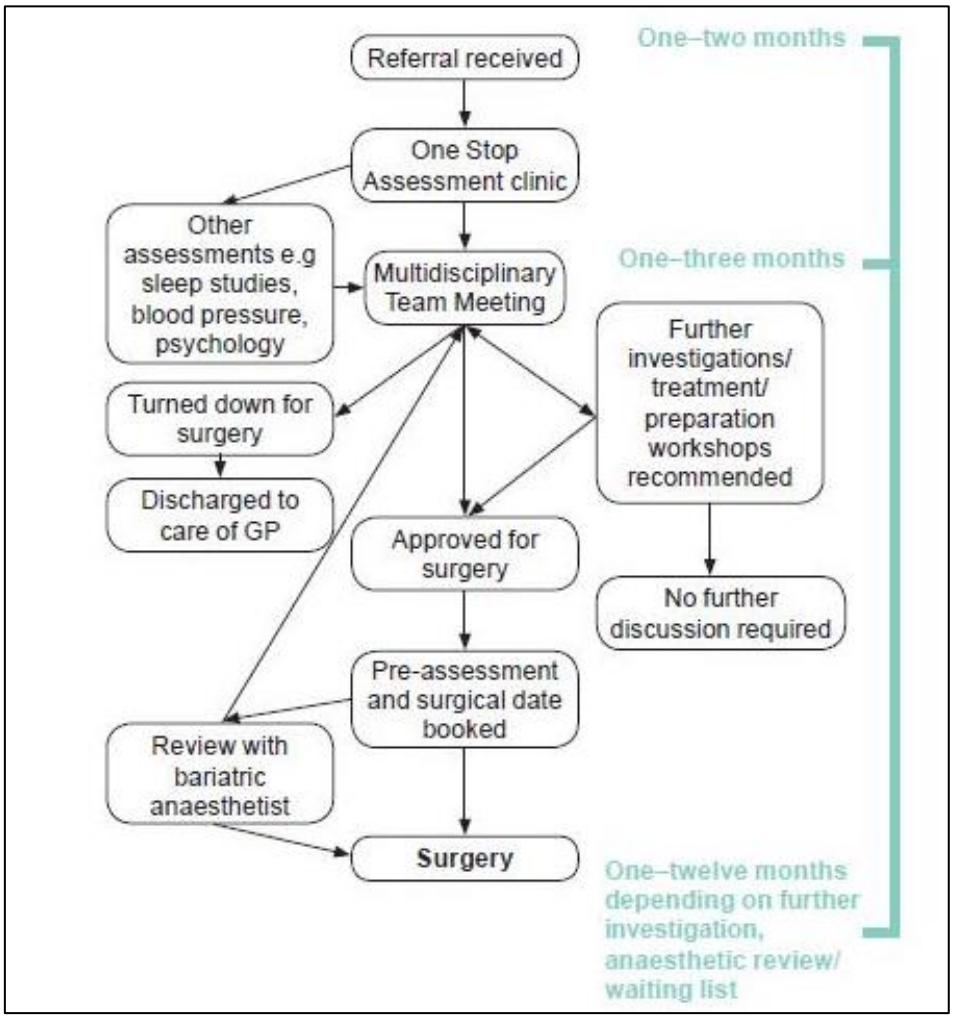


Figure 2-2: The plan of bariatric surgery (NHS- Services 2015)**.**
According to the NICE guidelines, the eligible candidates should be referred from the primary care for bariatric surgery. The initial assessment offered a range of alternative interventions in an attempt to give the patients a chance to lose weight and improve their comorbidities, which usually takes from one to three months until the candidate is approved for surgery by the MDT. All patients will have undergone a pre-assessment, then booked a date for surgery. This process takes up to 12 months depending on further investigation. After the surgery, the patient is referred back into the primary care service for continued follow-up if necessary (NHS-Services 2015).

2.2.3.1.2 Pre-assessment

Patients attended a presentation to help them prepare for surgery and this assessment was run by the bariatric nurse specialist one month prior to the surgery. Patients were asked to have a blood test, an electrocardiogram (ECG) and a breathing test performed during the appointment and some patients were referred to the anaesthetist.

2.2.3.1.3 Assessment of sexual function

Sexual function was assessed using the 15 questions in the International Index of Erectile Function (IIEF; Appendix A) (Rosen *et al.* 1997), in the same way as the previous audit (see section 1.2.5).

2.2.3.1.4 Obesity assessment

The choice of surgical procedure performed during the audit (see section 1.1.6) was based on specific selection criteria: patients with BMI >35 kg/m^2 and listed for bariatric surgery; the patient must be aged or over 30, and they must have no other serious illness such as cancer or neurodegenerative diseases currently diagnosed.

Obesity was measured by using the body mass index (BMI; kg/m^2). The BMI score was used to compare and analyse the health effects of body weight on human bodies of all heights (NHS Choices information 2013).

The audit also used the percentage of excess weight loss (%EWL) to describe weight loss after bariatric surgery, and 25 kg/m^2 was used as the upper limit for a normal BMI (Welbourn *et al.* 2014). The formula used to calculate %EWL is shown on page 19. The baseline for %EWL calculations was taken as the weight one month prior to surgery (T1).

2.2.3.1.5 Assessment of urinary functions

Urinary function was assessed using the seven questions of the International Prostate Symptom Score (IPSS; (Plante *et al.* 1996).

The quality of life due to urinary conditions was assessed using the last question in the IPSS questionnaire, to analyse the impact of urinary function on daily living, and the answers assigned ranged from ‘delighted’ to ‘terrible’ (Appendix A).

2.2.3.2 Follow- up

The patients were administered the IIEF and IPSS questionnaires after the bariatric procedure at the one, three and six month post-surgery visits. As a part of their routine clinical follow-up, the blood tests were repeated either during their follow-up visit or one day before to give fasting blood test results.

Table 2-2: Plan of the follow-up appointments of bariatric surgery patients.

Follow-up appointments after surgery	Appointment with	Questionnaires administered
4 weeks	nurse specialist	IIEF and IPSS
8 weeks	nurse specialist	
12 weeks	dietician	IIEF and IPSS
6 months	nurse specialist	IIEF and IPSS
9 months	dietician	
12 months	nurse specialist or surgeon or dietician	
Yearly	member of the team	

2.2.4 Ethical considerations

Ethical approval to conduct the audit was obtained from Cranfield University Health Research Ethics Committee (CUHREC; Appendix B) in February 2013 (Project reference No 03.13: on 13th February 2013). The relevant documents were then submitted to the urology department within UCL hospitals NHS Foundation Trust in February 2013. The researcher undertook the role of an honorary audit assistant within the centre for weight loss, metabolic and endocrine surgery, surgical specialties, surgery and cancer board, UCLH.

The patient information sheets explained the aims of the study and what was being asked of the patient, and clearly stated that participation in the study would not affect the patient's medical care in any way. Patients were only asked to complete two questionnaires once they had met with the surgeon or one of the audit members, and read and understood the information sheet (Appendix B).

2.2.5 Statistics

Statistical analysis methods used in this audit were the same as those used for the baseline characteristics audit described in section 2.1.

The time-points used were: baseline or one month pre-operation (T1), one month post-operation (T2), three months post-operation (T3), and six months post-operation (T4) Changes in the variables across the time-points were assessed by Friedman's test, which is the non-parametric alternative to the parametric one-way repeated measures ANOVA by ranks (Corder *et al.* 2014). It aims to test the differences between two groups (ED, NO-ED) based on the mean rank differences of the groups amongst the three time points (T2, T3 and T4). The probability distribution of Friedman's test was calculated by chi-squared (X^2) and p values; p values <0.05 were considered significant (Altman 1990).

Wilcoxon signed rank test[16] is also a non-parametric test which was used to compare repeated measurements between the two groups (ED and NO-ED groups) and between two time points to compare their population mean ranks (Corder *et al.* 2014).

[16] Wilcoxon signed rank test can be used as an alternative to the paired Student's t-test in normally distributed samples (Corder *et al.* 2014).

3 RESULTS

This chapter presents the analysis of questionnaires and other parameters from two audits; the baseline characteristics of urogenital function and bariatric surgery impact on urogenital functions.

3.1 Baseline characteristics of urogenital function audit

3.1.1 Data distribution

The distribution of the data was analysed and the skewness test was performed with cut-off values of -1 and +1. If the skewness test result was < -1 or > +1, the data was considered to be not normally distributed (Table 3-1).

Table 3-1: Test of normality for baseline characteristics of urogenital function audit (N=60).

Descriptive statistics						
Variable	**Minimum**	**Maximum**	**Median**	**Mean**	**Skewness test**	**Normality**
Age	22.0	67.0	47.5	46.2	-0.1	**Yes**
Weight (kg)	57.4	110.3	81.9	83.9	0.3	**Yes**
Height (cm)	158.4	192.7	173.4	174.4	0.2	**Yes**
BMI	20.1	38.4	26.4	27.6	0.9	**Yes**
Fasting blood glucose	3.7	26.8	4.9	5.4	7.1	No
HbA1c	27.0	102.0	36.0	38.2	4.1	No
Prolactin	99.0	291.0	160.5	181.6	0.3	**Yes**
Testosterone	4.7	44.0	17.1	18.0	1.5	No
Free testosterone	0.1	6.1	0.3	0.5	5.1	No
Bioavailable testosterone	0.3	29.0	6.9	7.9	2.2	No
White blood cells	4.6	11.6	6.22	6.8	1.0	No
Red blood cells	3.5	5.7	5.15	5.0	-0.8	**Yes**
Haemoglobin	97.0	171.0	151.5	151.0	-1.3	No
HCT	0.3	0.5	0.5	0.6	-0.9	**Yes**
MCV	81.2	95.2	90.8	90.2	-0.7	**Yes**
MCH	26.6	33.2	30.1	30.1	-0.4	**Yes**
MCHC	33.0	354.0	332.5	323.6	-5.1	No
RDW	12.1	15.5	13.4	13.6	0.5	**Yes**
Platelet count	99.0	340.0	231.0	231.3	-1.0	No

Descriptive statistics						
Variable	**Minimum**	**Maximum**	**Median**	**Mean**	**Skewness test**	**Normality**
MPV	9.9	13.7	11.6	11.6	0.6	**Yes**
Neutrophils	2.3	7.0	3.6	4.0	0.9	**Yes**
Lymphocytes	1.04	3.6	2.1	2,1	0.4	**Yes**
Monocytes	0.1	0.9	0.5	0.5	0.5	**Yes**
Eosinophil	0.04	1.0	0.2	0.2	3.4	No
Basophils	0.01	0.1	0.04	0.04	0.6	**Yes**
FSH	1.9	41.0	3.7	6.2	3.6	No
TSH	0.8	6.5	2.03	2.1	1.8	No
Free T4	1.2	23.0	14.4	14.9	-1.3	No
Alkaline phosphate	45.0	309.0	66.0	71.2	6.2	No
Alkaline transaminase	12.0	124.0	25.0	33.2	2.8	No
Bilirubin total	3.0	19.0	10.0	10.5	0.4	**Yes**
Albumin	37.0	51.0	47.0	46.6	-1.1	No
LH	1.2	18.7	4.6	5.2	2.2	No
Sodium	132.0	146.0	141.0	140.8	-0.8	**Yes**
Potassium	0.4	5.5	4.40	4.3	- 4.0	No
Creatinine	62.0	198.0	88.0	89.8	2.8	No
ESR	2.0	33.0	2.0	3.1	5.9	No
Urea	2.4	10.7	5.0	5.1	1.6	No
Estimated GFR	.00	89.0	89.0	83.0	-0.1	**Yes**
Cholesterol	3.0	9.1	4.4	4.4	3.0	No
Triglyceride	0.7	3.6	1.0	1.1	3.2	No
HDL	0.8	2.1	1.4	1.4	0.2	**Yes**
LDL	1.1	6.2	2.50	2.6	1.7	No
Ratio Cholesterol to HDL	1.7	7.0	3.3	3.4	1.3	No
SHBG	18.0	234.0	46.0	47.2	4.8	No
T2DM	0.0	1.0	0.0	0.1	2.2	No
Psoriatic Arthritis	0.0	1.0	0.0	0.03	5.3	No
Obstructive Sleep Apnoea	0.0	1.0	0.0	0.1	2.2	No
Hypercholesterolemia	0.0	1.0	0.0	0.02	5.3	No
Anxiety	0.0	1.0	0.0	0.02	7.7	No
Depression	0.0	1.0	0.0	0.1	3.5	No
Non Alcoholic Fatty Liver	0.0	1.0	0.0	0.02	7.7	No
Gout	0.0	1.0	0.0	0.02	7.7	No
Hyperlipidaemia	0.0	1.0	0.0	0.02	7.7	No
Irritable Bowel Syndrome	0.0	1.0	0.0	0.02	7.7	No
Peyronie's disease	0.0	1.0	0.0	0.1	3.5	No

Descriptive statistics						
Variable	**Minimum**	**Maximum**	**Median**	**Mean**	**Skewness test**	**Normality**
Fertility Problem	0.0	1.0	0.0	0.1	2.7	No
Proteinuria	0.0	1.0	0.0	0.02	7.7	No
Right Testicular Atrophy	0.0	1.0	0.0	0.03	5.3	No
Left Testicular Atrophy	0.0	1.0	0.0	0.02	7.7	No
Klinefelter syndrome	0.0	1.0	0.0	0.02	7.7	No
AIDS	0.0	1.0	0.0	0.02	7.7	No
Hypertension	0.0	1.0	0.0	0.03	5.3	No
Coughlan syndrome	0.0	1.0	0.0	0.02	7.7	No
Asthma	0.0	1.0	0.0	0.02	7.7	No
Hydrocele testis	0.0	1.0	0.0	0.02	7.7	No
Overweight (25 ≥ BMI<30)	0.0	1.0	1.0	0.5	-0.1	**Yes**
Morbidly obese (BMI>30)	0.0	1.0	0.0	0.3	1.1	No
Erectile function	1.0	30.0	11.0	13.8	0.4	**Yes**
Orgasmic function	0.0	10.0	6.5	6.1	-0.3	**Yes**
Sexual desire	2.0	10.0	6.0	5.5	0.1	**Yes**
Intercourse satisfaction	0.0	15.0	6.0	6.2	0.3	**Yes**
Overall satisfaction	1.0	10.0	4.5	5.1	0.4	**Yes**
IIEF total score	6.0	74.0	31.5	36.7	0.4	**Yes**
Incomplete emptying	0.0	5.0	1.0	1.7	0.8	**Yes**
Frequency	0.0	5.0	2.0	1.8	0.6	**Yes**
Intermittency	0.0	5.0	0.5	1.3	1.0	No
Urgency	0.0	5.0	1.0	1.5	0.8	**Yes**
Weak stream	0.0	5.0	1.0	1.5	0.9	**Yes**
Straining	0.0	5.0	0.0	1.1	1.3	No
Nocturia	0.0	5.0	1.0	1.7	0.9	**Yes**
QoL(Quality of life)	0.0	6.0	3.0	2.6	0.1	**Yes**
IPSS total score	0.0	32.0	8.0	10.5	0.7	**Yes**

3.1.2 Patient cohort profile: general demographics

Overall, the sample contained 60 patients. These patients ranged in age between 22 and 67 years old, with a mean (± SD) age of 46.2 ± 13.6 years (Figure 3-1)

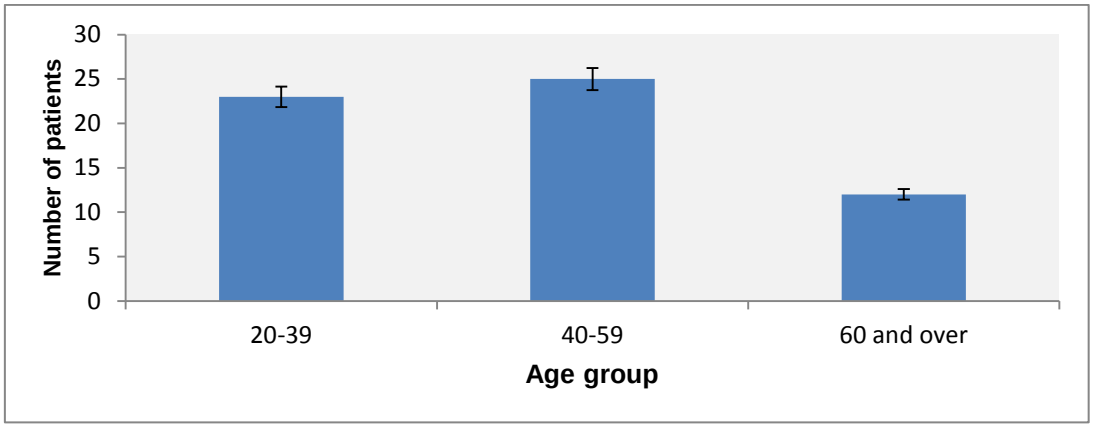


Figure 3-1: The patient cohort profile- age distribution.

Patient weight ranged between 57.4 kg and 110.3 kg and the mean weight was 83.9 ± 12.3 kg. Patient height in the sample ranged from 158.4 cm to 192.7 cm, with a mean of 174.4 ± 6.9 cm. Each patient's BMI was calculated based on weight and height (weight (kg)/height (m) ^{2}); BMI in current sample ranged from 20.1 to 38.4, with a mean of 27.6 ± 4.0 kg/m^2 (Table 3-2).

Table 3-2: Descriptive statistics of the general demographic details of patients.

	Total Sample (n=60)	
	Mean (±SD)	**95% CI**
Age (year)	46.2 (13.7)	(42.7, 49.6)
Height (cm)	174.4 (6.9)	(172.7, 176.1)
Weight (kg)	83.9 (12.3)	(80.8, 87)
BMI (kg/m^2)	27.6 (4.0)	(26.6, 28.6)

The above statistics indicate that most of the patients were overweight (25≤BMI<30). Table 3-3 outlines patient characteristics separated into two study groups (ED and NO-ED; patients who scored <25 in EF-IIEF were placed in the ED group). The results in Table 3-3 show that both of the study groups were overweight (25≤BMI<30). The two groups were compared using independent samples t-test (Welch's t- test); height was the only variable found to differ significantly between groups (Table 3-3).

Table 3-3: General descriptive statistics of the ED and NO-ED groups.

	ED [a] Group (n=48)	NO-ED [b] (n=12)	
	Mean (±SD)	**Mean (±SD)**	**p**
Age (year)	47.1 (13.7)	42.4 (13.5)	0.29[c]
Height (cm)	175.8 (6.95)	169.0 (3.3)	**0.002[c]**
Weight (kg)	84.4 (10.5)	82.0 (18.3)	0.68[c]
BMI (kg/m^2)	27.4 (3.3)	28.6 (6.2)	0.50[c]

[a] ED group when the score of the erectile function (EF) domain in the IIEF (IIEF-EF) was less than 25.
[b] NO-ED group (IIEF-EF score 25 or more).
[c] Welch's t- test.

3.1.3 Multiple medical conditions

From the medical records, it was found that 80.0% of the patients (n=48) in the current sample (n=60) suffer from erectile dysfunction (Figure 3-2). The second most common medical problem was found to be obesity (BMI over 25 kg/m^2), which affected 78.3% of the patients (n=47). Furthermore, 13.3% of the patients (n=8) had type 2 diabetes (T2DM), and a similar percentage (13.3%) had obstructive sleep apnoea (n=8). In total, 10% of the patients suffered from fertility problems (n=6). Other, rarer medical disorders (less than 10.0% of the sample) were hypercholesterolemia, psoriatic arthritis, anxiety, depression, non-alcoholic fatty liver disease, gout, irritable bowel syndrome, Peyronie's disease, proteinuria, and asthma. Moreover, 37.5% of patients (18 paitients out of 48) had ED and one additional chronic disease, and 52.1% of patients (25 paitients out of 48) had ED and two or more additional chronic diseases. The distribution of medical conditions observed in the patient group is shown in Figure 3-3. There was no difference in the incidence of these medical conditions in ED and NO-ED groups except the incidence of being overweight (BMI ≥ 25) was significantly higher in the ED group (Table 3-4; p=0.007).

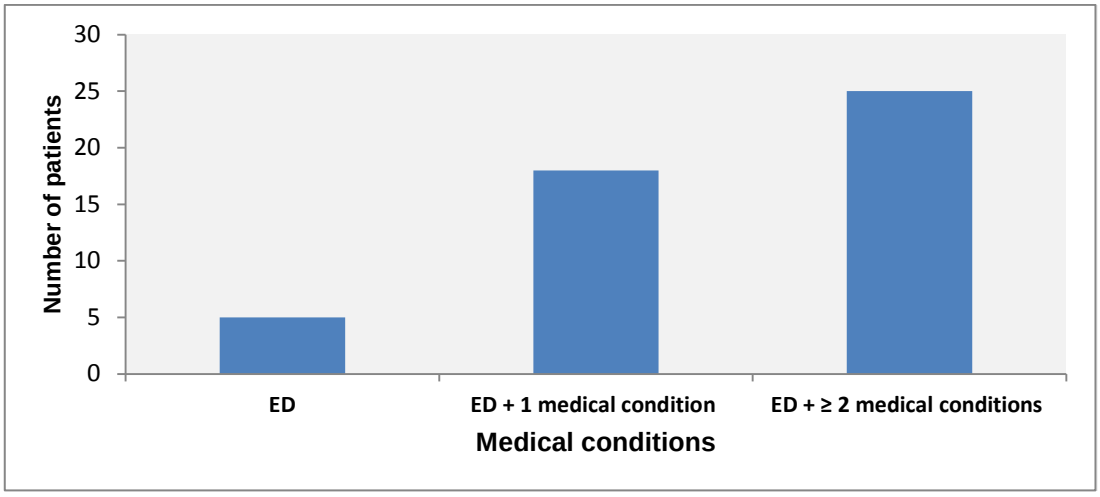


Figure 3-2: Patient distribution with ED and other medical conditions (N=48).
Distribution of the occurrence of multiple conditions according to the data derived from patients with erectile dysfunction (N=48) out of the total number (N=60).

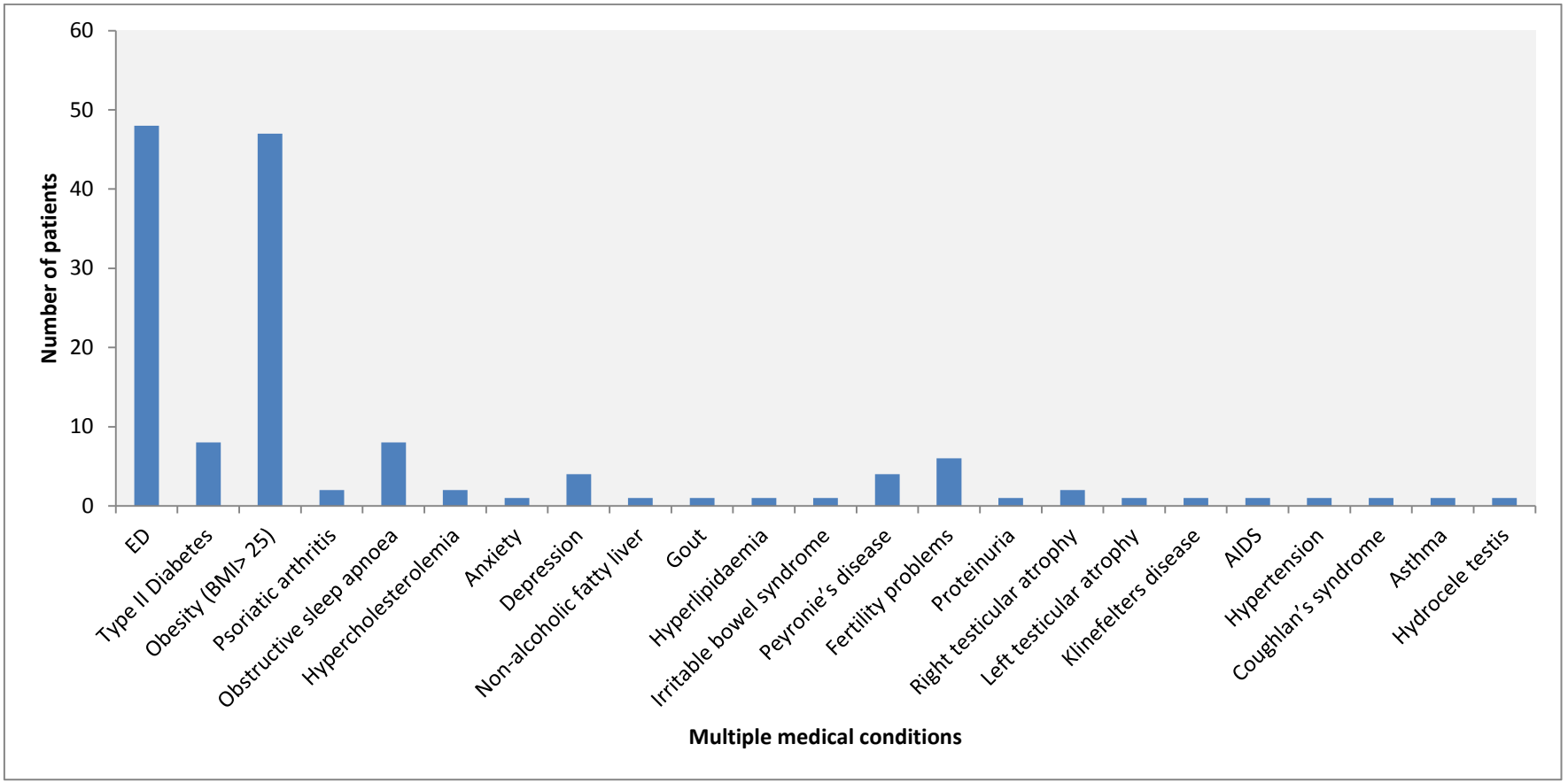


Figure 3-3: An overview of all patients showing the frequencies of multiple chronic conditions (N=60).
Distribution of multiple chronic conditions occurrence according to the data derived from patients (N=60) it was found that erectile dysfunction (ED; n=48) and obesity (BMI > 25 kg/m^2; n=47) was present in most patients. Obstructive sleep apnoea (n=8), fertility problems (n=6), Peyronie's disease (n=4) were the next most common conditions, with other medical conditions being present in only one patient per condition.

Table 3-4: Medical diagnosis differences between the ED and NO-ED groups.

Diagnosis	ED (n=48) %	NO-ED (n=12) %	difference	p[a]
Type II Diabetes	16.7	0.0	16.7	0.34
Obesity (BMI > 25 kg/m^2)	83.3	58.3	25	0.11
Psoriatic arthritis	2.1	8.3	-6.3	0.36
Obstructive sleep apnoea	16.7	0.0	16.7	0.34
Hypercholesterolemia	2.1	0.0	2.1	1.0
Anxiety	2.1	0.0	2.1	1.0
Depression	8.3	0.0	8.3	0.57
Non-alcoholic fatty liver	2.1	0.0	2.1	1.0
Gout	2.1	0.0	2.1	1.0
Hyperlipidaemia	2.1	0.0	2.1	1.0
Irritable bowel syndrome	2.1	0.0	2.1	1.0
Peyronie's disease	8.3	0.0	8.3	0.57
Fertility problems	8.3	16.7	-8.3	0.59
Proteinuria	2.1	0.0	2.1	1.0
Right testicular atrophy	4.2	0.0	4.2	1.0
Left testicular atrophy	2.1	0.0	2.1	1.0
Klinefelter syndrome	2.1	0.0	2.1	1.0
AIDS	2.1	0.0	2.1	1.0
Hypertension	4.2	0.0	4.2	1.0
Coughlan's syndrome	4.2	0.0	4.2	1.0
Asthma	2.1	0.0	2.1	0.20
Hydrocele testis	0.0	8.3	-8.3	1.0

[a] Fisher's exact test results.

3.1.4 Blood biochemistry and haematology

A total of 24 biochemistry and 15 haematology blood tests were completed for all patients. Table 3-5 to Table 3-8 presented below show descriptive statistics for these tests. As indicated previously in Table 3-1 these variables were largely non-normally distributed. The data from the biochemistry and haematology tests illustrate that all patients' blood test results were within normal ranges

(Table 3-5 and Table 3-6). There was no difference between ED and NO-ED groups with respect to any of the blood tests except testosterone levels and eosinophil counts (Table 3-7 and Table 3-8). Although both groups' serum testosterone levels were within the normal range, NO-ED group had higher average testosterone than ED group (Table 3-7; p=0.038). However, there was no difference between ED and NO-ED groups in terms of free testosterone and bioavailable testosterone levels.

Similarly, both groups' eosinophil counts were within the normal range, but the NO-ED group had higher average eosinophil counts than the ED group (Table 3-8; p=0.0033).

Table 3-5: Descriptive statistics of blood biochemistry tests for all patients.

Blood test	Median (IQR)[a]	Normal range [b]
Fasting blood glucose(mmol/L)	4.9 (4.70, 5.40)	3.9 - 5.8
HbA1c level (mmol/mol)	36.0 (34.00, 38.00)	20 - 42
Prolactin test (miu/L)	160.5 (139.50, 234.00)	86 - 324
Testosterone level (nmol/L)	17.1 (13.95, 20.03)	7.6 - 31.4
Free testosterone (nmol/L)	0.3 (0.25, 0.77)	>0.225 [c]
Bioavailable testosterone (nmol/L)	6.9 (6.7, 9.1)	61-213 (ng/dL)[d]
SHBG (nmol/L)	46.0 (35.50, 51.00)	16-55
FSH (IU/L)	3.6 (2.90, 6.13)	1.5 - 12.4
TSH (miu/L)	2.0 (1.40, 2.66)	0.2 - 4.0
Free T4 (pmol/L)	14.4 (13.40, 16.90)	10 - 20
Alkaline Phosphate (IU/L)	66.0 (57.00, 75.00)	40- 129
Alkaline transaminase (IU/L)	25.0 (23.00, 35.25)	10- 50
Bilirubin total (umol/L)	10.0 (7.25, 13.00)	0- 20
Albumin (g/L)	47.0 (45.00, 48.00)	34- 50
Luteinising Hormone (LH) (IU/L)	4.5 (3.13, 5.80)	1.7-8.6
Sodium (mmol/L)	141.0 (139.00, 142.75)	135-145
Potassium (mmol/L)	4.4 (4.10, 4.60)	3.5- 5.1
Creatinine (umol/L)	88.0 (78.50, 92.00)	66- 112
ESR (mm/hr)	2.0 (2.00, 2.00)	0-20
Urea (mmol/L)	5.0 (4.30, 5.68)	1.7- 8.3
Estimated GFR (ml/min/1.73 sqm)	89.0 (78.25, 90.00)	90 - 120
Cholesterol (mmo/L)	4.4 (4.03, 4.80)	2.5 - 5
Triglyceride (mmo/L)	1.0 (0.90, 1.20)	0.4 - 2.3

Blood test	Median (IQR)[a]	Normal range [b]
HDL Cholesterol (mmo/L)	1.4 (1.20, 1.60)	0.9 - 1.5
LDL Cholesterol (mmo/L)	2.5 (2.13, 2.90)	0 - 3.5
Cholesterol: HDL ratio	3.3 (2.50, 3.80)	

[a] The interquartile range (IQR).
[b] Normal range of blood tests according to the UCLH standards.
[c] According to the BSSM guidelines (2010), there are no accepted lower limits of free testosterone for the diagnosis of hypogonadism. However, a free testosterone level below 0.225 nmol/l can provide supportive evidence for treatment with testosterone (Wylie *et al.* 2010).
[d] Reference value for age 40-49 (Thrower *et al.* 2013).

Table 3-6: Descriptive statistics of blood haematology tests for all patients (N=60).

Variable	Median (IQR)	Normal range [a]
White blood cells (10^9/L)	6.22 (5.18 - 7.34)	3-10
Red blood cells (10^9/L)	5.15 (4.80 - 5.34)	4.4-5.8
Haemoglobin (g/dL)	15.15 (14.17 – 16.1)	13- 17
HCT (L/L)	0.46 (0.43 - 0.48)	0.37- 0.5
MCV (fL)	90.80 (87.40 - 92.68)	80- 99
MCH (Pg)	30.10 (29.50 - 30.80)	27- 33.5
MCHC (g/dL)	33.25 (32.92 – 34.0)	32- 36
RDW %	13.40 (13.10 - 14.10)	11.5 -15
Platelet (10^9/L)	231.00 (214.00 - 259.75)	150- 400
MPV (fL)	11.45 (10.83 - 12.10)	7-13
Neutrophils (10^9/L)	3.62 (2.99 - 4.50)	2-7.5
Lymphocytes (10^9/L)	2.10 (1.81 - 2.41)	1.2- 3.65
Monocytes (10^9/L)	0.47 (0.41 - 0.58)	0.2- 1
Eosinophil (10^9/L)	0.16 (0.10 - 0.20)	0.0- 0.4
Basophil (10^9/L)	0.04 (0.02 - 0.05)	0.0- 0.1

[a] Normal range of blood tests according to the UCLH standards.

Table 3-7: Blood biochemistry tests: Statistical comparison between the ED and NO-ED groups.

Variable/Blood test	ED (n=48)	NO-ED (n=12)	
	Mean (±SD)[a] Median (IQR)[b]	Mean (±SD)[a] Median (IQR)[b]	p
Fasting blood glucose(mmol/L)	5.0 (4.7, 5.4)	4.8 (4.4, 5.2)	0.24
HbA1c level (mmol/mol)	36.0 (34.6, 39.6)	35.5 (32.0, 36.6)	1.00
Prolactin test (miu/L)	178.2 (±53.7)	195.5 (±49.5)	0.31
Testosterone level (nmol/L)	16.2 (13.1, 19.1)	18.1 (16.4, 24.8)	**0.038**

Variable/Blood test	ED (n=48)	NO-ED (n=12)	
	Mean (±SD)[a] Median (IQR)[b]	Mean (±SD)[a] Median (IQR)[b]	p
Free testosterone (nmol/L)	0.3 (0.2, 0.9)	0.3 (0.2, 0.4)	0.69
Bioavailable testosterone (nmol/L)	6.9 (6.6, 9.5)	6.8 (5.0, 9.6)	0.86
SHBG (nmol/L)	45.0 (30.0, 51.0)	47.5 (39.8, 55.8)	0.36
FSH (IU/L)	3.6 (2.8, 6.1)	5.2 (3.1, 6.4)	0.23
TSH (miu/L)	2.0 (1.4, 2.7)	1.89(1.39, 2.64)	0.78
Free T4 (pmol/L)	14.8 (13.4, 16.9)	14.4 (14.1, 16.8)	0.86
Alkaline Phosphate (IU/L)	66.0 (58.0, 75.0)	62.0 (53.0, 77.8)	0.31
Alkaline transaminase (IU/L)	25.0 (22.0 , 41.3)	29.0 (25.0, 32.5)	0.29
Bilirubin total (umol/L)	10.5 (±3.6)	10.4 (±4.6)	0.96
Albumin (g/L)	47.0 (45.0, 48.0)	46.5 (46.0, 48.0)	0.92
Luteinising Hormone (LH) (IU/L)	4.4 (3.0, 5.8)	5.1 (4.5 , 7.8)	0.09
Sodium (mmol/L)	140.7 (±3.4)	141.4 (±1.7)	0.45
Potassium (mmol/L)	4.4 (4.1, 4.6)	4.5 (3.9, 4.6)	0.96
Creatinine (umol/L)	88.0(74.0, 92.0)	89.5 (87.3, 98.3)	0.13
ESR (mm/hr)	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)	0.13
Urea (mmol/L)	5.1 (4.3, 5.7)	4.6 (3.7, 5.8)	0.36
Estimated GFR	83.0(±12.3)	83.3 (± 8.0)	0.92
Cholesterol (mmo/L)	4.40(4.10, 4.80)	4.35(3.70, 4.58)	0.26
Triglyceride (mmo/L)	1.0 (0.9, 1.2)	1.0 (0.9, 1.0)	0.34
HDL Cholesterol (mmo/L)	1.4 (±0.3)	1.3 (±0.2)	0.45
LDL Cholesterol (mmo/L)	2.5 (2.3, 3.0)	2.3 (2.1, 2.7)	0.10
Cholesterol: HDL ratio	3.4 (2.4, 3.8)	3.2 (2.6, 3.7)	0.61

[a] Independent two samples t-test (parametric test for normally distributed samples).
[b] Mann-Whitney U test (nonparametric test for non-normally distributed samples).

Table 3-8: Haematology tests: Statistical comparison between the ED and NO-ED groups.

Variable	ED (n=48)	NO-ED (n=12)	
	Mean (±SD)[a] Median (IQR)[b]	Mean (±SD)[a] Median (IQR)[b]	p
White blood cells (10^9 /L)	6.2 (5.18 - 7.36)	6.2 (5.07 - 7.31)	0.73
Red blood cells (10^9 /L)	5.0 (± 0.5)	5.0 (± 0.4)	0.80
Haemoglobin (g/dL)	155.5 (141.45 - 162.75)	149.0 (142.25 - 153.0)	0.37
HCT (L/L)	0.5 (±0.06)	0.5 (± 0.03)	0.57
MCV (fL)	90.4 (± 3.2)	89.5 (±2.4)	0.34
MCH (Pg)	30.1 (1.3)	29.7 (1.0)	0.30
MCHC (g/dL)	332.5 (329.25 - 339.75)	332.0 (326.50 - 341.0)	0.50
RDW %	13.7 (±0.8)	13.4 (± 0.6)	0.22

Variable	ED (n=48)	NO-ED (n=12)	
Platelet (10^9/L)	230.5 (214.00 - 260.00)	240.0 (216.50 - 253.0)	0.77
MPV (fL)	11.5 (±0.9)	11.7 (±0.9)	0.51
Neutrophils (10^9/L)	4.1 (±1.4)	3.6 (±0.9)	0.32
Lymphocytes (10^9/L)	2.1 (±0.6)	2.1 (±0.2)	0.90
Monocytes (10^9/L)	0.5 (±0.2)	0.5 (±0.2)	0.43
Eosinophil (10^9/L)	0.15 (0.08 - 0.18)	0.20 (0.15 - 0.85)	**0.004**
Basophil (10^9/L)	0.04 (±0.02)	0.04 (±0.02)	0.84

[a] Independent two samples t-test.
[b] Mann-Whitney U test.

3.1.5 International Index of Erectile Function (IIEF) results

All patients were asked to complete and answer 15 questions about their sex life over four weeks prior to the test. The data from the IIEF questionnaire were normally distributed. The results of this questionnaire are presented in Table 3-9. In all domains there was a significant difference between NO-ED and ED groups (P<0.05).

Table 3-9: Descriptive statistics of IIEF results for the ED and NO-ED groups.

Variables	ED (n=48)	NO-ED (n=12)	p
	Mean (±SD)[a]	Mean (±SD)[a]	
Erectile function	11.0 (± 7.7)	25.0 (± 8.9)	**<0.001****
Orgasm function	5.5 (± 3.3)	8.5 (± 1.5)	**0.003***
Sexual desire	4.9 (± 2.3)	7.5 (± 2.2)	**0.001***
Intercourse satisfaction	5.1 (± 3.8)	10.5 (± 4.3)	**<0.001****
Overall satisfaction	4.5 (± 2.6)	7.7 (± 2.9)	**<0.001****

[a] Independent two samples t-test.
* $p < 0.005$
** $p \leq 0.001$

3.1.6 International Prostate Symptom Scale (IPSS) results

The IPSS total score was generated from 7 sub-domain scores as seen in section 1.3.6. IPSS total scores ranged between 0 and 35. Results for the total score and the seven sub-domains of the IPSS are presented in Table 3-10. Data from the IPSS questionnaire were normally distributed except for

intermittency and straining which were not normally distributed. No statistically significant differences between NO-ED and ED groups were observed in any of the IPSS domains (Table 3-10).

Table 3-10: Descriptive statistics of IPSS results for the ED and NO-ED groups, with statistical comparison between groups using the Mann-Whitney U test.

Variables	ED (n=48)	NO-ED (n=12)	p
	Mean (±SD)[a] Median (IQR)[b]	Mean (±SD)[a] Median (IQR)[b]	
Incomplete emptying	1.7 (±1.7)[a]	1.7 (±2.0)[a]	1.0
Frequency	1.9 (±1.6)[a]	1.6 (±1.1)[a]	0.58
Intermittency	0.0 (0.00, 2.00)[b]	2.0 (0.00, 3.00)[b]	0.16
Urgency	1.4 (±1.5)[a]	1.4 (±1.4)[a]	0.89
Weak stream	1.6 (±1.6)[a]	1.3 (±1.7)[a]	0.63
Straining	0.0 (0.00, 1.00)[b]	1.0 (0.00, 2.75)[b]	0.37
Nocturia	1.8 (±1.4)[a]	1.2 (±1.1)[a]	0.15
Q o L	2.7 (±1.8)[a]	2.4 (±2.0)[a]	0.70
IPSS total	10.5 (±8.7)[a]	10.5 (±8.2)[a]	0.99

[a] Mean and standard deviation, independent two samples t-test was used (parametric test for normally distributed samples).
[b] Median and IQR, Mann-Whitney U test was used (nonparametric test for non-normally distributed samples).

3.1.7 Correlations between different variables

All possible correlations between any of the variables were tested. All of the results are shown in Figure 5-1, Appendix C. The significant correlations are listed in Table 3-11 below and the detailed analysis of these correlations is also presented.

Table 3-11: List of significant correlations between variables in baseline characteristics of urogenital function audit

Number of the variables in (Appendix C)	**Significant correlation between variables, p<0.05**

Number of the variables in (Appendix C)	**Significant correlation between variables, p<0.05**
1 -69	Age - IIEF-OF
1 - 68	Age – IIEF- EF
1 - 70	Age – IIEF-SD
4 -70	BMI- IIEF-SD
4 -72	BMI- IIEF- OS
8 -68	Testosterone - IIEF-EF
8 -70	Testosterone - IIEF-SD
8 – 69	Testosterone - IIEF-OF
8 – 72	Testosterone - IIEF- OS
13 – 73	MCV - IPSS-Incomplete emptying
13 – 75	MCV - IPSS- Intermittency
13 – 78	MCV- IPSS- Straining
14 -75	MCH - IPSS- Intermittency
14 – 78	MCH - IPSS- Straining
15 – 70	MCHC - IIEF-SD
15 – 73	MCHC - IPSS-Incomplete emptying
16 – 77	RDW - IPSS- Weak stream
19 – 70	Neutrophils - IIEF-SD
19 - 74	Neutrophils - IPSS- Frequency
20 – 74	Lymphocytes - IPSS- Frequency
22 – 68	Eosinophil - IIEF-EF
22 – 71	Eosinophil - IIEF- IS
26 – 80	Free T4 - IPSS- QoL
31 - 70	LH - IIEF-SD
33 – 75	Potassium - IPSS- Intermittency
33 – 76	Potassium - IPSS- Urgency
35 -68	ESR - IIEF-EF
35 – 69	ESR - IIEF-OF
35 -71	ESR - IIEF- IS
35 – 77	ESR - IPSS- Weak stream
65 -74	Smoker - IPSS- Frequency
68-29	IIEF-EF- Total Bilirubin
76-37	IPSS- Urgency- Estimated GFR
76-79	IPSS- Urgency - IPSS- Nocturia
77 – 37	IPSS- Weak stream - Estimated GFR
79 - 68	IPSS- Nocturia - IIEF-EF
79 - 72	IPSS- Nocturia - IIEF- OS
82 - 26	Free testosterone - Free T4

Number of the variables in (Appendix C)	Significant correlation between variables, p<0.05
82 – 45	Free testosterone - Psoriatic arthritis
82 – 61	Free testosterone - Hypertension
82 – 66	Free testosterone - Overweight (25 ≥ BMI<30)
83 – 49	Bioavailable testosterone - Depression
83 - 61	Bioavailable testosterone - Hypertension

3.1.7.1 Correlation between erectile function and obesity

As the data were normally distributed, Pearson correlation coefficients were used to investigate whether patients who are considered overweight or obese (BMI >25kg/m^2) have different scores in IIEF and IPSS compared to those who are not overweight or obese. A significant correlation was found between sexual desire and BMI (p=0.01). Furthermore a significant correlation was also observed between overall satisfaction and BMI (p=0.01) as seen on Table 3-12.

Table 3-12: Correlation between IIEF domains and BMI (N=60).

IIEF domain	Pearson correlation	p
Erectile function	0.12	0.4
Orgasmic function	0.06	0.7
Sexual desire	0.33	**0.01**
Intercourse satisfaction	0.16	0.2
Overall satisfaction	0.32	**0.01**

When the two groups (ED and NO-ED) were analysed, the correlation between sexual desire domain and BMI remained significant for both groups while the correlation between overall satisfaction and BMI was lost when analysing either group individually (Table 3-13).

Table 3-13: Correlation between BMI and IIEF domains in the ED and NO-ED groups.

IIEF domains and BMI	Pearson correlation		p[a]
	ED (n=48)	NO-ED (n=12)	
Erectile function	-0.04	0.25	0.4
Orgasm function	-0.01	0.12	0.7
Sexual desire	0.30	0.40	**<0.001**
Intercourse satisfaction	0.01	0.32	0.2
Overall satisfaction	0.16	0.16	0.9

[a] Independent two samples t-test was used (parametric test for normally distributed samples).

3.1.7.2 Correlation between IPSS domains and obesity

The IPSS results indicated no significant correlation between any of the IPSS domains and BMI when all patients were taken into consideration (Table 3-14).

Table 3-14: Correlation between IPSS domains of and BMI (N=60).

IPSS domain	Spearman's correlation [a] Pearson correlation [b]	p
Incomplete emptying	0.10[b]	0.5
Frequency	-0.10[b]	0.5
Intermittency	-0.06 [a]	0.7
Urgency	-0.12 [b]	0.3
Weak stream	-0.12 [b]	0.9
Straining	-0.05 [a]	0.7
Nocturia	-0.12 [b]	0.4
QoL	-0.14 [b]	0.3
IPSS total score	-0.10 [b]	0.6

[a] Spearman's rho correlation was used as non-parametric test.
[b] Pearson correlation was used as parametric test.

When the patient cohort was split into ED and NO-ED groups, the lack of correlation remained unchanged (Table 3-15).

Table 3-15: Correlation between BMI and IPSS domains in the ED and NO-ED groups.

IPSS domains and BMI	Spearman's correlation [a] Pearson correlation [b]		p
	ED (n=48)	NO-ED (n=12)	
Incomplete emptying [a]	0.02[a]	0.23[a]	0.9[c]
Frequency [a]	-0.14[a]	-0.05[a]	0.5[c]
Intermittency [b]	-0.13[b]	-0.10[b]	0.4[d]
Urgency [a]	-0.17[a]	-0.08[a]	0.9[c]
Weak stream [a]	0.07[a]	-0.27[a]	0.7[c]
Straining [b]	-0.04[b]	-0.14[b]	0.2[d]
Nocturia [a]	-0.11[a]	-0.20[a]	0.2[c]
Q o L [a]	-0.08[a]	-0.30[a]	0.9[c]
IPSS total [a]	-0.05[a]	-0.04[a]	0.8[c]

[a] Spearman's rho correlation was used as non-parametric test.
[b] Pearson correlation was used as parametric test.
[c] Mann-Whitney U test was used (nonparametric test for not normally distributed samples).
[d] Independent two samples t-test was used (parametric test for normally distributed samples).

3.1.7.3 Correlation between IIEF and IPSS domains

Correlations between any of the IIEF and IPSS domains in all patients (N=60) were investigated using Pearson correlation coefficient except for intermittency and straining where Spearman's rank correlation coefficient was used. No significant correlation was found in any of the pairs of variables except nocturia and three IIEF domains (erectile function, sexual desire and overall satisfaction) (Table 3-16). The strongest correlation was between nocturia and sexual desire (Table 3-16). Moreover, the correlations between any of the IIEF and IPSS domains in ED (N=48) and NO-ED (N=12) were investigated using independent two samples t-test for all domains except with two domains; intermittency and straining where Mann-Whitney U test was used. Significant different correlations were found between IIEF-sexual desire and IPSS-incomplete emptying, urgency and weak stream, p=0.002, p=0.004 and p=0.035 respectively (Table 3-17).

Table 3-16: Correlations between IIEF and IPSS domains (N=60).

IPSS domains	Erectile function		Orgasmic function		Sexual desire		Intercourse satisfaction		Overall satisfaction	
	r/rho	p	r/rho	p	r/rho	p	r/rho	p	r/rho	P
Incomplete emptying [a]	0.07	0.6	0.07	0.6	0.09	0.5	-0.02	0.9	0.09	0.5
Frequency [a]	-0.02	0.9	0.01	0.9	-0.08	0.5	-0.04	0.7	0.02	0.9
Intermittency [b]	0.01	0.9	0.03	0.9	-0.03	0.8	-0.02	0.9	0.09	0.5
Urgency [a]	0.01	1.0	-0.08	0.5	-0.22	0.09	0.04	0.8	-0.11	0.4
Weak stream [a]	-0.20	0.2	-0.11	0.4	-0.17	0.2	-0.20	0.1	-0.10	0.4
Straining [b]	-0.08	0.5	-0.06	0.7	-0.13	0.3	-0.06	0.6	-0.01	0.9
Nocturia [a]	-0.26	**0.046**	-0.25	0.05	-0.34	**0.008**	-0.24	0.07	-0.26	**0.045**
QoL [a]	-0.18	0.18	-0.20	0.2	-0.2	0.1	-0.12	0.12	-0.08	0.5
IPSS total score [a]	-0.08	0.6	-0.07	0.6	-0.15	0.3	-0.1	0.44	-0.06	0.

[a] Pearson correlation coefficient (parametric correlation test).
[b] Spearman's rho correlation coefficient (nonparametric correlation test).

Table 3-17: Correlations between IIEF and IPSS domains in the ED (N=48) and NO-ED (N=12) groups.

IPSS domains	Pearson correlation [a] Spearman's correlation [b]														
	Erectile function			Orgasmic function			Sexual desire			Intercourse satisfaction			Overall satisfaction		
	ED	NO-ED	p	ED	NO-ED	p	ED	NO-ED	p	ED	NO-ED	p	ED	NO-ED	p
Incomplete emptying [a]	0.11	0.03	0.28[c]	0.09	0.03	0.23[c]	0.04	0.35	**0.002**[c]	-0.03	0.004	0.66[c]	0.06	0.25	0.13[c]
Frequency [a]	0.10	-0.41	0.40[c]	0.09	-0.47	0.33[c]	-0.05	-0.13	0.14[c]	0.07	-0.41	0.52[c]	0.12	-0.34	0.61[c]
Intermittency [b]	0.13	-0.10	0.33[d]	0.03	-0.34	0.16[d]	0.01	-0.24	0.66[d]	-0.01	-0.19	0.37[d]	0.12	-0.30	0.56[d]
Urgency [a]	0.38	-0.47	0.13[c]	-0.05	-0.50	0.41[c]	-0.20	-0.46	**0.004**[c]	0.15	-0.35	0.42[c]	-0.06	-0.35	0.15[c]
Weak stream [a]	0.12	-0.51	0.58[c]	-0.10	-0.35	0.59c	-0.08	-0.43	**0.035**[c]	-0.15	-0.41	0.80[c]	0.02	-0.45	0.79[c]
Straining [b]	-0.05	-0.20	0.65[d]	-0.11	-0.35	0.37[d]	-0.12	-0.17	0.39[d]	-0.04	-0.22	0.74[d]	0.06	-0.39	0.94[d]
Nocturia [a]	-0.001	-0.49	0.41[c]	-0.19	-0.37	0.91[c]	-0.25	-0.58	0.90[c]	-0.08	-0.59	0.41[c]	-0.16	-0.41	0.25[c]
QoL [a]	-0.13	-0.31	0.71[c]	-0.15	-0.34	0.21[c]	-0.25	0.01	0.11[c]	-0.11	-0.49	0.93[c]	0.05	-0.43	0.88[c]
IPSS total score [a]	0.01	-0.52	0.47[c]	-0.04	-0.44	0.89[c]	-0.12	-0.35	0.91[c]	-0.03	0.15	0.38[c]	0.01	-0.36	0.24[c]

[a] Pearson correlation coefficient (parametric correlation test).
[b] Spearman's rho correlation coefficient (nonparametric correlation test).
[c] Independent two samples t-test was used (parametric test for normality distributed samples).
[d] Mann-Whitney U test was used (nonparametric test for not normality distributed samples).

3.1.7.4 Correlation between age and IIEF/IPSS domains

The correlation between age and IIEF and IPSS domains was measured through Pearson and Spearman's correlation coefficient.

3.1.7.4.1 Correlation between age and IIEF domains

No significant correlation was found between age and most IIEF domains except orgasmic function domain when all patients were included in the analysis (Table 3-18). Within the ED group, significant correlations were found between age and erectile function, orgasmic function and sexual desire (Table 3-19).

Table 3-18: Correlation between age and IIEF domains (N=60).

IIEF domain	Pearson correlation	p
Erectile function	-0.25	0.05
Orgasmic function	-0.31	**0.017**
Sexual desire	-0.25	0.05
Intercourse satisfaction	-0.22	0.09
Overall satisfaction	0.03	0.8

Table 3-19: Correlation between age and IIEF domains within the ED group (N=48).

IIEF domain	Pearson correlation	p
Erectile function	-0.31	**0.03**
Orgasmic function	-0.33	**0.02**
Sexual desire	-0.29	**0.047**
Intercourse satisfaction	-0.21	0.16
Overall satisfaction	0.04	0.98

3.1.7.4.2 Correlation between age and IPSS scores

The data indicated no significant correlation between any of the IPSS domains and age (Table 3-20). There was no significant correlation between age and any of the IPSS domains within the ED or NO-ED groups (Table 3-21).

Table 3-20: Correlation between age and IPSS domains (N=60)

IPSS domain	Pearson correlation [a] Spearman's correlation [b]	p
Incomplete emptying [a]	-0.10	0.4
Frequency [a]	-0.02	0.9
Intermittency [b]	-0.12	0.4
Urgency [a]	0.004	0.9
Weak stream [a]	0.10	0.5
Straining [b]	-0.09	0.5
Nocturia [a]	0.18	0.2
QoL [a]	0.12	0.3
IPSS total score [a]	-0.02	0.87

[a] Pearson correlation coefficient.
[b] Spearman's rho correlation coefficient.

Table 3-21: Correlation between age and IPSS domains in the ED and NO-ED groups.

IPSS domains aginst age	Spearman's correlation [a] Pearson correlation [b]		p
	ED (n=48)	NO-ED (n=12)	
Incomplete emptying [a]	-0.19[a]	0.33[a]	0.8[c]
Frequency [a]	-0.12[a]	0.60[a]	0.7[c]
Intermittency [b]	0.72[b]	-0.002[b]	0.4[d]
Urgency [a]	0.02[a]	0.01[a]	0.9[c]
Weak stream [a]	0.06[a]	-0.31[a]	0.5[c]
Straining [b]	0.65[b]	-0.13[b]	0.2[d]
Nocturia [a]	0.15[a]	0.32[a]	0.7[c]
Q o L [a]	0.10[a]	0.22[a]	0.7[c]
IPSS total [a]	-0.04[a]	0.30[a]	0.9[c]

[a] Spearman's rho correlation was used as non-parametric test.
[b] Pearson correlation was used as parametric test.
[c] Mann-Whitney U test was used.
[d] Independent two samples t-test was used.

3.1.7.5 Correlations among clinical biomarkers, ED, LUTS and obesity

3.1.7.5.1 Biochemistry test correlations

Spearman's rho correlation coefficient was used to measure the relationship between most biochemistry blood tests and IIEF and IPSS domains, while Pearson correlation coefficient was used for others such as prolactin, bilirubin total, sodium, estimated GFR and HDL. In this section only significant ($p<0.05$) correlations will be reported.

Overall a significant positive correlation was found between testosterone and erectile function ($rho(58)=0.36$, $p<0.001$), orgasmic function ($rho(58)=0.42$, $p<0.001$), sexual desire ($rho(58)=0.26$, $p<0.04$) and intercourse satisfaction ($rho(58)=0.33$, $p<0.01$).

Further significant correlations were found between free testosterone and free thyroxine (free T4) ($rho(58)=0.34$, $p=0.008$), other medical conditions; hypertension ($rho(58)=-0.27$, $p=0.036$), psoriatic arthritis ($rho(58)=0.86$, $p=0.043$), and being overweight (BMI>25) ($rho(58)=0.28$, $p=0.03$). Also, significant negative correlations were observed between bioavailable testosterone and depression ($rho(58)=-0.28$, $p=0.03$) and between bioavailable testosterone and hypertension ($rho(58)=-0.26$, $p=0.047$).

Significant positive correlations were found between free thyroxine (free T4) and IPSS –quality of life (QoL) ($rho(58)=0.31$, $p<0.02$) and between luteinizing hormone (LH) and IIEF- sexual desire, ($rho(58)=0.29$, $p<0.02$)

Significant positive correlations were also found between potassium level and two domains of IPSS, intermittency and urgency ($rho(58)=-0.31$, $p<0.010$ and $rho(58)=-0.37$, $p<0.0010$, respectively).

The ESR level showed a negative significant correlation with erectile function, ($rho(58)=-0.26$, $p=0.04$), orgasmic function ($rho(58)=-0.29$, $p<0.03$) and

intercourse satisfaction (rho(58)=-0.28, p<0.03) and a positive significant correlation with IPSS- weak stream (rho(58)=0.27, p<0.03).

A positive Pearson correlation was observed between total bilirubin level and IIEF-orgasmic function (r(58)=0.27, p<0.03).

Moreover, negative Pearson correlations were found between estimated GFR and IPSS-urgency and IPSS- weak stream (r(58)=-29, p<0.02) and (r(58)=-0.35, p<0.01, respectively). For the complete results please see Appendix C.

3.1.7.5.2 Haematology test correlations

A Spearman's rho correlation test was performed to measure the relationship between haematology tests and the IIEF and IPSS scores of the patients.

MCV was found to be negatively correlated with three IPSS domains - incomplete emptying, intermittency and straining (rho(58)=-0.33, p=0.01; rho(58)=-0.32, p=0.01; rho(58)=-0.38, p<0.001, respectively).

MCH was negatively correlated with two IPSS domains - incomplete emptying and straining (rho(58)=-0.27, p=0.04 and rho(58)=-0.29, p=0.02, respectively).

MCHC was found to be positively correlated to sexual desire and IPSS-incomplete emptying (rho(58)=0.30, p=0.02 and rho(58)=0.29, p=0.03 respectively) while RDW was also positively correlated with IPSS-weak stream (rho(58)=0.38, p=<0.001).

Moreover, neutrophil count was negatively correlated with sexual desire (rho(58)= -0.29, p=0.02) and positively correlated to IPSS-frequency (rho(58)=0.27, p=0.04).

It was also found that eosinophil count was positively correlated with erectile function (rho(58)=0.26, p=0.04) and with intercourse satisfaction (rho(58)=0.27, p=0.03) while lymphocyte count was positively correlated with sexual desire (rho(58)=0.26, p=0.03). All these correlation results can be found in Appendix C.

3.1.7.5.3 Comparison of IIEF scores between smokers and non-smokers (N=60)

There was no difference between smokers and non-smokers for any of the IIEF domains as shown in Table 3-22, Table 3-23 and Table 3-24.

Table 3-22: Comparison of IIEF scores between smokers and non-smokers (N=60).

Variables	Non-smokers (n=42)	Smokers(n=18)	Mean Difference	p[a]
	Mean (±SD)	Mean (±SD)		
Erectile function	13.1 (±10.5)	14.1 (±9.5)	0.98	0.49
Orgasm function	5.9 (±3.6)	6.2 (±3.1)	0.30	0.36
Sexual desire	5.2 (±2.4)	5.5 (±2.6)	0.32	0.60
Intercourse satisfaction	5.7 (±4.9)	6.4 (±4.3)	0.71	0.59
Overall satisfaction	4.5 (±2.6)	7.7 (±2.9)	0.19	0.24

[a] Independent two samples t-test (parametric test for normally distributed samples).

Table 3-23: Comparison of IIEF scores between smokers and non-smokers within the ED group (N=48).

Variables	Non-smoker (n=33)		Smoker (n=15)	
	Pearson correlation	p	Pearson correlation	p
Erectile Function	0.26	0.4	-0.002	0.9
Orgasm Function	-0.27	0.4	0.03	0.8
Sexual Desire	0.31	0.3	-0.06	0.7
Intercourse Satisfaction	0.31	0.3	-0.07	0.6
Overall Satisfaction	0.13	0.6	0.02	0.9

Table 3-24: Comparison of IIEF scores between smokers and non-smokers within the NO-ED group (N=12).

Variables	Non-smokers (n=9)		Smokers (n=3)	
	Spearman's correlation	p	Spearman's correlation	p
Erectile Function	0.8	0.1	-0.03	0.8
Orgasm Function	-0.46	0.2	0.05	0.7
Sexual Desire	0.33	0.2	-0.04	0.8

	Non-smokers (n=9)		Smokers (n=3)	
Intercourse Satisfaction	0.29	0.6	-0.10	0.5
Overall Satisfaction	-0.07	0.8	0.03	0.8

3.2 Bariatric surgery audit

The distribution of data was analysed and skewness test with cut-off values of -1 and +1 was applied. If the skewness test result was < -1 or > +1, the data was considered to be not normally distributed (Table 3-25).

Table 3-25: Skewness test of the bariatric surgery audit (N=35).

Descriptive Statistics						
	Minimum	**Maximum**	**Median**	**Mean**	**Skewness test**	**Normality**
Age	30	68	48	47.2	0.1	**Yes**
Height (m)	1.6	2	1.8	1.8	0.2	**Yes**
BMI T1	37.1	74.4	47.1	48.3	1.5	No
BMI Dos	36.3	71.2	45.5	47.1	1.4	No
BMI-T2	34.4	70.3	44.2	46.3	1.3	No
BMI-T3	30.7	63.2	39	41.5	1.2	No
BMI-T4	29.2	60.3	36.1	39.3	1.2	No
%EWL Dos	-2	17.6	5.3	5.9	0.9	**Yes**
%EWL T2	0.4	34.3	6.3	10	1	**Yes**
%EWL T3	-2.2	67.1	33.6	31.3	-0.1	**Yes**
%EWL T4	-1.1	75.3	40.5	41.2	-0.4	**Yes**
HbA1c-T1	32	95	43	47.7	1.9	No
HbA1c-T2	30	87	40	43	2.3	No
HbA1c- T3	29	80	39	42.8	1.9	No
HbA1c-T4	29	79	39	41.3	2	No
Blood glucose-T1	4.4	19	5.4	6.3	3.1	No
Blood glucose-T2	4.1	19	5	5.7	4.2	No
Blood glucose-T3	4.1	16	5	5.5	4.2	No
Blood glucose-T4	4	48	4.9	6.6	5.4	No
Erectile function-T1	2	30	24	19.5	-0.5	Yes
Erectile function-T2	1	30	20	19.3	-0.5	**Yes**
Erectile function-T3	3	30	27	23.5	-1.2	No
Erectile function-T4	3	30	28	24.6	-1.7	No
Orgasmic function-T1	1	10	9	7.8	-1.2	No
Orgasmic function-T2	0	10	8	7.4	-1.2	No
Orgasmic function-T3	1	10	10	8.6	-2.2	No

Descriptive Statistics						
	Minimum	Maximum	Median	Mean	Skewness test	Normality
Orgasmic function-T4	2	10	10	9	-2.6	No
Sexual desire-T1	2	10	7	6.8	-0.3	**Yes**
Sexual desire-T2	2	10	7	6.7	-0.3	**Yes**
Sexual desire-T3	2	10	8	7.9	-1	**Yes**
Sexual desire-T4	1	10	10	8.6	-2	No
Intercourse satisfaction-T1	0	15	9	8.1	-0.4	**Yes**
Intercourse satisfaction-T2	0	15	8	8.3	-0.4	**Yes**
Intercourse satisfaction-T3	0	15	12	10	-1	**Yes**
Intercourse satisfaction-T4	0	15	13	10.8	-1.2	No
Overall satisfaction-T1	1	10	7	6.3	-0.4	**Yes**
Overall satisfaction-T2	1	10	7	6.5	-0.4	**Yes**
Overall satisfaction-T3	1	10	9	8	-1.3	No
Overall satisfaction-T4	3	10	9	8.4	-1.5	No
Incomplete emptying-T1	0	5	1	1.5	0.8	**Yes**
Incomplete emptying-T2	0	5	1	1.3	1.1	No
Incomplete emptying-T3	0	4	1	0.9	1.1	No
Incomplete emptying-T4	0	3	0	0.6	1.2	No
Frequency-T1	0	5	1	1.8	0.6	**Yes**
Frequency-T2	0	5	1	1.3	1.1	No
Frequency-T3	0	5	1	1.3	1.3	No
Frequency-T4	0	5	0	0.8	1.8	No
Intermittency-T1	0	5	1	1.4	0.8	**Yes**
Intermittency-T2	0	5	1	1.1	1.2	No
Intermittency-T3	0	5	0	0.7	2.3	No
Intermittency-T4	0	3	0	0.5	1.7	No
Urgency-T1	0	5	1	1.4	1	**Yes**
Urgency-T2	0	5	1	1	1.7	No
Urgency-T3	0	4	0	0.7	1.7	No
Urgency-T4	0	4	0	0.5	2.5	No
Weak stream-T1	0	5	1	1.2	1.4	No
Weak stream-T2	0	4	1	0.9	1.7	No
Weak stream-T3	0	5	0	0.6	2.4	No
Weak stream-T4	0	4	0	0.3	3.3	No
Straining-T1	0	2	0	0.5	1.1	No
Straining-T2	0	2	0	0.5	1	**Yes**
Straining-T3	0	1	0	0.3	1.2	No

Descriptive Statistics						
	Minimum	Maximum	Median	Mean	Skewness test	Normality
Straining-T4	0	4	0	0.3	4.1	No
Nocturia-T1	0	5	1	1.4	1.2	No
Nocturia-T2	0	4	1	1.1	0.8	**Yes**
Nocturia-T3	0	3	1	0.7	1	**Yes**
Nocturia-T4	0	4	0	0.5	2.4	No
Q o L-T1	0	6	2	2.3	0.2	**Yes**
Q o L-T2	0	5	2	2.4	0.3	**Yes**
Q o L-T3	0	4	2	1.8	0.5	**Yes**
Q o L-T4	0	4	1	1.3	1.2	No
IPSS total score -T1	0	28	7	9.2	0.8	**Yes**
IPSS total score -T2	0	26	7	7.3	1.3	No
IPSS total score -T3	0	23	3	5.2	1.6	No
IPSS total score -T4	0	19	2	3.5	1.9	No
Surgery type	1	3	2	1.8	0.5	**Yes**

T1: one month pre-operation; T2: one month post-operation; T3: three month post-operation; T4: six month post-operation.

3.2.1 Analysis of variance

Repeated measures ANOVA is a statistical method used to analyse the differences among multiple measurements taken from the same sample of individuals. Valid use of this method relies on the data adhering to certain parametric assumptions, including sample size and normality of model residuals. If these data assumptions are not met, then Friedman's test is a suitable nonparametric alternative.

In the current audit, the surgery type represents the intervention being assessed, specifically, this audit was used to assess changes in ED-related outcome measures at multiple time-points both prior to and following surgery. Specifically, measurements were taken at the baseline or one month pre-operation (T1), and then again at one month (T2), three months (T3), and six months (T4) post-operation. Outcomes were measured over time to examine any changes that may have occurred in the patients' sexual and urological health following the intervention.

Changes over time in sexual and urological health (using IIEF, IPSS, BMI, fasting blood glucose and HbA1c) were assessed independently for both ED and NO-ED patients. The results of these analyses are presented in the current section.

3.2.2 The patient cohort profile (bariatric surgery audit)

Out of 49 eligible patients only 35 completed the study; these patients were divided in to three groups according to their sexual function: ED, NO-ED and control (sham) as described below.

The first group consisted of patients with ED (ED group), which, contained twenty patients. Within this group, eighteen individuals were considered to be true ED patients (IIEF-EF score below 25); the remaining two were not considered to be true ED patients as, although EF scores for these two patients were below 25, they were not considered true ED because their loss of sexual activity stemmed from the lack of a partner, as illustrated in Figure 3-4 and Figure 3-5.

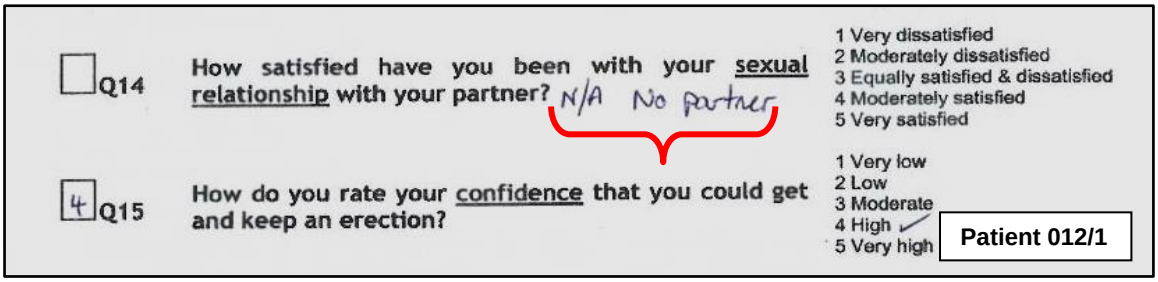


Figure 3-4: Not true ED patient (example1).

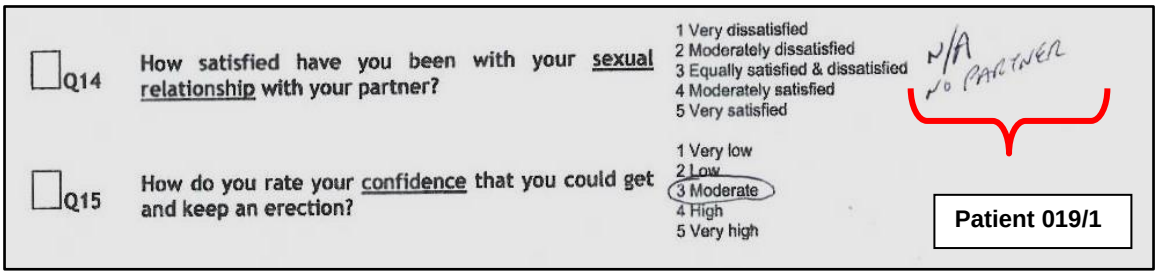


Figure 3-5: Not true ED patient (example2).

The second group consisted of patients without ED (NO-ED group); patients were defined as having NO-ED when their erectile function (EF) score was equal to, or greater than 25. Twelve patients fell into this group.

The third group was the control group (sham), which contained three patients, two of whom presented with true ED (sham ED) and one without ED (sham NO-ED) (Figure 3-6). The sham group consisted of patients who were listed for surgery, but whose surgery was abandoned during the operation due to the discovery of a large cirrhotic liver and a poor response to standard liver shrinkage. It was therefore deemed unsafe to proceed with the operation. As a result of the abandoned surgery, these patients enrolled in the POLER programme (Prolonged Preoperative Weight Loss Programme), and were then listed for a second attempt at the surgery. These two sham groups were excluded from statistical calculation due to the small sample size.

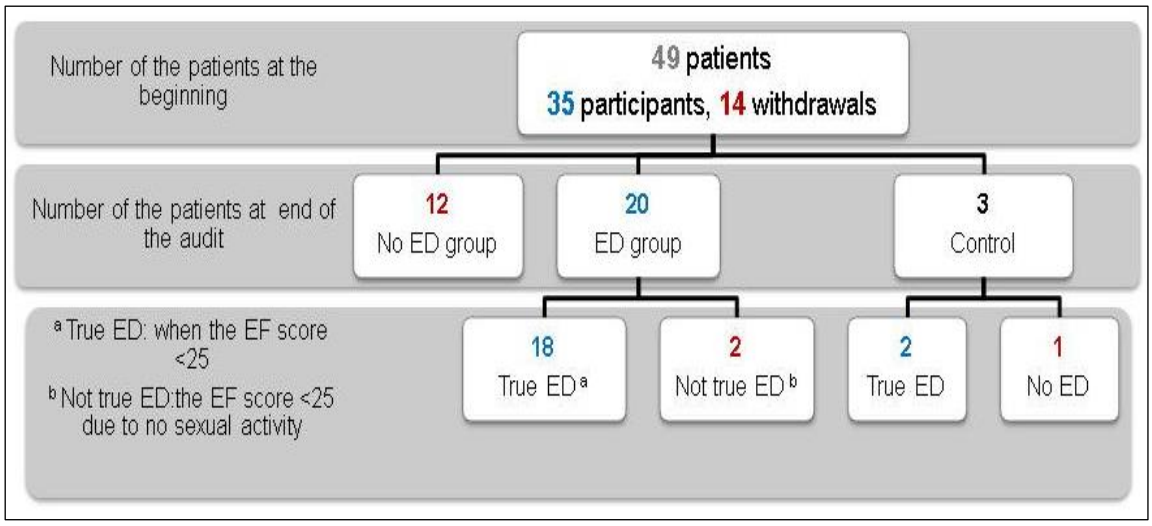


Figure 3-6: Patient distribution chart
Out of 49 eligible patients, 35 completed the study and 14 withdrew before surgery. 35 patients were divided into three groups according to their sexual activity. The first group consisted of patients with ED (ED group, n=20), 2 of these were not considered to be true ED because of the lack of a partner. The second group consisted of patients without ED (NO-ED group, n=12). The third group is the control group (sham), which contained three patients, 2 of whom presented true ED (sham ED) and 1 who did not present ED (sham NO-ED).

3.2.3 Age range

Patients age ranged from 30 to 68 years old with mean age of 47.23 ± 8.1 and was categorized by decade Figure 3-7.

An independent sample t-test found that there was no difference in age between the ED group (48.9 ±7.0 years) and the NO-ED group (44.1±6.9 years; t (29)=2.1; p=0.10).

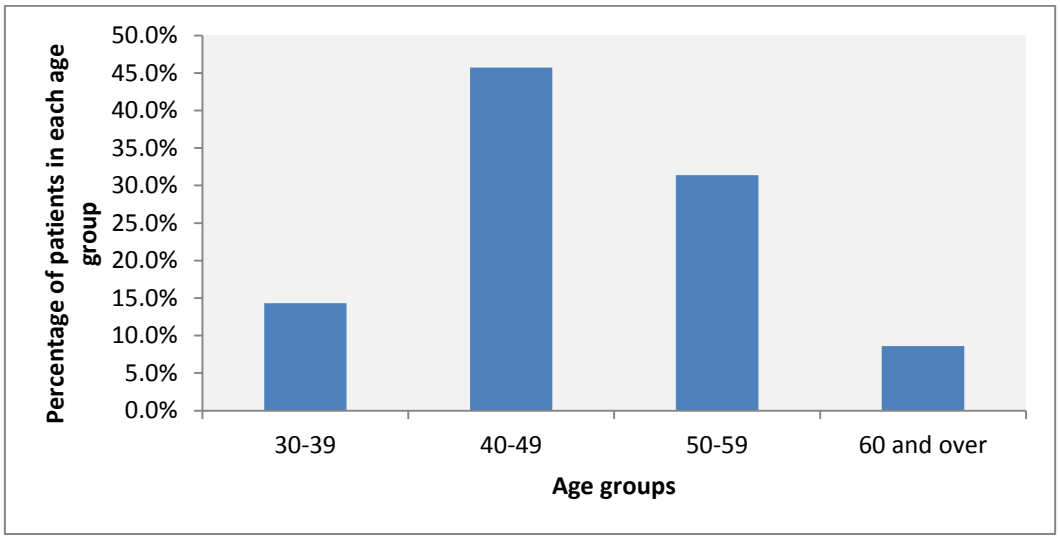


Figure 3-7: Age distribution of patients for bariatric surgery audit.
Age distribution data derived from 35 patients showed that 45.7% of patients were between 40 and 49, 31.4% between 50 and 59, 14.3% between 30 and 39 and 8.6% were 60 years old and above.

3.2.4 Bariatric surgery types

The three types of bariatric surgery chosen in this audit were gastric sleeve (45.7% of surgeries), gastric bypass (31.4% of surgeries) and gastric band (22.9% of surgeries). Within the ED group the distribution of surgeries was gastric sleeve - 44.4%, gastric bypass - 33.3% and gastric band - 22.2%. Within the NO-ED group, the distribution was gastric sleeve - 41.6%, gastric bypass - 25.0% and gastric band - 33.3%. There was no difference between the ED group and NO-ED group for any of the surgery types calculated using one way ANOVA (F(29)=0.24, p=0.79) (Figure 3-8).

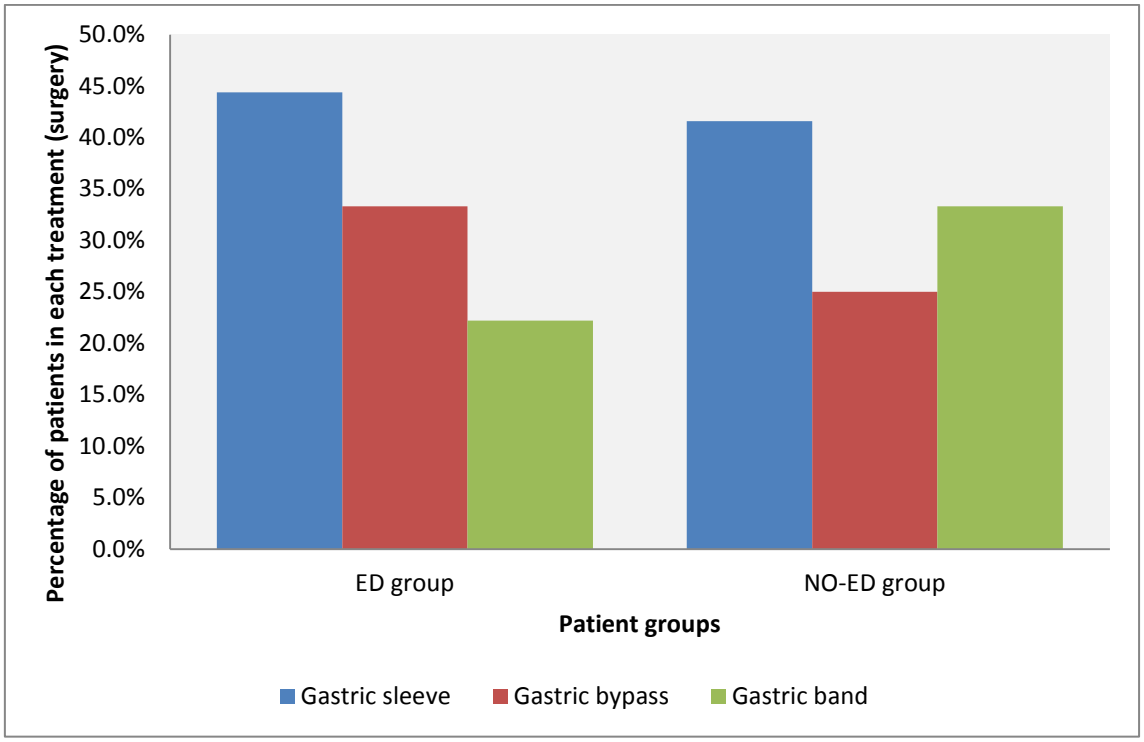


Figure 3-8: Distribution of bariatric surgery type among patients groups.
Data showed no difference between ED (N=18) and NO-ED (N=12); the other groups (Not true ED (n=2), Sham-ED (n=2) and Sham-NO-ED (n=1)) were statistically excluded because of the small sample size.

3.2.5 Change in body weight associated with bariatric surgery.

Interrogation of the data indicated that most of the BMI and %EWL data were skewed and were not normally distributed as shown in the skewness test (Table 3-25) and the histogram check (Appendix C), thus nonparametric tests were applied.

3.2.5.1 BMI and EWL in the ED group

The results showed that BMI and %EWL improved over time ($p<0.01$) in the ED group after the bariatric surgery which was reflected in a decreasing mean rank across the time-points measured (Figure 3-9, Figure 3-10 and Table 3-26).

3.2.5.2 BMI and EWL in the NO-ED group

Patients without ED also showed improvement in BMI and %EWL over time reflected in a decrease in mean rank over time as shown in (Figure 3-9, Figure 3-10 and Table 3-26).

Moreover, the BMI and %EWL results were compared between T1 (baseline) and the other three periods (T2, T3 and T4). Table 3-27 shows the significant values (p) to highlight if a significant difference exists. For BMI and %EWL there was a significant improvement at T2, T3 and T4 compared to the baseline T1 ($p<0.01$).

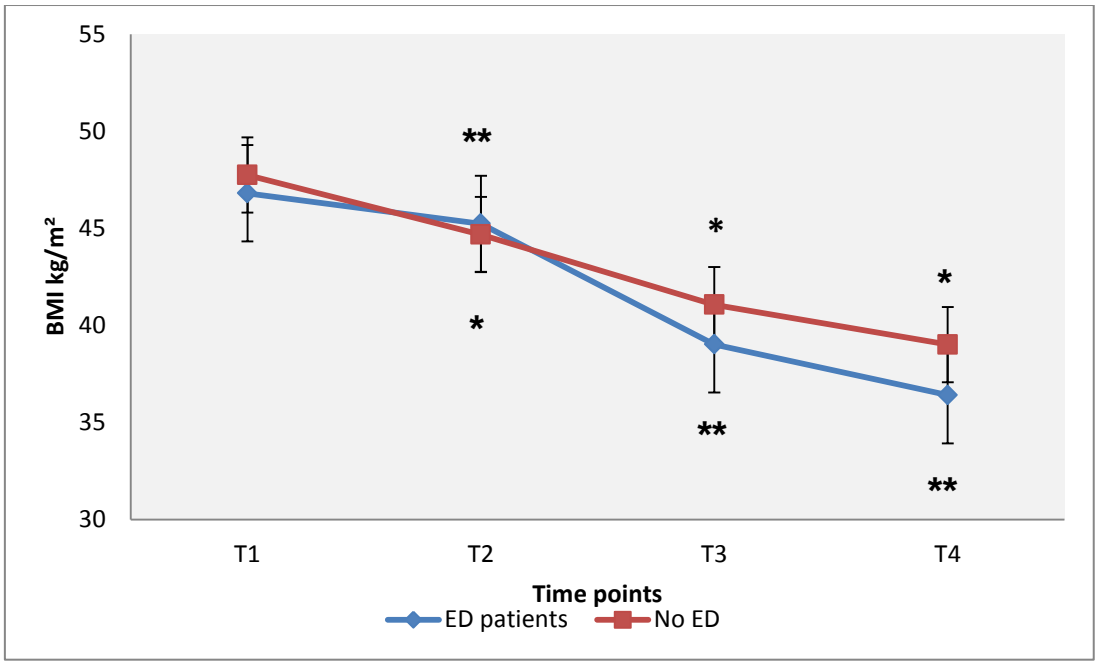


Figure 3-9: Changes in BMI for the ED and NO-ED groups over time.
BMI data derived from the ED (blue diamonds; n=18) and NO-ED groups (red squares; n=12) were significantly improved across time after bariatric surgery ($p<0.001$).
* Significant improvement was found at one month post-op (T2) compared to T1 and continued until six months post-op (T4) for patients in the NO-ED group ($p=0.002$).
** Significant improvement was detected at one month post op (T2) compared to T1 and continued until six months post-op (T4) for patients in the ED group ($p<0.001$).
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

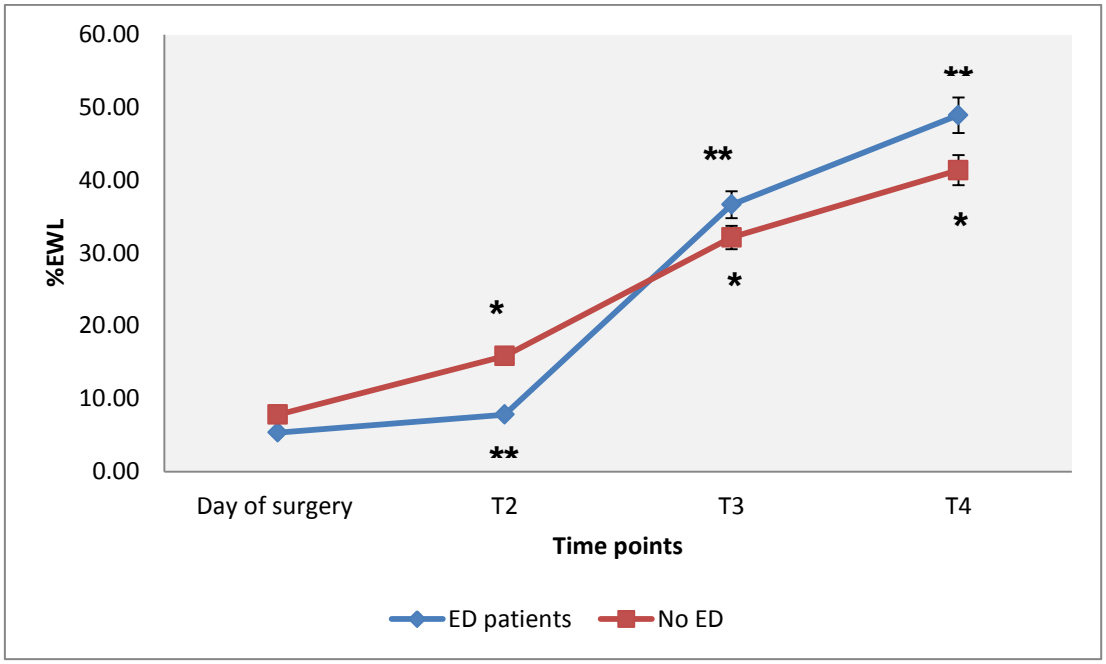


Figure 3-10: Changes in %EWL in the ED and NO-ED groups over time.
The weight at T1 was taken as baseline for %EWL calculations. %EWL values derived from patients in the ED (n=18) and NO-ED groups (n=12) were significantly improved over time ($p<0.001$).
* Significant improvement was found at one month post-op (T2) compared to T1and continued until six months post-op (T4) for patients in the NO-ED group ($p=0.003$).
** Significant improvement was found at one month post-op (T2) compared to T1 and continued until six months post-op (T4) for patients with ED ($p=0.005$).
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-26: BMI and %EWL of the ED and NO-ED groups across time points.

	Mean rank					
Variables	**T1/DOS**	**T2**	**T3**	**T4**	**Chi-square (X^2)**	**p[a]**
BMI (ED group)	3.8	3.3	1.9	1.2	68.7	<0.001
%EWL (ED group)	1.3	1.8	3.1	3.9	49.1	<0.001
BMI (NO-ED group)	4.0	3.1	1.8	1.2	45.1	<0.001
%EWL (NO-ED group)	1.9	3.2	3.8	3.9	32.9	<0.001

[a] Friedman's test was used.
T1: one month pre-operation; DOS: day of surgery; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-27: The significance of differences for BMI and %EWL between time points in the ED and NO-ED groups.

	Significance level (p) against T1[a]		
Variables	**T2**	**T3**	**T4**
BMI (ED group)	<0.001	<0.001	<0.001
%EWL (ED group)	0.005	<0.001	<0.001
BMI (NO-ED group)	0.002	0.002	0.002
%EWL (NO-ED group)	0.003	0.002	0.002

[a] Wilcoxon signed rank test was used.
T2: one month post-operation; T3: three months post-operation; T4: six months post-operation; all times compared with T1 (one month pre-operation, baseline).

3.2.5.3 BMI and EWL according to surgery type

BMI and %EWL improved over time with no difference between the types of surgery used, as shown in Figure 3-11, Figure 3-12, Table 3-28 and Table 3-29. The BMI and %EWL results were compared between T1 (baseline) and the other three periods (T2, T3 and T4). Table 3-30 shows that BMI was significantly different between surgery types at T2 compared to the baseline T1 (p=0.01). %EWL showed no difference between surgery types at all-time points compared to the baseline T1 (p>0.05). The comparison between surgery types showed a significant difference between gastric sleeve and gastric band at baseline T1 (p=0.016) as well as at T2 (p=0.012) and T3 (p=0.016) against T1 (Table 3-31).

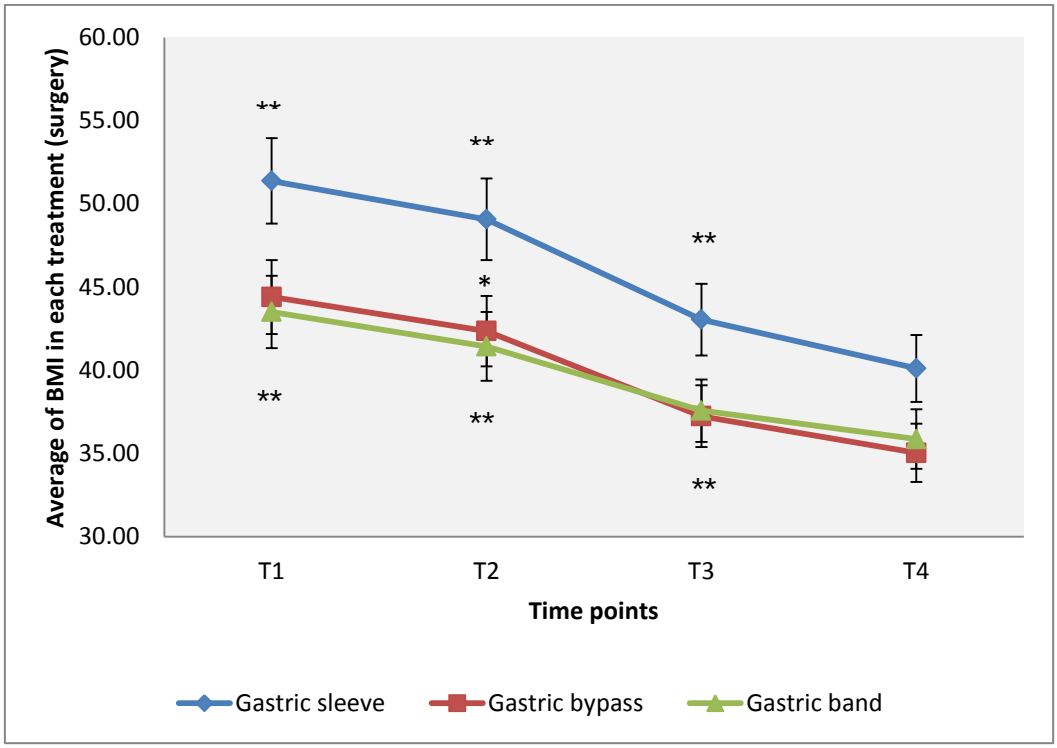


Figure 3-11: Changes in BMI comparing different surgery types across time points.

BMI data derived from different types of surgery: gastric sleeve (blue diamonds; n=13), gastric bypass (red squares; n=9) and gastric band (green triangle; n=8) were all significantly changed over time ($p<0.001$).

* Significant difference between types of surgery was found at one month post-op (T2) compared to T1 ($p=0.01$), but not continued until six month post op (T4), (Table 3-30).

** Significant difference between the BMI of patients listed for gastric sleeve and gastric band was detected at baseline (T1) and one month post-op (T2) compared to T1 and continued until three months post-op (T3) ($p<0.02$), (Table 3-31).

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

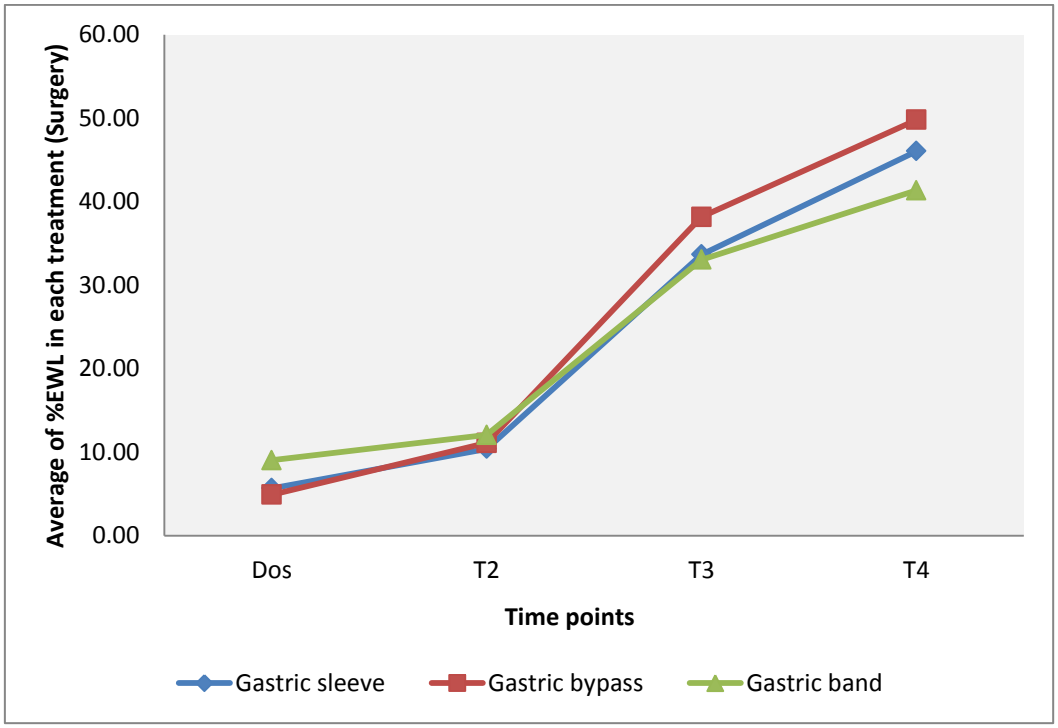


Figure 3-12: Changes in %EWL comparing different surgery types across time points.

%EWL data derived from different types of surgery: gastric sleeve (blue diamonds; n=13), gastric bypass (red squares; n=9) and gastric band (green triangle; n=8) were all significantly changed across time ($p<0.001$), (Table 3-29). No significant differences were detected between the types of surgery on %EWL (Table 3-30).

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-28: Changes in BMI comparing types of surgery across time points.

	Mean rank of BMI					
Variables	**T1/DOS**	**T2**	**T3**	**T4**	**Chi-square (X^2)**	**p[a]**
Gastric sleeve	2.9	2.7	2.3	2.1	51.4	**<0.001**
Gastric bypass	2.7	2.5	2.4	2.2	46.3	**<0.001**
Gastric band	1.8	1.7	1.6	1.4	45.2	**<0.001**

[a] Friedman's test was used.

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-29: Changes in %EWL comparing types of surgery across time points.

	Mean rank of %EWL					
Variables	**T1/DOS**	**T2**	**T3**	**T4**	**Chi-square (X^2)**	**p[a]**
Gastric sleeve	1.0	2.2	4.3	5.7	51.4	**<0.001**
Gastric bypass	1.3	2.1	2.8	4.3	46.3	**<0.001**
Gastric band	2.1	2.7	5.5	6.1	45.2	**<0.001**

[a] Friedman's test was used.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-30: The significance of differences for BMI and %EWL between time points in different types of surgery.

	Significance level (p) against T1[a]		
Variables	**T2**	**T3**	**T4**
BMI	**0.01**	0.08	0.22
%EWL	0.61	0.52	0.26

[a] Wilcoxon signed rank test was used.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-31: Comparison between types of surgery.

Variable/ surgery type	**Gastric bypass against gastric sleeve**			**Gastric band against gastric sleeve**			**Gastric bypass against gastric band**		
	Mean rank	Mann Whitney U test	p[a]	Mean rank	Mann Whitney U test	p[a]	Mean rank	Mann Whitney U test	p[a]
BMI-T1	10.8	52.5	0.08	14.9	25.0	**0.016**	8.6	33.0	0.36
BMI-T2	11.0	55.0	0.10	7.4	23.0	**0.012**	8.3	30.0	0.24
BMI-T3	11.1	56.0	0.11	7.7	25.5	**0.016**	8.4	31.0	0.28
BMI-T4	12.0	66.0	0.28	9.4	39.0	0.12	9.3	38.5	0.64
%EWL-Dos	13.9	87.0	0.96	15.4	41.0	0.15	12.5	24.0	0.09
%EWL-T2	15.2	75.0	0.52	14.6	47.0	0.29	10.5	40.0	0.74
%EWL-T3	16.2	64.0	0.23	13.1	59.0	0.76	8.6	33.0	0.39
%EWL-T4	15.4	73.0	0.46	12.6	62.0	0.92	8.8	34.0	0.44

[a] Mann Whitney U test was used.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

3.2.6 Change in erectile function following bariatric surgery over time

All patients were asked to complete and answer the IIEF and IPSS questionnaires over four weeks prior to the surgery. The results of these questionnaires are presented in Table 3-32. In all IIEF domains there was a significant difference between the ED and NO-ED groups ($p<0.05$). Data from the IPSS questionnaire have shown statistically significant differences between the ED and NO-ED groups in five domains; incomplete emptying, urgency, weak stream, QoL and IPSS total score ($p<0.05$). While four domains; frequency, intermittency, straining and nocturia showed no significant difference between groups ($p>0.05$).

Table 3-32: The difference in IIEF and IPSS scores in the ED and NO-ED groups at baseline (T1).

Variables	ED (n=18) Median (IQR)	NO-ED (n=12) Median (IQR)	p[a]
IIEF- erectile function	13.0 (2.0, 25.0)	29.0 (27.0, 30.0)	**<0.001**
IIEF- orgasm function	8.0 (1.0, 10.0)	10.0 (6.0, 10.0)	**0.03**
IIEF- sexual desire	6.0 (2.0, 8.0)	8.5 (4.0, 10.0)	**0.005**
IIEF- intercourse satisfaction	6.0 (0.0, 13.0)	12.5 (6.0, 15.0)	**0.001**
IIEF- overall satisfaction	5.5(2.0, 10.0)	9.0 (4.0, 10.0)	**0.002**
IPSS- incomplete emptying	1.5 (0.0, 5.0)	0.0 (0.0, 2.0)	**0.004**
IPSS- frequency	2.0 (0.0, 5.0)	0.5 (0.0, 5.0)	0.12
IPSS- intermittency	1.5 (0.0, 5.0)	0.0 (0.0, 4.0)	0.14
IPSS- urgency	2.0 (0.0, 5.0)	0.0 (0.0, 3.0)	**0.003**
IPSS- weak stream	1.0 (0.0, 2.0)	0.0 (0.0, 2.0)	**0.012**
IPSS- straining	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.85
IPSS- nocturia	1.0 (0.0, 5.0)	1.0 (0.0, 3.0)	0.60
IPSS- Q o L	3.0 (0.0, 6.0)	2.0 (0.0, 3.0)	**0.010**
IPSS total score	12.5 (0.0, 28.0)	4.5 (1.0, 14.0)	**0.007**

[a] Mann-Whitney U test was used.

3.2.6.1 ED group: overall improvement

Data from the IIEF questionnaires were not normally distributed therefore a Friedman's test was used to analyse the data (Table 3-25). Eighteen patients were classified as having ED. Using Friedman's test, a significant change was

observed in all domains from pre- to post-surgery (Figure 3-13, Figure 3-14 and Table 3-33).

The difference between time points was evaluated using Wilcoxon signed rank test in order to find out at what time point IIEF scores improved compared to baseline (T1). For erectile function domain there was a significant improvement at T2 compared to baseline (T1; $p<0.05$), a significant improvement in orgasmic function was observed at T4 ($p<0.01$), and sexual desire at T3 ($p<0.01$). For intercourse satisfaction the significant change occurred at T2 and overall satisfaction was significantly improved at T3 ($p<0.01$) (Table 3-34).

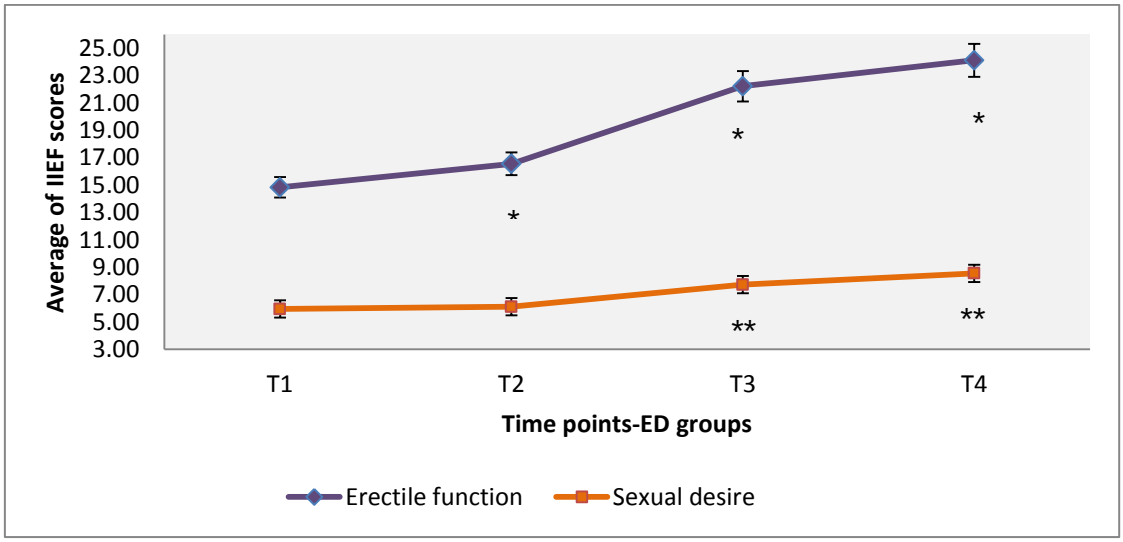


Figure 3-13: Changes in erectile function and sexual desire domains- IIEF for ED group through time.

IIEF questionnaire data derived from patients with ED (n=18) were significantly improved for all domains cross the time ($p<0.001$).

* Significant improvement for erectile function ($p=0.02$) domain was found at T2 compared to T1 and continued until T4.

** Sexual desire ($p=0.002$) reached significance at T3 compared to T1 continued until T4 ($p \leq 0.002$).

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

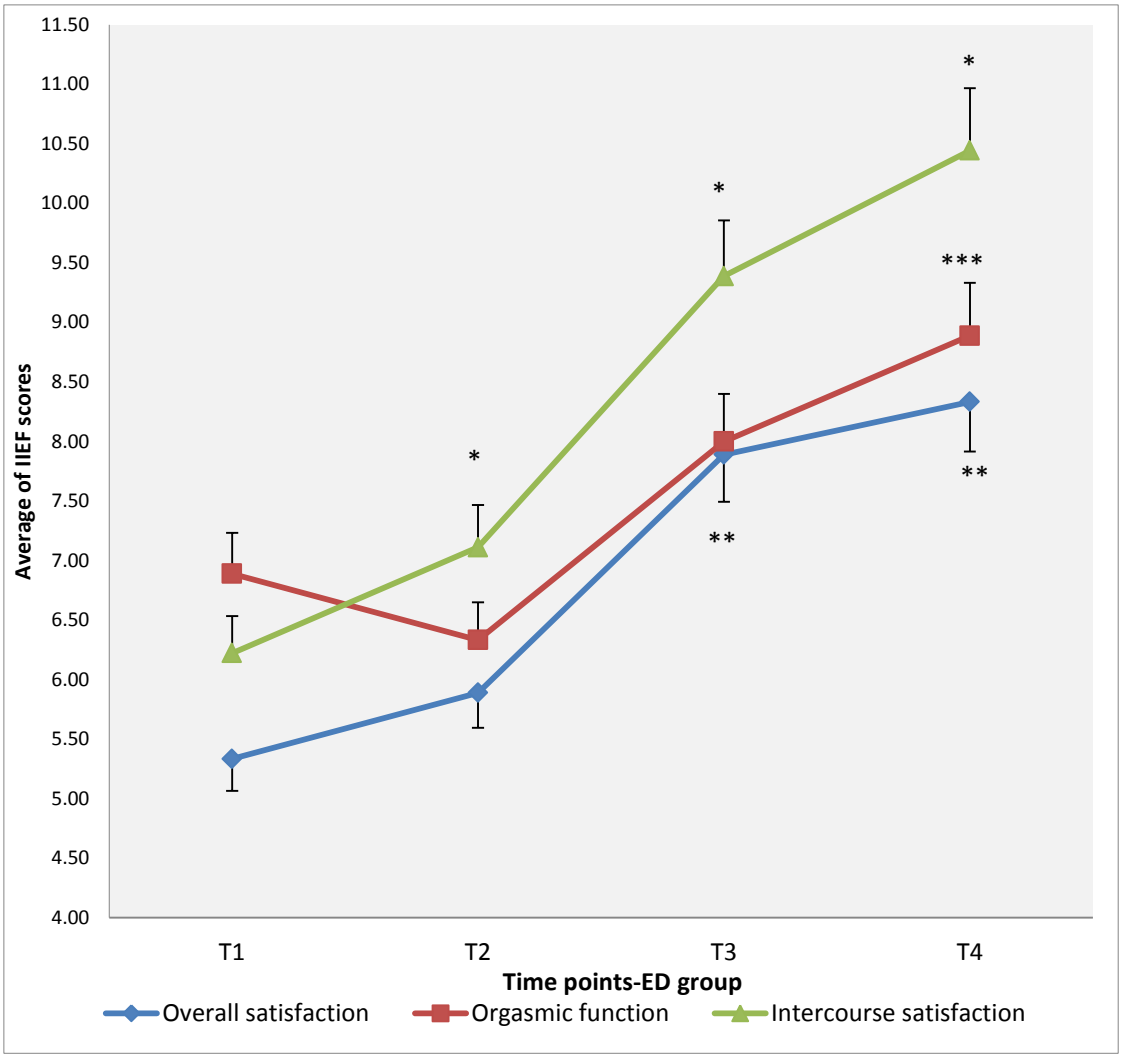


Figure 3-14: Changes in overall satisfaction, orgasmic function and intercourse satisfaction –IIEF domains for ED group through time

IIEF questionnaire data derived from patients with ED (n=18) were significantly improved for all domains cross the time ($p<0.001$).

***** Significant improvement for intercourse satisfaction ($p=004$) domain was found at T2 compared to T1 and continued until T4.

****** Overall satisfaction ($p=0.001$) reached significance at T3 compared to T1 continued until T4 ($p \leq 0.002$).

******* Orgasmic function reached significant level at T4 ($p=0.004$).

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

For clarity, the chart was split into two parts (Figure 3-13 and Figure 3-14) and different error bars were used (negative error bars for overall satisfaction, positive error bars for orgasmic function and intercourse satisfaction). These are two separate graphs; their figure legends should be separate.

Table 3-33: IIEF scores of patients from the ED group over time.

Variables	Mean rank					
	T1	T2	T3	T4	Chi-square (X^2)	p[a]
Erectile function	1.3	1.9	3.2	3.5	37.8	<0.001
Orgasmic function	2.3	1.7	2.6	3.5	23.1	<0.001
Sexual desire	1.6	1.8	2.9	3.6	30.9	<0.001
Intercourse satisfaction	1.5	2.1	2.9	3.5	32.7	<0.001
Overall satisfaction	1.6	1.8	3.1	3.5	36.4	<0.001

[a] Friedman's test was used.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-34: The significance of differences in IIEF scores between time points in the ED group

Variables	Significance level (p) against T1[a]		
	T2	T3	T4
Erectile function	**0.02**	**<0.001**	**0.001**
Orgasmic function	0.27	0.07	**0.004**
Sexual desire	0.42	**0.002**	**<0.001**
Intercourse satisfaction	**0.004**	**0.001**	**0.001**
Overall satisfaction	0.15	**0.001**	**0.001**

[a] Wilcoxon signed rank test was used.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

3.2.6.2 NO-ED group: overall improvement

The IIEF questionnaires data of the 12 patients in the NO-ED group were not normally distributed (Table 3-25); therefore Friedman's test was used to test whether the erectile function improved over time. The test results showed that there was indeed a significant overall improvement in total IIEF score ($X^2(3,18)=14.1$, p=0.003). The mean rank for erectile function domain was shown to drop at T2 then it was similar at T3 and T4. No significant effect was

found on orgasmic function (X^2(3,18)= 3.9, p=0.27) the mean rank was shown to be similar across all times (Figure 3-15; Figure 3-16; Table 3-35). The sexual desire domain significantly improved over time (X^2(3,18)=11.28, p=0.01), but showed a decrease at T2. Intercourse satisfaction also showed a significant improvement over time (X^2(3,18)=14.35, p=0.002 but again the mean rank dropped at T2 and then increased with T3 and T4. The mean rank for overall satisfaction appeared to drop in T2 and then was found to be similar in T3 and T4, (X^2(3,18)=13.65, p=0.003) (Table 3-36).

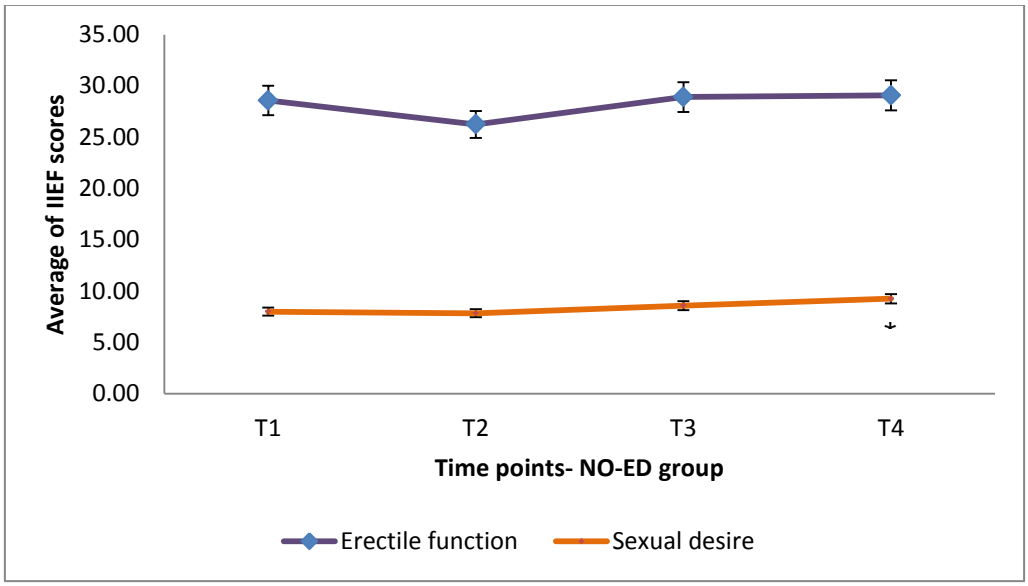


Figure 3-15: Changes in erectile function and sexual desire- IIEF domains for the NO-ED group over time.

IIEF questionnaire data derived from patients without ED (n=12) were significantly improved in all domains except orgasmic function over time (p≤0.01).
* Significant improvement for sexual desire (p=0.02) domain was found at T4 compared to T1.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

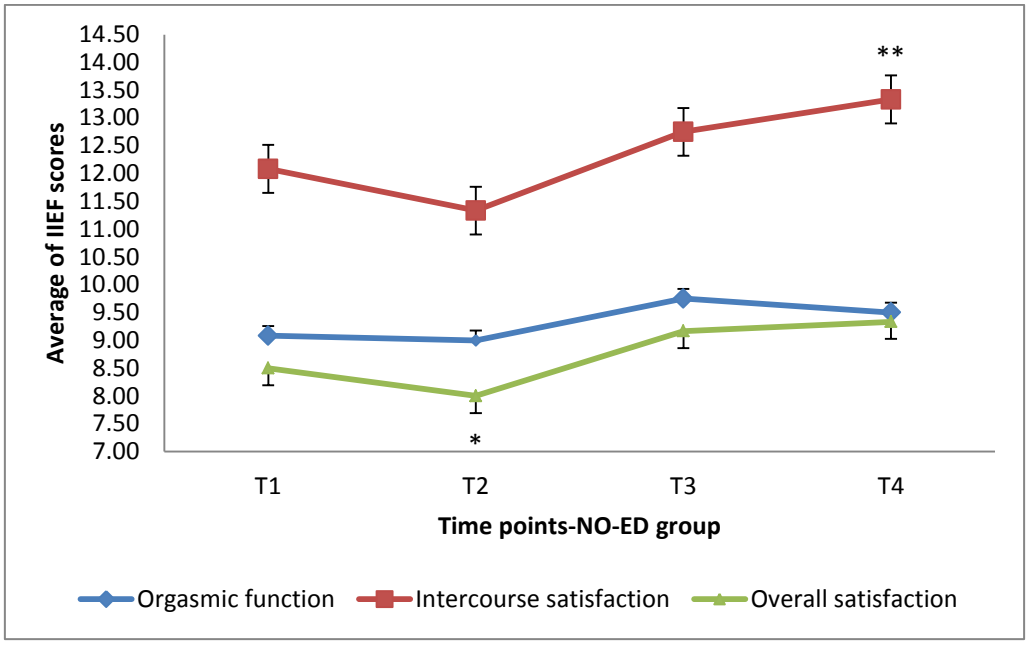


Figure 3-16: Changes in orgasmic function, intercourse satisfaction and overall satisfaction- IIEF domains for the NO-ED group over time.

IIEF questionnaire data derived from patients without ED (n=12) were significantly improved in all domains except orgasmic function over time ($p \leq 0.01$).

* Significant improvement for the overall satisfaction ($p=0.03$) domain was found at T2 compared to T1 but not continued at T3 and T4.

** Significant improvement for intercourse satisfaction ($p=0.01$) domain was found at T4 compared to T1.

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

For clarity, the chart was split into two parts (Figure 3-15 and Figure 3-16) and different error bars were used (negative error bars for overall satisfaction, positive error bars for orgasmic function).

Table 3-35: IIEF scores of the NO-ED group over time.

Variables	Mean rank					
	T1	T2	T3	T4	Chi-square (X^2)	p[a]
Erectile function	2.17	1.67	3.00	3.17	14.08	**0.003**
Orgasmic function	2.25	2.25	2.92	2.58	3.94	0.27
Sexual desire	2.13	1.96	2.71	3.21	11.28	**0.01**
Intercourse satisfaction	2.00	1.83	2.79	3.38	14.35	**0.002**
Overall satisfaction	2.25	1.71	3.00	3.04	13.65	**0.003**

[a] Friedman's test was used.

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation. All times compared with T1 (one month pre-operation, baseline).

Table 3-36: The significance level of differences between time points in IIEF scores in the NO-ED group.

Variables	Significance level (p) against T1[a]		
	T2	T3	T4
Erectile function	0.15	0.29	0.14
Orgasmic function	0.73	0.14	0.44
Sexual desire	0.53	0.16	**0.02**
Intercourse satisfaction	0.38	0.08	**0.01**
Overall satisfaction	**0.03**	0.10	0.06

[a] Wilcoxon signed rank test was used.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

3.2.7 Change in urological function following bariatric surgery over time

3.2.7.1 ED group: overall improvement

IPSS questionnaire data were not normally distributed, therefore Friedman's test was used to analyse the data (Table 3-25). Twelve patients were classified to have NO-ED. Using Friedman's test, a significant change was observed in all domains from pre- to post- surgery ($p < 0.005$), except in one domain (straining) in which no significant effect was found (Figure 3-17; Figure 3-18; Figure 3-19; Figure 3-20; Table 3-37). The difference between time points was evaluated using Wilcoxon signed rank test in order to find out at what time point IPSS scores improved compared to the baseline (T1). There was a significant improvement at T2 compared to the baseline (T10 ($p<0.05$) for frequency, intermittency, weak stream, nocturia and quality of life (Qol) domains. The significant improvement in incomplete emptying and urgency domains were observed in T3 compared to the baseline (T1) ($p \leq 0.01$), and for straining no significant improvement was observed over time (Table 3-38).

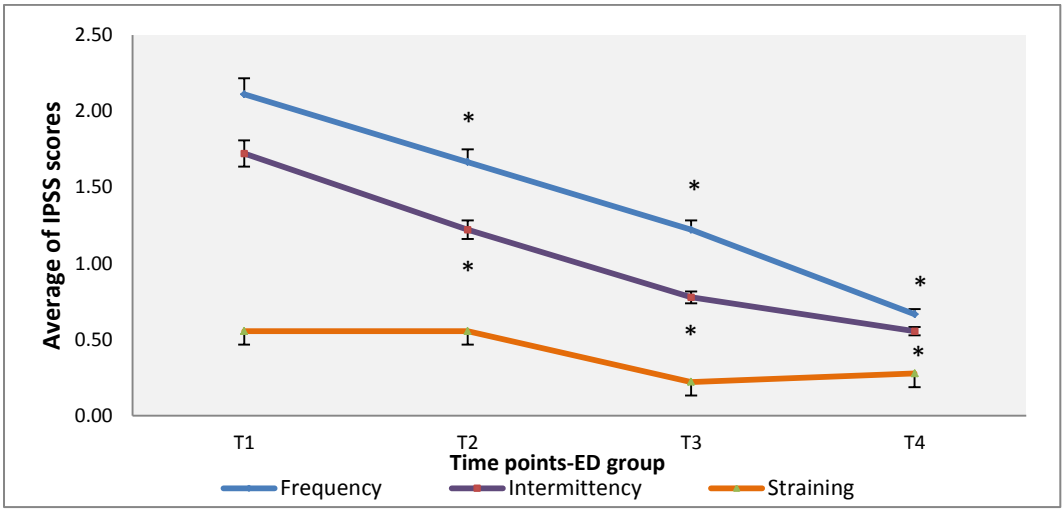


Figure 3-17: Changes in frequency, intermittency and straining - IPSS domains for the ED group over time.

IPSS questionnaire data derived from patients with ED (n=18) were significantly improved in all domains over time (p≤0.004), exception of straining (p=0.10).

* Significant improvements in frequency (p=0.02) and intermittency (p=0.01) domains were found at T2 compared to T1 and continued until T4.

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

For clarity, the chart was split into four parts (Figure 3-17; Figure 3-18; Figure 3-19; Figure 3-20) and different error bars were used (positive error bars for frequency, incomplete emptying and urgency and negative error bars for straining and weak stream).

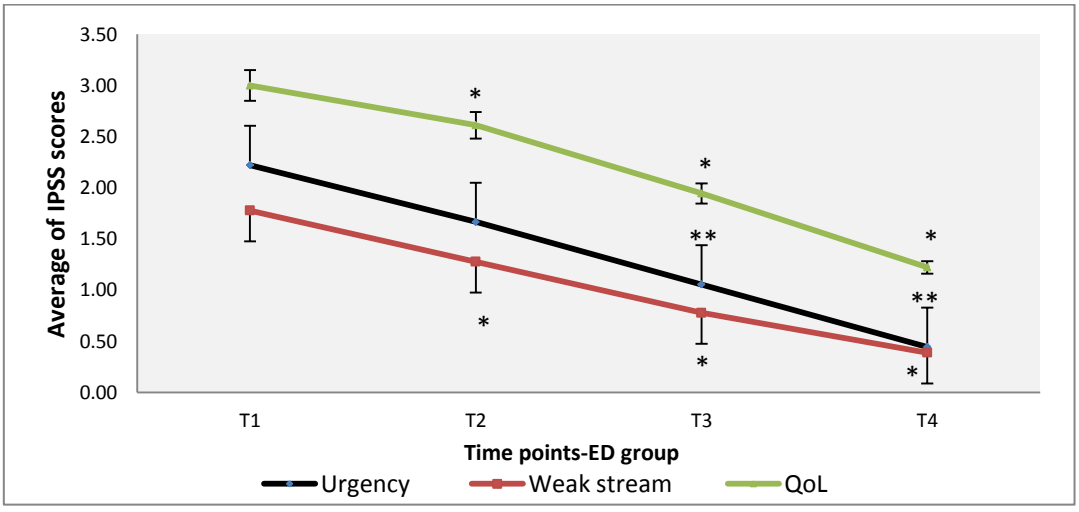


Figure 3-18: Changes in urgency, weak stream and Qol - IPSS domains for the ED group over time.

IPSS questionnaire data derived from patients with ED (n=18) were significantly improved in all domains over time (p≤0.004), exception of straining (p=0.10).

* Significant improvements in weak stream (p=0.01) and quality of life (Qol) (p=0.03) were found at T2 compared to T1 and continued until T4.

** Significant improvement in urgency (p=0.003) was found at T3 compared to T1 and continued until T4.

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.
For clarity, the chart was split into four parts (Figure 3-17; Figure 3-18; Figure 3-19; Figure 3-20) and different error bars were used (positive error bars for frequency, incomplete emptying and urgency and negative error bars for straining and weak stream).

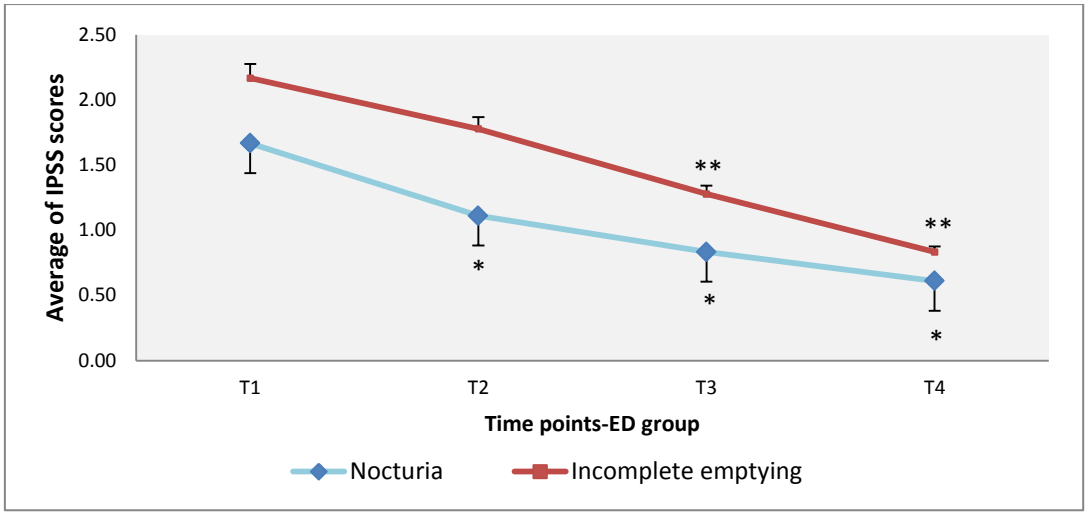


Figure 3-19: Changes in nocturia and incomplete emptying - IPSS domains for the ED group over time.
IPSS questionnaire data derived from patients with ED (n=18) were significantly improved in all domains over time (p≤0.004), exception of straining (p=0.10).
* Significant improvements in nocturia (p=0.002) was found at T2 compared to T1 and continued until T4.
** Significant improvement in incomplete emptying (p=0.01) was found at T3 compared to T1 and continued until T4.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.
For clarity, the chart was split into four parts (Figure 3-17; Figure 3-18; Figure 3-19; Figure 3-20) and different error bars were used (positive error bars for frequency, incomplete emptying and urgency and negative error bars for straining and weak stream).

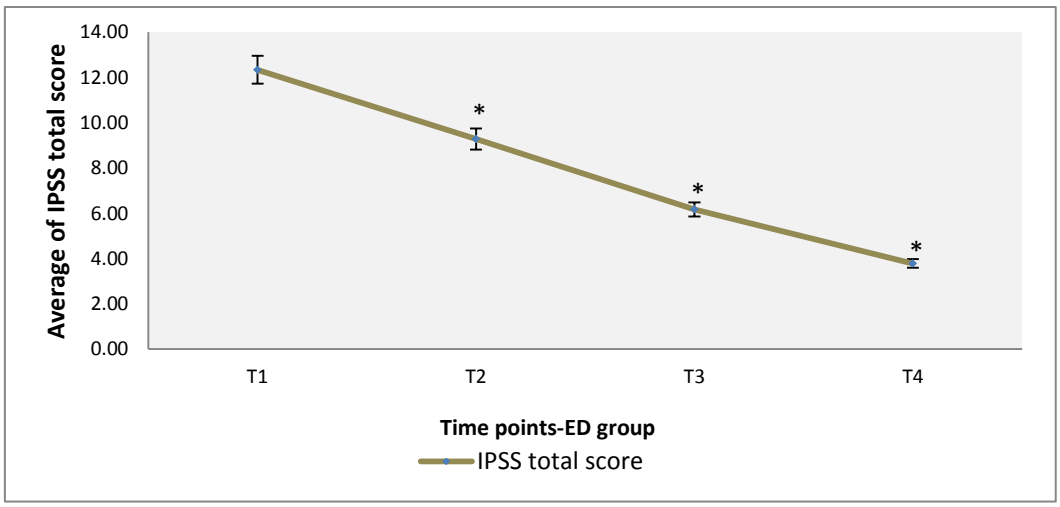


Figure 3-20: Changes in IPSS total score for the ED group over time.
IPSS questionnaire data derived from patients with ED (n=18) were significantly improved in all domains over time (p≤0.004), exception of straining (p=0.10).

* Significant improvements in IPSS total score domain (p=0.002) was found at T2 compared to T1 and continued until T4.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-37: IPSS scores of the ED group over time.

Variables	Mean rank				Chi-square (X^2)	p[a]
	T1	T2	T3	T4		
Incomplete emptying	3.11	2.86	2.22	1.81	20.46	**<0.001**
Frequency	3.19	2.69	2.39	1.75	17.55	**0.001**
Intermittency	3.17	2.58	2.14	2.11	13.57	**0.004**
Urgency	3.25	2.94	2.08	1.72	22.48	**<0.001**
Weak stream	3.47	2.86	2.06	1.61	32.87	**<0.001**
Straining	2.72	2.78	2.28	2.22	6.22	0.10
Nocturia	3.42	2.50	2.14	1.94	23.68	**<0.001**
Q o L	3.28	2.31	2.31	1.44	31.29	**<0.001**
IPSS total score	3.58	2.69	2.06	1.67	24.19	**<0.001**

[a] Friedman's test was used.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-38: The significance of differences in IPSS scores between time points in the ED group.

Variables	Significance level (p) against T1[a]		
	T2	T3	T4
Incomplete emptying	0.08	**0.01**	**0.004**
Frequency	**0.02**	0.06	**0.02**
Intermittency	**0.01**	**0.01**	**0.01**
Urgency	0.07	**0.003**	**0.002**
Weak stream	**0.01**	**0.002**	**<0.001**
Straining	1.00	0.11	0.29
Nocturia	**0.002**	**0.002**	**0.002**
Q o L	**0.03**	**0.007**	**0.001**
IPSS total score	**0.002**	**0.02**	**0.001**

[a] Wilcoxon signed rank test was used.
T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation; all times compared with T1 (one month pre-operation, baseline).

3.2.7.2 NO-ED group: overall improvement

IPSS questionnaire data were not normally distributed therefore a Friedman's test was used to analyse the data (Table 3-25). Friedman's test presented a significant effect over time in two domains (nocturia and quality of life due to urological function) and the total IPSS score (Table 3-39). Thus, the mean rank showed decreased symptoms over time ($p < 0.05$). However, no significant effects were found on incomplete emptying, frequency, intermittency, urgency, weak stream or straining ($p > 0.05$) (Figure 3-21; Figure 3-22; Figure 3-23; Figure 3-24). No significant differences were observed between IPSS domains compared to the baseline (T1) ($p > 0.05$). However, QoL was significantly improved at T2 compared to baseline (T1) but did not continue until six months post-operation. The IPSS total score and nocturia were significantly different at T4 compared to the baseline (T1) ($p < 0.05$; Table 3-40).

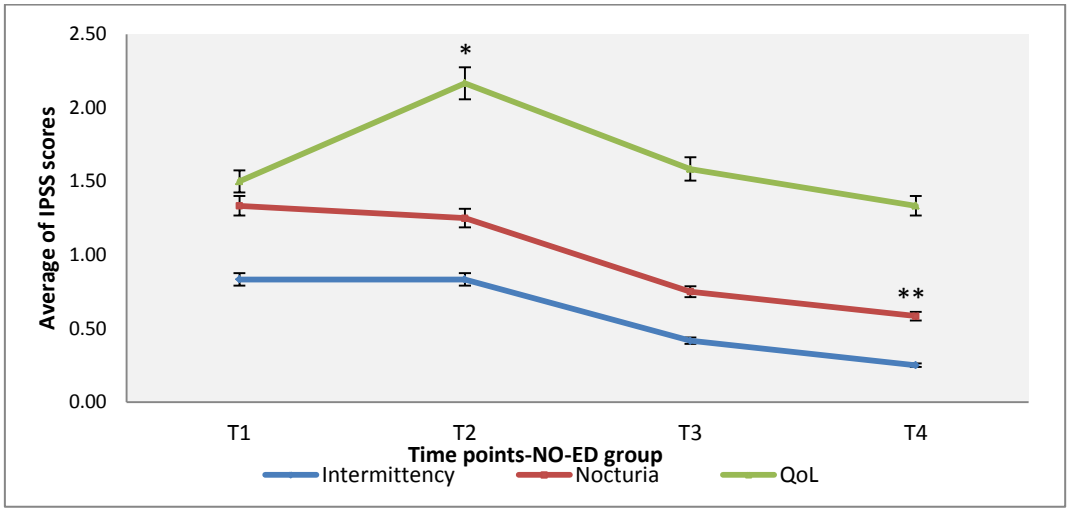


Figure 3-21: Changes in intermittency, nocturia and Qol -IPSS domains for the NO-ED group over time.

IPSS questionnaire data derived from patients without ED (NO-ED; n=12) were significantly improved in nocturia (p=0.01) and quality of life (Qol) (p=0.03) domains over the time.

* Significant improvement for Qol (p=0.047) domain was found at T2 compared to T1 but not continued until T4.

** Significant improvement for Nocturia (p=0.03) domain was found at T4 compared to T1.

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

For clarity, the chart was split into four parts (Figure 3-21; Figure 3-22; Figure 3-23; Figure 3-24).

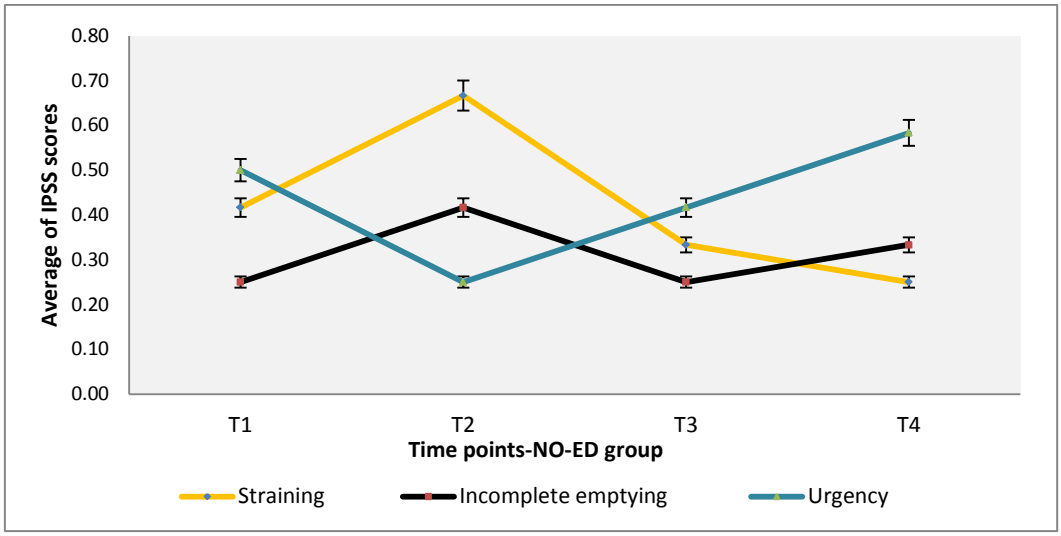


Figure 3-22: Changes in straining, incomplete emptying and urgency - IPSS domains for the NO-ED group over time.

IPSS questionnaire data derived from patients without ED (NO-ED; n=12) were no significant detected in straining, incomplete emptying and urgency domains over the time (p>0.05).

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

For clarity, the chart was split into four parts (Figure 3-21; Figure 3-22; Figure 3-23; Figure 3-24).

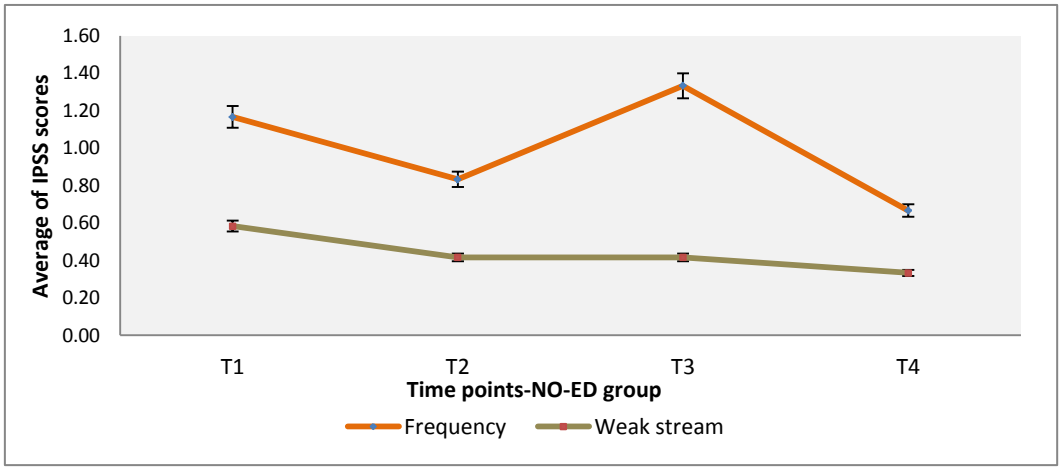


Figure 3-23: Changes in frequency and weak stream -IPSS domains for the NO-ED group over time.

IPSS questionnaire data derived from patients without ED (NO-ED; n=12) were no significant detected in frequency and weak stream domains over the time (p>0.05).

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

For clarity, the chart was split into four parts (Figure 3-21; Figure 3-22; Figure 3-23; Figure 3-24).

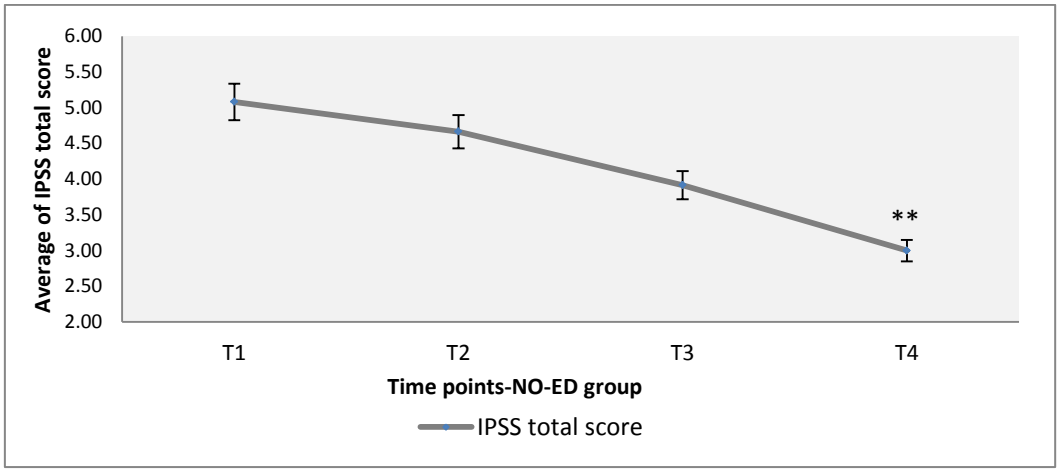


Figure 3-24: Changes in IPSS total score domain for the NO-ED group over time.

IPSS questionnaire data derived from patients without ED (NO-ED; n=12) was significantly improved in IPSS total score (p=0.01) domain over the time.

* Significant improvement for IPSS total score (p=0.049) domain was found at T4 compared to T1.

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

For clarity, the chart was split into four parts (Figure 3-21; Figure 3-22; Figure 3-23; Figure 3-24).

Table 3-39: IPSS scores for the NO-ED group over the time.

Variables	Mean rank				Chi-square (X^2)	p[a]
	T1	T2	T3	T4		
Incomplete emptying	2.01	2.00	1.98	1.82	2.28	0.52
Frequency	2.02	2.00	1.85	1.74	6.03	0.11
Intermittency	3.00	2.50	2.14	2.10	7.76	0.05
Urgency	2.25	2.10	2.08	1.98	1.64	0.65
Weak stream	2.45	2.22	2.06	1.99	2.23	0.52
Straining	2.70	2.55	2.27	2.20	2.78	0.43
Nocturia	2.30	2.02	2.00	1.93	11.41	**0.01**
Q o L	3.20	2.10	2.01	1.94	8.79	**0.03**
IPSS total score	2.51	2.32	2.03	1.67	11.93	**0.01**

[a] Friedman's test was used.

Table 3-40: Wilcoxon signed rank test comparing IPSS scores in the NO-ED group over multiple time-points.

Variables	Significance level against T1[a]		
	T2	T3	T4
Incomplete emptying	0.26	1.00	0.71
Frequency	0.48	0.71	0.14
Intermittency	0.76	0.06	0,10
Urgency	0.41	1.00	1.00
Weak stream	0.48	0.56	0.16
Straining	0.16	1.00	0.41
Nocturia	0.71	0.05	**0.03**
Q o L	**0.047**	0.74	0.59
IPSS total score	0.81	0.58	**0.049**

[a] Wilcoxon signed rank test was used.
T2; one month post-operation, T3; three months post operation, T4; six months post-operation, all times compared with T1 (one month pre operation, baseline).

3.2.8 Change in metabolic biomarkers following bariatric surgery over time

Fasting blood glucose (FBG) and HbA1c values were largely not normally distributed (Table 3-25). The median and IQR of FBG for ED and NO-ED groups were 5.3 (4.6, 8.3) mmol/L and 5.4 (4.4, 14.0) mmol/L) respectively at T1. The median and IQR values for HbA1c were 43.5 (37.0, 58.0) mmol/mol and 44.0 (32.0, 95.0) mmol/mol, respectively at T1. There was no significant difference between the ED and NO-ED groups at the baseline (T1; Table 3-41).

Table 3-41: The difference in fasting blood glucose and HbA1c values in the ED and NO-ED groups at baseline (T1).

Variables	ED (n=18)	NO-ED (n=12)	p[a]
	Median (IQR)	Median (IQR)	
Fasting blood glucose	5.3 (4.6, 8.3)	5.4 (4.4, 14.9)	0.71
HbA1c	43.5 (37.0, 58.0)	44.0 (32.0, 95.0)	0.81

[a] Mann-Whitney U test was used.

Moreover, 38.9% of patients with ED had FBG levels above the normal range (above 5.8 mmol/L) and 61.1% of patients had HbA1c levels above the normal range (42 mmol/mol), while 41.7% of patients without ED (NO-ED) had FBG levels and 50.0% of patients had HbA1c levels above the normal range.

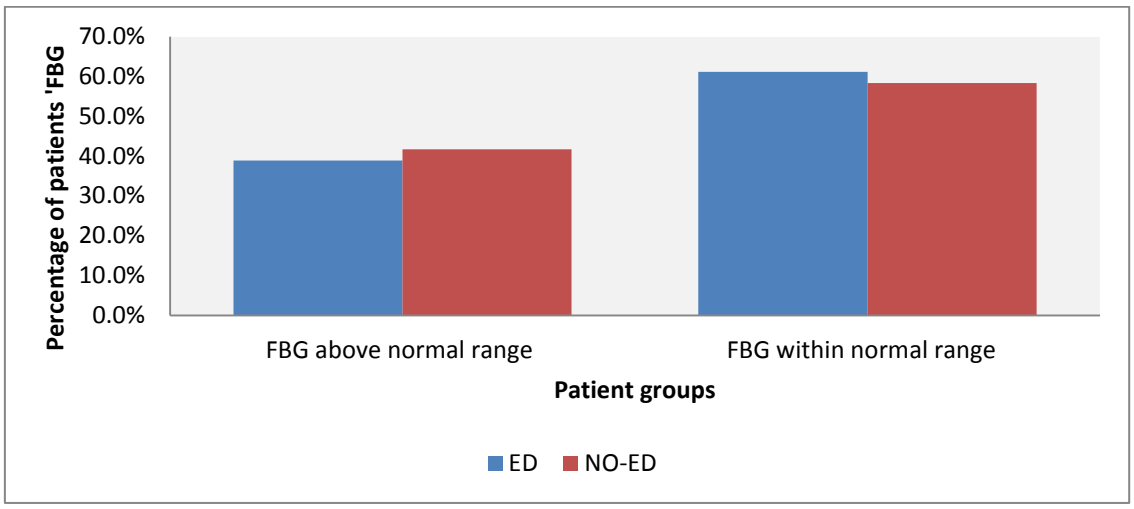


Figure 3-25: Percentage of patients' fasting blood glucose above or within the normal range.
Data showed that 38.9% of patients with ED (n=18) had fasting blood glucose (FBG) levels above the normal range (above 5.8 mmol/L) and 61.1% of patients presented value within the normal range (3.9-5.8 mmol/L). Also 41.7% of patients without ED (NO-ED; n=12) had levels above the normal range while 58.3% fell within normal range. There was no significant difference between ED and NO-ED groups in FBG (p>0.05) (Table 3-41).

Using Friedman's test showed an improvement over time in FBG and HbA1c in the ED and NO-ED groups (p<0.01; Figure 3-26, Figure 3-27 and Table 3-42.

The difference between the time points was evaluated using Wilcoxon signed rank test compared to the baseline (T1). The results of FBG and HbA1c in the ED group were $X^2(3,18)= 32.6$ (p<0.001) and $X^2(3,18)=44.48$, (p=<0.001) respectively. This showed an improvement at T2 compared to T1 and continued until T4.

The results of the NO-ED group showed an improvement in HbA1c at T2 compared to T1 and continued to T4 (p <0.005). However, FBG results showed improvement at only T4 compared to T1 (p=0.047) (Table 3-43).

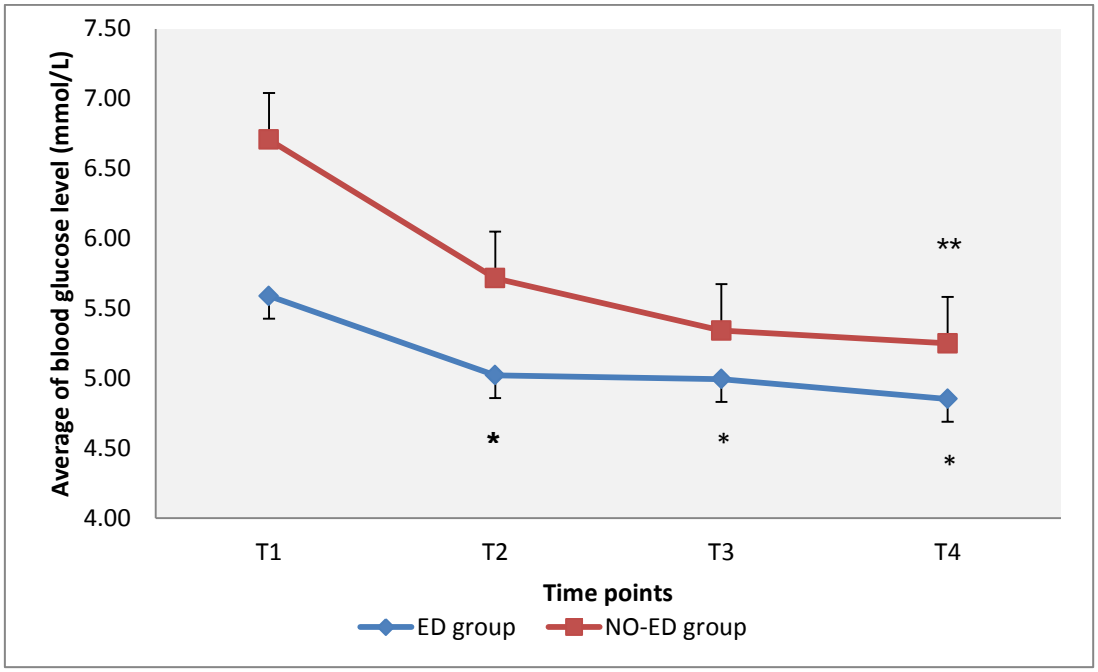


Figure 3-26: Changes in fasting blood glucose level in the ED and NO-ED groups over time.

Fasting blood glucose data derived from patients from the ED (n=18) and NO-ED (n=12) groups were significantly improved over the time ($p \leq 0.001$ and $p=0.01$, respectively).

*Significant improvement for fasting blood glucose level in the ED group ($p<0.001$) was found at T2 compared to T1 and continued until T4.

** Significant improvement was found at T4 compared to T1 for NO-ED group ($p=0.047$).

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

For clarity, different error bars were used (negative error bars for the ED group, positive error bars for the NO-ED group).

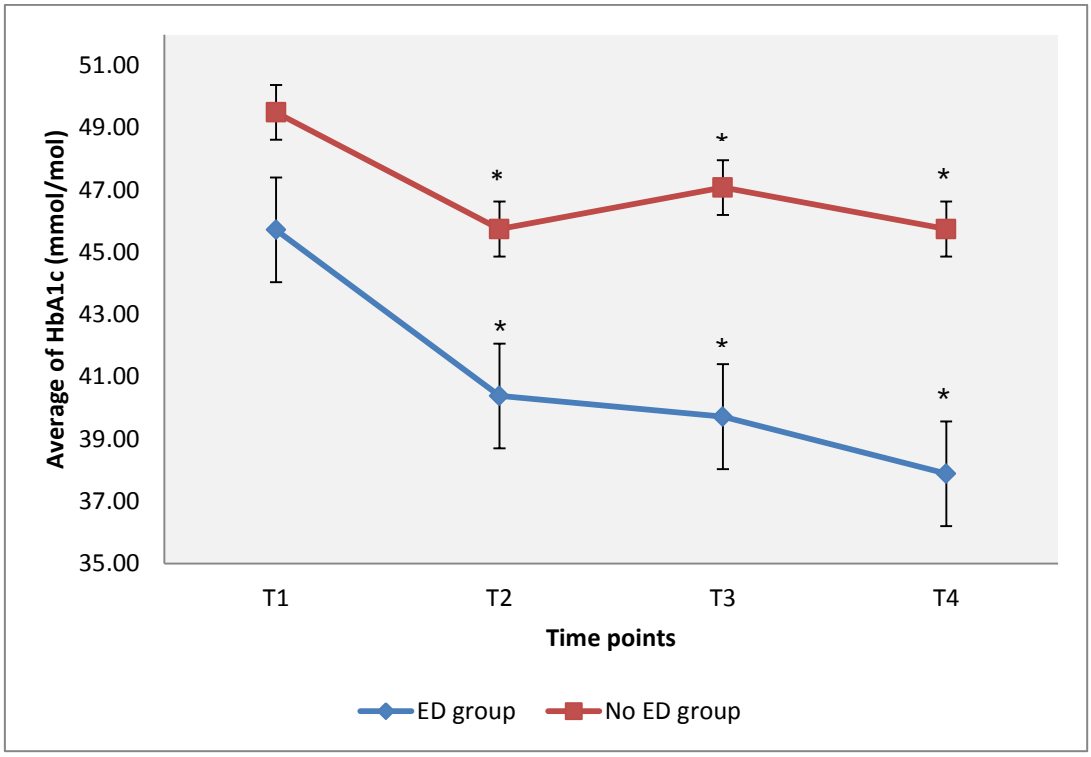


Figure 3-27: Changes in HbA1c level in the ED and NO-ED groups over time.

HbA1c data derived from patients in the ED (n=18) and NO-ED (n=12) groupswere significantly improved over time (p≤0.001 and p=0.001, respectively).

* Significant improvement for HbA1c levels in the ED (p<0.001) and NO-ED groups (p=0.004) were detected at T2 and continued until T4.

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-42: Fasting blood glucose level and HbA1c in the ED and NO-ED groups over time.

Variables	Mean rank					
	T1	T2	T3	T4	Chi-square (X^2)	p[a]
Fasting blood glucose level (ED group)	3.94	2.08	2.14	1.83	32.6	**<0.001**
HbA1c (ED group)	4.00	2.36	2.39	1.25	44.48	**<0.001**
Fasting blood glucose level (NO-ED group)	3.17	2.83	2.29	1.71	11.14	**0.01**
HbA1c (NO-ED group)	3.38	2.50	2.50	1.63	12.60	**0.001**

[a] Friedman's test was used.

T1: one month pre-operation; T2: one month post-operation; T3: three months post-operation; T4: six months post-operation.

Table 3-43: The significance of differences between time points for fasting blood glucose level and HbA1c in the ED and NO-ED groups.

Variables	significance level against T1[a]		
	T2	T3	T4
Fasting blood glucose level (ED group)	**<0.001**	**<0.001**	**0.003**
HbA1c (ED group)	**<0.001**	**<0.001**	**<0.001**
Fasting blood glucose level (NO-ED group)	0.051	0.056	**0.047**
HbA1c (NO-ED group)	**0.004**	**0.001**	**0.001**

[a] Wilcoxon signed rank test was used.
T2; one month post-operation, T3; three months post-operation, T4; six months post-operation, all times compared with T1 (one month pre-operation; baseline).

4 DISCUSSION

This chapter interprets the audit findings in light of the existing literature. In sections 4.1 and 4.2, the results associated with each of the two research questions are contextualised and discussed, as are any broader implications. The end of each section concludes with the limitations of the present audit which should be borne in mind.

The aim of this project, as described in section 1.5, was to evaluate the baseline characteristics of patients with an erectile dysfunction, and to determine the impact of bariatric surgery on erectile and urological function in morbidly obese men. This information would then be used to investigate on a large scale, the hypothesis that obesity is a hidden factor responsible for urogenital dysfunction. The information gained would also be validated for use in the design of a multi-centre observational longitudinal cohort study.

The objectives of the audit were as follows:

1. To conduct an audit to investigate the baseline characteristics of men over 18 years of age who were attending the urological clinic, using IIEF and IPSS questionnaires.
2. To perform a study to explore the effect of BMI on the urogenital function of men over 18 years of age attending the urological clinic, using IIEF and IPSS questionnaires.
3. To collate and analyse other baseline characteristics such as age, smoking and medical history.
4. To conduct a second audit to investigate the effect of bariatric surgery on the urogenital function and BMI of morbidly obese men over 30 years of age with a body mass index of 35 or over.
5. To utilise and obtain urogenital function and biomarker data from the second audit on morbidly obese men undergoing elective bariatric surgery.
6. To analyse and present the data and recommend further work based on the results.

The following two sections discuss the results of the work carried out to achieve each of these six objectives.

4.1 Baseline characteristics audit

In accordance with NICE (National Institute for Health and Care Excellence) and the Healthcare Commission, and in order to complete the objectives of this audit, participants were selected according to specific criteria by the surgeons working for the NHS trust.

The methods used in selecting and recruiting these participants, as described in section 2.1.3, were based on prior experience of the clinical team and the literature on clinical audits (Kupelian *et al.* 2006, Demir *et al.* 2009, Tsao *et al.* 2008, Copeland 2005).

The audit was conducted using a multidimensional scale for the assessment of erectile dysfunction (the International Index of Erectile Function (IIEF)) (Rosen *et al.* 1997) as described in section 1.2.5 and the International Prostate Symptom Score (IPSS) (Plante *et al.* 1996), as described in section 1.3.6.

Additional information such as medical history and blood tests, were also acquired from patients' records using the UCLH database and following the guidelines of UCL data protection (UCL Library Services 2015).

Furthermore, the audit was conducted over a nine month period during 2014, involving sixty patients with any urological condition. According to the responses from answering the IIEF erectile function domain, the patients were divided into two groups: ED and NO-ED. A cut-off score of 25 or less was used for the diagnosis of ED (Cappelleri *et al.* 1999).

Overall, it can be stated that the recruiting method that was used was successful in recruiting forty eight patients with erectile dysfunction (ED) and twelve patients with NO-ED for the study, during nine months covering one urology clinic per week. This was achieved mainly by following good local clinical audit criteria from the NHS trust (Cappelleri *et al.* 1999) which is

endorsed by NICE and the healthcare commission in the United Kingdom (NICE 2015).

4.1.1 Correlations in the baseline characteristics audit

The aim of the correlations presented in this section was to observe sexual function among participants with obesity in particular. Sexual dysfunction is highly predominant in the general population and is associated with a lower quality of life (Sarwer *et al.* 2012). Obesity is clearly linked with sexual dysfunction in men (Feldman *et al.* 2000, Esposito *et al.* 2005).

4.1.1.1 Age

The average age of the patients was 46.2 ±13.7 years old, which is representative of patients at urology clinics and in line with the literature (Feldman *et al.* 1994, Johannes *et al.* 2000). The average age of ED patients was 47.1 ±13.1 years. Although age is a primary risk factor for erectile dysfunction and ED is usually associated with older age (Kirby *et al.* 2014), several studies have reported ED in the younger male population for those ≤60 years old (Feldman *et al.* 1994, Cappelleri *et al.* 2005).

The literature shows a clear relationship between age and ED (Prins *et al.* 2002). Although there was no apparent significant difference in age between the ED and NO-ED groups, there were significant correlations in the audit population between age and IIEF domains; erectile function, orgasmic function and sexual desire.

The most significant finding from this study is that ED occurs in 80% of the audit population, and in men younger than 60 years, although there is no definite explanation of why this phenomenon occurs in younger men (Prins *et al.* 2002, Camacho *et al.* 2013). Some studies suggest that erectile dysfunction has a biological reason behind it (Thrower *et al.* 2013, Camacho *et al.* 2013). It is still a matter of argument whether age-related changes in androgen levels play a role in the decline of sexual function in ageing men, despite sexual activity declining even in old men who are healthy and have partners (Sariyildiz *et al.*

2013). Moreover, several studies suggest that testosterone levels in men decline significantly with increasing age as part of the natural biological process (Prins *et al.* 2002, Camacho *et al.* 2013). The testosterone results from the audit further support the possible involvement of androgens in development of ED in men younger than 60 years old which will be further discussed.

4.1.1.2 Height

There was a statistically significant difference in the height between ED and NO-ED groups. The audit suggests that taller men have a higher incidence of ED, although height is not considered to be a classical risk factor for ED. However, Cappelleri, *et al* (1999) evaluated the erectile function domain of IIEF as a diagnostic tool to differentiate between men with and without ED. The study showed the baseline characteristics including physical measures such as height, weight and age of 1035 men who reported ED and 116 controls. The authors showed that the ED group was taller than the control group, although this finding was not supported by any explanations in this study (Cappelleri *et al.* 1999).

4.1.1.3 Medical conditions

The presence of more than two medical conditions may create a higher risk of having ED, and this is compatible with a previous study by (Johannes *et al.* 2000). Moreover, an Italian study conducted by urologists, surveyed over 2,000 men aged 18 years or over. This study showed that multiple medical conditions such as diabetes combined with heart disease increased the risk of developing ED eight-fold (Parazzini *et al.* 2000). Also, the results from a Massachusetts male ageing study concluded that ED was directly and strongly correlated with the presence of several medical conditions such as diabetes, heart disease, hypertension and depression (Feldman *et al.* 1994).

4.1.1.4 Clinical biomarkers

4.1.1.4.1 Testosterone

The objective of the work presented in section 3.1.7.5 was to observe the impact of clinical biomarkers that influence sexual and urological functions. From the literature, it had been shown that testosterone is the hormone most widely associated with erectile function, but its role in the treatment of erectile dysfunction has been debated (Shamloul *et al.* 2013, Corona *et al.* 2010, Feldman *et al.* 2002). The average testosterone serum levels in ED and NO-ED groups were 16.2 nmol/L and 18.1 nmol/L respectively; the difference was significant. The impact of testosterone was revealed in the audit (see Table 3-7) to be the main difference between ED and NO-ED groups, and was confirmed by the significant correlation with IIEF domains: erectile function, orgasm function, sexual desire and intercourse satisfaction.

The role of testosterone in men's sexual function and its role in treatment of ED has been subject of debate (Feldman *et al.* 1994, Feldman *et al.* 2002, Rhoden *et al.* 2002, Mikhail 2006).One of the debated topics in this field is whether elderly men should be given testosterone as a prophylactic . Shores *et al* (2012), concluded from their observational study of mortality in testosterone-treated compared with untreated men aged older than 40 years that testosterone treatment was associated with decreased mortality compared with no testosterone treatment between January 2001 and December 2002 (Shores *et al.* 2012). Moreover, Isidori *et al* (2005) conducted a systematic review and meta-analysis of available studies on the useful effect of testosterone treatment for erectile function. The results from the meta-analysis indicate that testosterone treatment might be useful for improving ED in patients with low or normal testosterone levels. However, the evidence for the long-term safety data is not available (Isidori *et al.* 2005).

Another argument suggests that testosterone should not be given to men unless there are important needs, for example according to a letter published in the British Medical Journal (BMJ) (2012) regarding reflections on testosterone.

Over the last two decades, the BMJ has pointed out that physicians should be wary of the harm that the androgens can do to patients by unnecessarily worrying them of side effects for which there is no evidence or raising spurious parallels to other unrelated disease areas (Gan *et al.* 2012). Moreover, the British Society for Sexual Medicine (BSSM) has issued guidelines on the management of sexual problems in men. The role of testosterone in maintaining wellbeing in men is well established, and men with confirmed ED and documented testosterone deficiency are candidates for testosterone therapy. The guidelines also state that failure to benefit within a reasonable time interval (up to six months) should result in discontinuation of treatment due to the risk of side effects (Hackett *et al.* 2008).

The Food and Drug Administration (FDA) has approved testosterone products as replacement therapy in men with hypogonadism (where the body doesn't produce enough testosterone) (Nguyen *et al.* 2015). Recently, testosterone use has increased noticeably among middle-aged and elderly men for age-related hypogonadism (Nguyen *et al.* 2015). The FDA refer to this condition as “late-onset hypogonadism,” which is identified in men who have no reason other than older age and testosterone concentrations below the normal range compared with healthy young men. An analysis by the FDA showed that more than 80% of prescription testosterone users are men between 40 and 74 years of age and 28% of men who received a new testosterone prescription had no evidence of a prior testosterone measurement (Nguyen *et al.* 2015). The FDA concluded in September 2014 that an indication for testosterone therapy only in men with classic hypogonadism and testosterone treatment had not been established for age-related hypogonadism. Also, the FDA recommends adding a statement to drug labels about the need to confirm low testosterone concentrations before initiating treatment. The FDA also recommends that a controlled clinical trial should be considered rather than observational studies (Nguyen *et al.* 2015).

In this study, free and bioavailable testosterone results have not shown any significance when compared with IPSS scores among patients with ED.

However, free and bioavailable testosterone has demonstrated a significant correlation with hypertension and low testosterone correlated with high blood pressure. Ziemens *et al.,* (2013) suggest an association between total testosterone and hypertension in women; also they suggest that high total testosterone levels are a risk factor for increased blood pressure, as well as prevalent hypertension, in women (Ziemens *et al.* 2013).

Likewise, free testosterone has demonstrated a significant correlation with psoriatic arthritis (Saber *et al.* 2010). However, this finding seems to be a chance occurrence due to the power of the sample size effect, as only two participants reported psoriatic arthritis from the sixty participants in total. Moreover, there are no links between free testosterone and psoriatic arthritis in the literature.

The small sample size may also have an effect on bioavailable testosterone and depression, where the results show a positive significant correlation. Other studies suggest a significant link between bioavailable testosterone and depression (Barrett-Connor *et al.* 1999, McIntyre *et al.* 2006).

Moreover, the free testosterone results in this audit suggest a significant correlation with being overweight (BMI>25 kg/m^2) with higher BMI leading to lower testosterone. Epidemiological studies support the relationship between serum testosterone and obesity (MacDonald *et al.* 2010, Brand *et al.* 2014). Adipose tissue affects testosterone levels by increasing the aromatisation of testosterone to oestradiol, for the reason that the aromatase enzyme is concentrated in fat cells (adipocytes) and decreases testosterone levels (Cohen 1999, Cohen 2001). The oestradiol produced by aromatisation reduces testosterone production in the Leydig cells in the testicles (they produce testosterone in the presence of luteinizing hormone (LH)) (Cohen 2001, Dandona *et al.* 2010). Moreover, increasing adipose tissue leads to increased insulin resistance, which affects the Leydig cells, in addition to inhibiting the release of luteinizing hormone (LH) through the release of adipokines (inflammatory cytokines) such as TNF-a (Cohen 2001, Dandona *et al.* 2010, Pitteloud *et al.* 2013).

Moreover, central obesity predicts low testosterone levels. A high BMI is associated with low testosterone and SHBG levels. This is due to obesity suppressing SHBG. Changes in SHBG confound the relationship between testosterone and obesity (MacDonald *et al.* 2010, Brand *et al.* 2014, Laaksonen *et al.* 2005).

Furthermore, there was no correlation detected in this audit between testosterone and age. This might be due to the fact that 80% of the audit population with ED was younger than 60 years. As discussed in section 4.1.1.1 numerous studies suggest that testosterone levels in men decline significantly with the increase of age as part of the natural biological process (Prins *et al.* 2002, Camacho *et al.* 2013).

4.1.1.4.2 Eosinophil

A significant correlation between blood eosinophil levels and two IIEF domains (erectile function and intercourse satisfaction) was found, although nothing was found during the literature review to support this finding. The functions of the eosinophil are varied, and it is involved in many inflammatory processes including bacterial and viral infections (Humbles *et al.* 2004). The responses of eosinophils are also important for their involvement in the acute pathogenesis of allergic diseases (Weller *et al.* 1996). Allergic inflammation is an important pathophysiological feature of several medical conditions such as allergic rhinitis and allergic asthma (Weller *et al.* 1996). Allergic reactions may usually be divided into two phases; the early phase which occurs within a short time (minutes) after allergen exposure; the late phase which occurs within hours (8-12 hours) (Rothenberg *et al.* 2006). Characteristically, the sensitive cells detected in allergic reactions contain a high proportion of eosinophil (Rothenberg *et al.* 2006). It should be also noted that the eosinophil counts were within normal range in all patients.

4.1.1.4.3 Fasting blood glucose and HbA1c

The results show no abnormalities in the average of FBG and HbA1c, which are the risk factors in ED and urological function (Fedele 2005, Parsons 2010,

Demir *et al.* 2009, Kaya *et al.* 2015). However, these findings are compatible with Demir *et al*., (2009) study, while they disagree with previous literature (Hatzimouratidis *et al.* 2009, Bansal *et al.* 2005, Corona *et al.* 2009) . This disagreement might have arisen from two important factors; the small size of the audit population was a major influence on the statistical calculations; only eight patients out of sixty reported abnormalities in their FBG and HbA1c; the other reason is the nature of the audit since it is an observational, single time point study.

4.1.1.5 Sexual function (IIEF)

As expected from the comparison of the presence of sexual dysfunction between the ED and NO-ED groups, there were statistically significant differences between the two groups in the IIEF domains scores: erectile function, orgasm function, sexual desire, intercourse satisfaction and overall satisfaction (p≤003). This finding is supported a study by Rosen *et al* (1997) which compared two groups - patients with ED and a control group. The results presented and discussed in the study show that all IIEF domains were significantly different between the two groups (p≤0.01)(Rosen *et al.* 1997).

4.1.1.6 Urological function (IPSS)

The results previously presented in section 3.1.7.3 reveal no significant correlation between ED and IPSS domains, while the literature suggests the presence of ED is significantly associated with LUTS (Tsao *et al.* 2008). This disagreement could be due to the small sample size in the audit, which was 48 patients, compared, for example, with Tsao *et al's.* (2008) study, where the sample size was 398 patients. Similar findings have been reported in another large observational, population-based, cross-sectional internet survey to assess the prevalence of LUTS in the USA, the UK and Sweden. The results showed that ED is significantly associated with LUTS, while the analysis included 14,139 male participants (Coyne *et al.* 2009). Other relevant epidemiologic studies of the correlation between LUTS and ED were reported by Martinez-Salamanca *et al*., (2011) and Rosen and Breyer, (2014). For example, Braun *et*

al., (2000) reported strong correlations between LUTS and ED for 4,489 German patients who participated in this study (Braun *et al.* 2000). Similar findings were suggested in 2003 by different authors: Rosen *et al*., Vallancien *et al*. and Boyle *et al*. The sample size for these studies was 12,815, 1,274 and 4,800 respectively (Vallancien *et al.* 2003, Rosen *et al.* 2003, Boyle *et al.* 2003).

Moreover, in this audit there were significant correlations between some of the IPSS domains (incomplete emptying, urgency and weak stream) and IIEF-sexual desire domain, as seen in Table 3-17. This finding is compatible with a large-scale study by Lukacs et al. (1996) who reported strongly correlations between LUTS and sexual desire (Lukacs *et al.* 1996).

4.1.1.7 Obesity (BMI)

Epidemiological studies suggest that a balanced healthy life style (Knoops *et al.* 2004, Kirby *et al.* 2006) with three regular meals a day, such as the Mediterranean diet which is largely based on vegetables, fruits, nuts, beans, cereal grains, olive oil and fish (NHS Choices 2015b), as well as including physical activity and not smoking (Knoops *et al.* 2004) might decrease mortality due to obesity by more than half (Knoops *et al.* 2004, Kirby *et al.* 2006). This life-style is associated with a reduced risk of ED, and modest improvements in sexual function have been previously documented from a reduction in weight (Dallal *et al.* 2008, Esposito *et al.* 2005).

4.1.1.7.1 IIEF/BMI

The results displayed in Table 3-13, showed that IIEF- sexual desire domain was correlated with BMI, but not the other domains. These results appear to be in parallel with other epidemiological studies which show that obesity could be one of the main causes of sexual dysfunction in men (Dallal *et al.* 2008, Esposito *et al.* 2004, Sarwer *et al.* 2012). As the relationship between obesity and ED is not entirely clear, Esposito *et al*, (2004) suggest that central adiposity plays an important role; this may contribute towards increased cardiovascular risk in the population (Esposito *et al.* 2005). Moreover, as described in section 4.1.1.4.1, adipose tissue leads to a decrease in testosterone levels by

increasing the aromatisation of testosterone to oestradiol (Cohen 2001). The patients with low testosterone levels have progressively lower levels of sexual desire than those who have normal testosterone levels (Corona *et al.* 2010). Additionally, the most testosterone dependent aspects of male sexual behaviour are sexual thoughts and motivations (Corona *et al.* 2010). Psychosocial status is a hidden reason that might contribute towards the relationship between obesity and impaired sexual functioning such as sexual desire (Sarwer *et al.* 2012). There are several psychosocial factors that may negatively impact upon sexual behaviour, for example depression may be one of the most common factors (Keddie 2011). Another factor that may be considered is body image dissatisfaction which is linked to sexual function in both men and women (Dixon *et al.* 2002). Likewise, physical limitations, especially due to extreme obesity, may make sexual activity unpleasant, problematic and painful (Sarwer *et al.* 2012, Dixon *et al.* 2002).

4.1.1.7.2 IPSS/BMI

There has been no correlation observed between obesity and any IPSS domain, as seen in Table 3-15. However, the literature reveals a link between obesity (BMI >30kg/m^2) and LUTS. Patients with a higher BMI tend to have more severe symptoms (Lee *et al.* 2012, Kuruba *et al.* 2007). This disagreement between the current results and the previous studies might be due to the small sample size of the study groups in this audit. Moreover, Kuruba *et al* (2007) analysed 201 patients with BMI 48±7 kg/m^2, while in Lee *et al*'s (2012) study the sample size was 409 patients and BMI average was 37.2 kg/m^2.

4.1.1.8 IIEF and IPSS

As previously discussed in section 3.1.7.3, ED and LUTS were assessed using the IIEF and IPSS respectively. The results show significant correlations between IPSS domains (incomplete emptying, urgency and weak stream) and IIEF-sexual desire as displayed in Table 3-17. These results are in accordance with previously published reports, and similar research has demonstrated that

LUTS is associated with ED (Tsao *et al.* 2008). Although the cause of this correlation remains unclear (Tsao *et al.* 2008), many theories have been proposed to explain the association between ED and LUTS (Rosen *et al.* 2014, Li *et al.* 2005b, Rosen *et al.* 2003, Glasser *et al.* 2007).

4.1.2 Limitation of the audit

The audit was carried out on 60 patients attending urological clinics at the UCLH to detect the baseline characteristics of their urogenital function. The audit suffers from several limitations, which are as follows:

First, it constitutes a single-institution, with prospective experience. It represents a high volume, tertiary-care practice whose patient composition may not correlate with that of the general community.

Second, patients showed little interest in taking part in this audit for several environmental and personal reasons; for example, the audit was undertaken in a busy clinic and many research studies were being run in the same waiting area.

This appears to contradict the widely held expectation that patients might want to directly benefit from such research.

Third, the audit did not analyse the severity or duration of diabetes or hypertension as a function of domain scores.

Another important consideration is that the audit patients may not be a random sample of the male population with urogenital dysfunction and the sample size is considered small. Increasing the sample size can give greater power to detect differences (Petrie *et al.* 2013).

The audit patient population revealed some previous history of tobacco abuse, but the amount of tobacco products consumed over time varied between patients. This shows the complex nature of statistically assessing the impact of smoking.

Another possible limitation concerns the use of self-report questionnaires for assessing sexual dysfunction (IIEF) and LUTS (IPSS). This presents a possible bias in responses, as participants may overstate or inaccurately report their sexual dysfunction or urinary symptoms. However, the questionnaires selected for the present audit (IIEF and IPSS) had all been previously validated on clinical (patients) and nonclinical (volunteers) participants (Plante *et al.* 1996, Rosen *et al.* 1997) and are widely used in research and practice. Also, it is claimed that sexual dysfunction and LUTS are fundamentally subjective in nature. The primary measure of these disorders is patient self-reporting which is biased by nature (Dallal *et al.* 2008).

4.2 Bariatric surgery audit

The objective of the work presented in section 1.5.2 was to observe the effect of bariatric surgery and if there is an improvement shown in the urogenital functions of morbidly obese men. The hypothesis was that the surgical intervention of bariatric surgery will have a direct effect on urogenital function, especially ED before weight loss.

In order to study the effect of bariatric surgery on urogenital function, the first variable that was considered was how to evaluate erectile function. From the literature review carried out, different questionnaires have been shown to be the most widely used method used for the evaluation of ED and they are the most widely method used in clinical practice. The IIEF questionnaire is brief yet reliable, with sensitivity shown and specificity for detecting treatment related changes in patients with ED (Rosen *et al.* 1997, Rosen *et al.* 2008), as described in section 1.2.5. The second variable considered was how to evaluate urological function. According to the literature review, an IPSS questionnaire is usually used for this purpose (Plante *et al.* 1996, Barry *et al.* 1992), as described in section 1.3.6. The third variable was evaluating weight loss after surgery; BMI was considered appropriate since, as described previously in the literature review (Lee *et al.* 2012, Kuruba *et al.* 2007, Ranasinghe *et al.* 2011), and as described in section 1.1. Moreover, BMI is the best method available for

measuring the prevalence of obesity at the population level. No specialised equipment is needed and therefore it is easy to measure accurately and consistently across large populations. It is also widely used around the world, not only in the UK, which enables comparisons between countries, regions and populations of sub-groups (NHS Choices information 2013).

In order to assess the effect of bariatric surgery on body weight, two parameters were included: BMI and %EWL. %EWL is a common metric for reporting weight loss after bariatric surgery (Montero *et al.* 2011). However, one of the obstacles to using the %EWL is that it can vary depending on the definition of ideal body weight (IBW) used and preoperative weight (Montero *et al.* 2011). The UK-National Bariatric Surgery Registry suggests the use of the term percentage excess weight loss (%EWL) to describe weight loss after bariatric surgery (Welbourn *et al.* 2014). It was suggested to use 25 kg/m^2 as the upper limit for normal BMI (Welbourn *et al.* 2014). Moreover, it was also highlighted that %EWL data must be understood with the fact that the patient with a high BMI may lose many kilogrammes, but their %EWL will be less than the patient with a lower BMI who loses the same number of kilogrammes (Welbourn *et al.* 2014). On the other hand, Deitel *et al*. (2007) reported that for obesity surgery BMI is preferred, as well as for a comparison of weight loss within a study or between studies. Also, Deitel *et al*. (2007) reported that %EWL has been used in many past studies, so this measure may still be acceptable to enable comparison (Deitel *et al.* 2007).

4.2.1 Effect of surgery type, sexual function (IIEF) and obesity (BMI)

The three most commonly performed bariatric surgery procedures in the UK are adjustable gastric banding, gastric bypass and sleeve gastrectomy respectively (National Obesity Observatory, 2010). The data from the audit is in parallel with the literature, as the three types of surgery used in this audit were gastric band (22.9%), gastric bypass (31.4%) and gastric sleeve (45.7%). The results show that the types of surgery have no effect on ED and NO-ED groups. Moreover, to

the researcher's knowledge, similar findings are not available in current literature.

The effect of surgery types on obesity presented by %EWL in this audit is comparable with the United Kingdom National Bariatric Surgery Registry (UKNBSR) of 2014. The highest %EWL at six month post-op in this audit of gastric sleeve was 46% while for the UKNBSR it was 48.3%. Gastric bypass and gastric band in the audit compared to the registry were 49.7% compared to 55.2% and 41.3% compared to 30.8% respectively, considering the difference in the sample size between the two comparisons as a major factor for the differences.

4.2.2 Effect of bariatric surgery on body weight (BMI)

The data presented in section 3.2.5 on the change in body weight following bariatric surgery showed a significant decrease in BMI and EWL over time points and the significance reached at time two (T2; 1 month post-operative) compared to time one (T1; 1 month pre-operative); this decrease was observed in both ED and NO-ED groups, as expected from prior evidence in the literature (Buchwald *et al.* 2004, Nijamkin *et al.* 2012, Deitel *et al.* 2002, Anderson *et al.* 2007). However, the different weight loss amounts between groups (ED and NO-ED) presented a differential response to bariatric surgery, while both groups presented a statistically significant decrease in BMI and EWL. To the researcher's knowledge, the differential weight loss noted above is the first description at one month post-operative for morbidly obese men (Karamanakos *et al.* 2008, Demaria *et al.* 2010). The previous studies have reported that the weight loss reached significant levels at three months (Anderson *et al.* 2007) and six months post-operatively (Nijamkin *et al.* 2012, Karamanakos *et al.* 2008). Moreover, BMI was significantly different between surgery types at T2 compared to the baseline T1 ($p=0.01$). %EWL showed no difference between surgery types at all-time points compared to the baseline T1 ($p>0.05$). The UK-NBSR suggested that %EWL data must be understood with the fact that patients with a high BMI may lose many kilogrammes, but their %EWL will be

less than the patient with a lower BMI who loses the same number of kilogrammes. Moreover, bariatric surgery parameters for example the % Excess Weight Loss (%EWL), the Body Mass Index (BMI) and the ideal body weight (IBW) are different methods for reporting weight loss after bariatric surgery (Dixon *et al.* 2005). However, weight loss measurement has not been standardized yet (Buchwald *et al.* 2009, Baltasar *et al.* 2011). Baltasar *et al.* (2011) recommended further studies should be made with a larger sample size of patients, enough follow-up and several bariatric surgery centres (Baltasar *et al.* 2011). The findings of the audits highlight the need for a standardized weight loss measurement, a larger sample size of patients for future studies, sufficient number of follow-ups and multiple bariatric surgery centres.

4.2.3 Effect of bariatric surgery on sexual function (IIEF)

The outcomes of the work presented in section 1.5.1 were to observe the effect of bariatric surgery in the short term (four weeks post-operative):

First outcome: if the recovery of erectile function occurs early (before weight loss) in parallel with normalised blood glucose, this proposes that the improvement of blood glucose has greater impact than body weight on the pathophysiology of urogenital dysfunction.

Second outcome; if the recovery of EF occurs later (in parallel with weight loss), this suggests that body weight is as important as, if not more than, the normalisation of blood glucose.

There are limited studies that have focused on erectile function (EF) in morbidly obese patients, and a very limited number are focusing on EF after weight loss (Reis *et al.* 2010). This is the first prospective study, to the researcher's knowledge, that copmares the impact of weight loss on sexual and urogical function in morbidly obese men at one month post-operative. As summarised in Table 4-1 there have been five studies which investigated the effect of bariatric surgery on erectile function. This study differs from the five studies in Table 4-1 as the only study which has investigated the effect at 1 month post-operatively.

Table 4-1: Comparison in sexual function between the audit and the literature.

Reference	Surgery type	Improvement in sexual function	Time points	Sample size of the study	Time of improvement
(Dallal *et al.* 2008)	Roux-en-Y gastric bypass	- All sexual function domains improved after surgery (p≤0.002). -The Brief Male Sexual Inventory (BMSFI) questionnaire was used. It consists of 11questions comprising 5 sexual function domains: sexual drive (2 items), erectile function (3 items), ejaculatory function (2 items), sexual problem assessment (3 items), and sexual satisfaction (1 item).	-Baseline: (1-3 months pre-op) -Time 1: once after surgery (at least 6 months follow-up). - Mean postoperative follow-up length was 19 months (range 6 to 45 months)	97 patients	24 months
(Mora *et al.* 2013)	Roux-en-Y gastric bypass and Laparosc-opic sleeve gastrectom-y sleeve	-IIEF improved after surgery (p=0.023)	-Baseline -Time 1: 12 months post-operation.	39 patients	12 months
(Reis *et al.* 2010)	Roux-en-Y gastric bypass	-Sexual function improves after surgery at (p=0.0469). - IIEF-5 questionnaire was used.	-Baseline -Time 1: 4 months post-operation. -Time 2: 24 months post-operation.	20 patients (10 underwent surgery and 10 control (exercise and diet)	24 months
(Hammoud *et al.* 2009)	Roux-en-Y gastric bypass	-Sexual quality of life was improved (p=0.038). -The IWQOL-Lite questionnaire was used. It is a validated 31-item self-report questionnaire designed to assess the impact of weight on quality of life in obese individuals. The IWQOL-Lite assesses five domains, including a sexual life domain.	-Baseline -Time 1: 24 months post-operation.	22 patients	24 months
(Ranasinghe *et al.* 2011)	Laparosc-opic gastric banding	-There was no improvement in sexual function after surgery. -Erectile index and orgasmic function worsened.	-Over the last 10 years (2001-2009)	145 male patients	N/A*

*N/A: not available.

A review of the literature as presented in section 1.4.1.1 shows numerous studies evaluating the sexual function after bariatric surgery (Reis *et al.* 2010, Dallal *et al.* 2008, Ranasinghe *et al.* 2011, Hammoud *et al.* 2009, Mora *et al.* 2013).

Dallal and colleagues (2008) examined 97 men with an average age of 48 and average BMI of 51 all of which went through gastric bypass surgery. The brief male sexual inventory (BMSFI) was given out to examine the sexual function of the patients twice before surgery (between one and three months prior to the surgery) and after the surgery by six months (Dallal *et al.* 2008). The objective of Dallal and colleagues study was to measure the sexual function in morbidly obese men before and after significant weight loss achieved by gastric bypass (Dallal *et al.* 2008). The study concluded with an improvement in sexual function at two years after gastric bypass surgery. Dallal and colleagues suggested that the improvement in sexual function was due to weight reduction, while the mechanism is multifactorial. The changes in glucose metabolism or the presence of cardiovascular disease may not be the main cause of obesity-associated erectile dysfunction (Dallal *et al.* 2008).

Mora and colleagues (2013) showed an improvement in sexual function in 39 men with the age range between 18- 65 years. The patients underwent gastric sleeve surgery or Roux-en-Y gastric bypass, using the full version of the IIEF questionnaire (IIEF) before surgery and at one year after surgery (Mora *et al.* 2013). Mora and colleagues suggested that the improvement in sexual function focused on; EF, SD, and OS scores, whereas OF and IS scores did not change significantly. It was suggested that this was, due to the weight reduction occurring after bariatric surgery further than the parallel improvement in testosterone level and metabolic profiles such as insulin sensitivity, C-reactive protein and lipid profile. Additionally, the post-operative improvement in sexual function accounted for improvements in EF, SD, and OS scores, whereas OF and IS scores did not change significantly. The results showed weight loss as a major contributor to the improved sexual function after bariatric surgery. While,

IS and OF domains seemed to depend on factors other than weight loss and hormonal or metabolic changes after bariatric surgery (Mora *et al.* 2013).

Reis and colleagues (2010) measured erectile function and hormonal changes after significant weight loss either surgically or non-surgically in morbidly obese males (Reis *et al.* 2010). All twenty patients completed the IIEF-5 questionnaire and blood chemistry values were taken (Reis *et al.* 2010). Reis and colleagues showed an improved sexual function in two year follow-up. Reis suggested the role that oestrogens play in erectile function remains unknown. More clinical studies are needed with the concern of the role of oestrogen in EF. While the sexual hormones were in the normal range before surgery they increased significantly with BMI reduction. It is possible to hypothesize that this effect is related to the increased tonic stimulation of the testes by the pituitary after reduction of the fat mass. This study suggested that erectile dysfunction is considered to be a reversible complication of obesity (Reis *et al.* 2010). It was suggested that new studies should include more patients, which could permit a more detailed analysis (Reis *et al.* 2010).

Hammoud and colleagues (2009) showed an improvement in sexual function after gastric bypass surgery, by using the Impact of Weight on Quality of Life-Lite (IWQOL-L) questionnaire (Hammoud *et al.* 2009). However, the study did not find an association between change in body fat and hormonal and sexual quality of life parameters, despite a correlation between these and change in weight (Hatzimouratidis *et al.* 2009).

Ranasinghe and colleagues (2011) found no improvement in sexual function despite a significant weight loss ($p < 0.0001$) after the gastric band (Ranasinghe *et al.* 2011). There was no improvement in any of the domains of IIEF when adjusted for weight loss. Unexpectedly, there was a trend towards decreasing erectile function and orgasmic function with time but not with age. Thus, the initial findings from this study do not support the suggestion that bariatric surgery is associated with the improvement of sexual function in morbidly obese men in the short term. Ranasinghe suggested these findings might be caused

by time and the ageing process. The study nature was retrospective over ten years (Ranasinghe *et al.* 2011).

The disagreement between Dallal's, Mora's, Reis's, Hammoud's studies and Ranasinghe's study might be due to the variations in the tools used in the studies, such as the biomedical tests, questionnaires, period of the study, and the number of participants that took part in the study (Reis *et al.* 2010, Dallal *et al.* 2008, Mora *et al.* 2013). Also, there is possible influence from the study design and the medical centre type: primary, secondary or tertiary and the number of medical centres participating (single or multi-centre). Overall, the evidence for the improvement of erectile function in males after bariatric surgery is debatable.

A strong correlation between BMI and EF was shown and confirmed by previously reported data (Kratzik *et al.* 2005). Dallal *et al*., (2008) also described the overall improvement in sexual function after gastric bypass surgery after twenty four months post-operation (Dallal *et al.* 2008). Moreover, in a randomised controlled trial of 110 obese men (BMI > 30 kg/m^2) who had erectile dysfunction, patients who ate a very low calorie diet reported improvement in erectile function with average IIEF-EF scores that improved from 13.9 to 17. This improvement in erectile function was independently associated with a decrease in BMI; however, it was a two year follow-up (Esposito *et al.* 2004).

The results displayed in section 3.2.6, show that eighteen obese men (BMI > 35 kg/m^2) noted an overall significant improvement in all IIEF domains, which is comparable with previous studies (Dallal *et al.* 2008, Esposito *et al.* 2004).

However, the results reveal significant improvement in erectile function (EF) and intercourse satisfaction (IS) with IIEF scores at one month post-operation, while sexual desire (SD) and overall satisfaction (OS) scores improved at three months post-operation, and significant improvement in orgasmic function was reached at six months post-operation. These results are the first of their kind to reveal the situation one month post-operatively, according to the researcher's knowledge. The significant improvement in EF at one month post-operative is

likely to be multifactorial. Although, it might be explained by the strong correlation of BMI to EF which is confirmed by previous studies (Reis *et al.* 2010, Dallal *et al.* 2008, Mora *et al.* 2013). Another factor suggested for this improvement is the short-term remission of FBG (Reis *et al.* 2010), while there was improvement in FBG parallel to weight loss and improvement of sexual function. A correlation of testosterone and other hormone levels to EF was shown and suggested by previous studies (Feldman *et al.* 1994, Feldman *et al.* 2002, Isidori *et al.* 2005), although these parameters were not obtained before and after the weight loss in this audit. Likely, the short-term improvement in IS after one month post-operative might be due to psychosocial status, which improved after the weight loss (Sarwer *et al.* 2012, Keddie 2011).

Furthermore, no changes in any of the IIEF domains for twelve obese men with NO-ED are revealed, except for SD and IS at six months post-operative. These patients had SD and IS-domain scores within the normal range before and after the surgery. Some improvement in the scores was shown for these domains after six months post-operative, although they remained within the normal range, but it may be suggested that this improvement was simply a chance occurrence. Also, the primary measure of these domains is patient self-reporting, which means that the results may have been affected by bias.

These results suggest that the recovery of EF could occur in parallel with weight loss, as other studies suggest that obesity could be one of the causes of sexual dysfunction in men and that significant weight loss normalises sexual function in the morbidly obese male (Dallal *et al.* 2008, Sarwer *et al.* 2012, Ranasinghe *et al.* 2011, Efthymiou *et al.* 2014). As described in section 1.5.1, there are two outcomes expected from this study, as follows. First outcome: if the recovery of erectile function occurs early in parallel with normalised blood glucose, this suggests that the improvement in blood glucose has a greater impact than body weight on the pathophysiology of urogenital dysfunction. Second outcome: if the recovery of EF occurs later, this suggests that body weight is as important as, if not more than, the normalisation of blood glucose. The results show there was a statistically significant decrease in BMI at one month post-operative in

parallel with glycaemic improvement. Also, sexual function in the ED group was significantly improved parallel to weight reduction and glycaemic improvement at one month post-operative. These findings suggest that body weight is important factor in improving sexual function in the early stages, at one month post-operative. However the study has unable to test the hypothesis since the weight loss occurred at one-month postoperatively which was unexpected.

Oral PDE5-inhibitors (PDE5-Is) are considered to be the first line of treatment for erectile dysfunction (Konstantinos *et al.* 2009). The main advantage of PDE5-Is lies in the improvement in sexual function but not sexual desire (Wespes *et al.* 2002). These medications are used with caution in patients with cardiovascular disease. Moreover, diabetes mellitus is considered a common cause for the failure of PDE5-inhibitors (Kendirci *et al.* 2006).

On the other hand, the results of this audit and a review of the literature showed that bariatric surgery can improve sexual function, including sexual desire (Reis *et al.* 2010, Dallal *et al.* 2008). Also, the literature has shown remission in diabetes after bariatric surgery (Pories *et al.* 1995), while the main reason for bariatric surgery is weight reduction in morbidly obese patients (Padwal *et al.* 2011).

Whilst both interventions showed some kind of improved effect on ED, PDE5-inhibitors are the only one given as a treatment. Even though bariatric surgery showed that it has some improved effect on ED it is not considered as a treatment for it. Sexual dysfunction is suggested as being one of several potentially reversible complications of obesity. Further research should be considered in larger studies.

4.2.4 Effect of bariatric surgery on urological function (IPSS)

This audit attempts to further examine the link between obesity and LUTS using the IPSS questionnaire as the main measuring tool. Obese patients are inclined to have more severe symptoms, with a higher total IPSS score (20 – 35) (Lee *et al.* 2012). Some studies have also provided evidence that obesity might be

considered a reason for the severity of urinary symptoms (Çinar *et al.* 2008, Kim *et al.* 2010).

Bariatric surgery has been shown to produce durable and maintainable weight loss, improvement in quality of life, and improvement or resolution of co-morbidities (Kuruba *et al.* 2007).

The IPSS questionnaire is an easy, reliable, and sensitive measure of urinary function and has been validated in previous studies (Plante *et al.* 1996). The results displayed in section 3.2.7 suggested that the ED group saw significant improvement in most of their urinary functions (frequency, intermittency, weak stream, nocturia, Qol and IPSS total score) at one month post-operative. Moreover, incomplete emptying and urgency improved at three month post-operative, while, straining did not significantly improve in both groups (ED and NO-ED). These improvements in the IPSS domains are in parallel with the weight reduction after bariatric surgery. Obesity plays an important role in the aetiology of LUTS, possibly by increasing the intra-abdominal pressure (Kuruba *et al.* 2007). A study by Bump *et al*. (1992) showed that weight reduction improves urinary incontinence by reducing abdominal pressure, thus improving the transmission of mechanical stress to the urethra (Bump *et al.* 1992). Likewise, Subak *et al*. (2009) indicated that obesity plays an important role in urinary symptoms, including incontinence, in women and men (Subak *et al.* 2009). Moreover, abdominal obesity has been associated with a 1.5 fold increase in LUTS (Rohrmann *et al.* 2004). It is also suggested that being obese in young adulthood may be associated with a higher prevalence of LUTS later in life (Rohrmann *et al.* 2004). Another reason that might be indicated with this improvement is sexual function improvement after bariatric surgery. The association between LUTS and sexual dysfunction has been investigated in community-based studies and it is suggested that these improvements run parallel to each other (Li *et al.* 2005b, Glasser *et al.* 2007, Frankel *et al.* 1998, Elliott *et al.* 2004).

Nonetheless, not all IPSS domains improved over the time points with NO-ED patients after surgically induced weight loss. The IPSS results present a

statistically significant correlation with post-operative BMI and percentage of excess body weight lost. These findings correspond with the published studies that suggest there are overall significant improvements in most IPSS domains after bariatric surgery (Lee *et al.* 2012, Kuruba *et al.* 2007, Ranasinghe *et al.* 2011). In addition, the results present an improvement in most IPSS domains with significant improvement in weight loss at one month post-operative; these findings have not been published previously according to the researcher's knowledge. This seems to confirm the impact of weight loss on urological function after bariatric surgery. It is hypothesised that this might be caused by a reduction in intra-abdominal pressure, as suggested by previous studies (Rosen *et al.* 2014, Bump *et al.* 1992, Cummings *et al.* 2000).

A review of the literature as presented in section 1.4.1.2 showed numerous studies evaluating the urological function after bariatric surgery (Kuruba *et al.* 2007, Ranasinghe *et al.* 2011, Burgio *et al.* 2007, Laungani *et al.* 2009).

Kuruba and colleagues (2007) prospectively collected data from 201 patients between 2004 and 2006 that underwent bariatric surgery. The patients were administered the questionnaires after bariatric surgery by telephone interview and/or during the three months post-operative visits in the first year. Out of the 201 patients 65 reported urinary incontinence (UI) and 45 out of the 65 patients with UI underwent bariatric surgery during the study period. This study showed that urinary incontinence was improved in 82% of patients after bariatric surgery and weight loss suggesting that weight loss after bariatric surgery played an important role in the aetiology of UI by inducing weight loss causing reduction intra-abdominal pressure (Kuruba *et al.* 2007). About 13% of the study patients reported improvement in UI by subjective measures with no significant change that was reported in post-operative severity index scores. Kuruba suggested this was due to the documented sensitivity of severity index scores. Moreover, no significant correlations were found between age, BMI, %EWL and improvement in UI, the small sample size might be the reason behind that (Kuruba *et al.* 2007).

Ranasinghe and colleagues (2011) examined, in a retrospective study, the effects of weight loss following laparoscopic gastric banding surgery (LGB) on urinary incontinence in both male and female patients. Moreover, post-operative weight loss improved overall UI, quality of life and stress incontinence in women, this improvement was suggested due to a reduction in intra-abdominal pressure (Ranasinghe *et al.* 2011). However, no improvement in urinary function, despite weight loss after LGB, was observed in males, although 23.54% of males reported UI before bariatric surgery, the study did not identify an association between weight loss and UI. Therefore, Ranasinghe suggested that raised intra-abdominal pressure may not contribute to UI in males. Also, the retrospective nature of the study and poor response rate from the patients might have allowed recall bias, and the use of questionnaires based on subjective assessment could have also reflected factors such as individual patient satisfaction with the surgery (Ranasinghe *et al.* 2011).

Burgio and colleagues (2007) examined, the changes in UI in morbidly obese women who underwent laparoscopic Roux-en-Y gastric bypass between October 2003 and February 2005 and were followed up to six and twelve months post-surgery. The Urogenital Distress Inventory (short form) and the Incontinence Impact Questionnaire (short form) were used in this study. Significantly BMI decreased after six months post-operative and the prevalence of UI decreased significantly at 6 months and continued to twelve months post-operative. Burgio suggested that the reduction in prevalence of the UI was significantly associated with decreases in BMI. Although the mechanism of improvement is unknown, it may be due to the relief of chronic pressure on the pelvic floor that may weaken the urinary continence mechanism (Burgio *et al.* 2007).

Lanugani and colleagues (2009) evaluated 470 morbidly obese women who underwent laparoscopic gastric bypass for urinary incontinence with the International Consultation on Incontinence Questionnaire Short Form at three and twelve months post-surgery. The UI had been resolved in more than 50% of the patients and improved overall in most of them. The significant

improvement in UI was reported within three months post-operative and continued to one year in parallel with weight loss (Laungani *et al.* 2009). Lanugani suggested as previous studies did (Kuruba *et al.* 2007, Ranasinghe *et al.* 2011, Burgio *et al.* 2007), that the mechanism of improvement might be due to weight loss and the decrease in intra-abdominal pressure (Laungani *et al.* 2009).

In summary, the occurrence and development of urological diseases depends on numerous factors, including obesity (Mydlo 2004), which has been shown to be a risk factor for urinary function (Kuruba *et al.* 2007). Similarly, Burgio et al (2007) showed that urinary function improved after weight reduction (Burgio *et al.* 2007) although, both studies were on female patients (Table 4-2). This reflects the need of more specialised studies examining the effect of obesity in depth.

Table 4-2: Comparison in urological function between the audit and the literature.

Reference	Surgery type	Improvement in urological function	Time points	Sample size of the study	Time of improvement
(Kuruba *et al.* 2007)	Roux-en-Y gastric bypass	- Significant improvement or resolution was reported after a mean duration of 4 months or a 50-lb weight loss. -Validated urinary incontinence questionnaire used to screen 201 consecutive prospective bariatric patients before and after weight loss surgery.	-Baseline: (1-3 months pre-op) -Time 1: 3 months post-op. Time 2: 6 months post-op. Time 3: 12 months post-op. -The median follow-up of 12 months (range 6–23)	201 patients (38 patients completed the study and previously reported urinary incontinence)	4 months
(Ranasinghe *et al.* 2011)	Laparosc-opic gastric banding	- Short Form (ICIQ-SF) and IPSS questionnaires were mailed to all study patients. - No significant improvement in UI with weight loss after bariatric surgery in males. - Surgical weight loss improved overall UI, quality of life and stress incontinence in women.	-Over the last 10 years (2001-2009)	145 male patients (36 responded)	N/A*
(Burgio *et al.* 2007)	Roux-en-Y gastric bypass	- Significant improvement in UI with weight loss after bariatric surgery. -The Urogenital Distress Inventory (short form) and the Incontinence Impact Questionnaire (short form) were used in this study	-Baseline -Time 1: 6 months post-op. -Time 2: 12 months post-op.	101 Female patients	6 months
(Laungani *et al.* 2009)	laparoscop ic gastric bypass	- Significant improvement in UI and quality of life with weight loss after bariatric surgery -The Incontinence Impact Questionnaire (short form) was used.	Baseline -Time 1: 3 months post-op. -Time 2: 12 months post-op.	309 Female patients	3 months

*N/A: not available.

4.2.5 Effect of bariatric surgery on biomarkers

As previously stated, the objectives of the audit were to observe the effect of bariatric surgery on fasting blood glucose (FBG) and HbA1c post-operatively. The expectation was that the surgery would have a direct effect on fasting blood glucose, corresponding with the published research which suggests the use of bariatric surgery as a treatment for obesity and T2DM (Wickremesekera *et al.* 2005, Pournaras *et al.* 2010, Isbell *et al.* 2010). However, the mechanism of the bariatric surgery on diabetes and the improvement of fasting blood glucose following surgery remains largely unclear (Proczko-Markuszewska *et al.* 2011, Pournaras *et al.* 2010). The results of the present study show no difference between ED and NO-ED groups for FBG and HbA1c before the surgery.

4.2.5.1 Fasting blood glucose

The data presented in section 3.2.8 for FBG show a significant improvement over time in both ED and NO-ED groups. The results suggest an improvement at one month post-operative with the ED group. However, the NO-ED group showed an improvement at six months post-operative and this improvement is compatible with the literature as presented in Table 1-7 (Wickremesekera *et al.* 2005, Pournaras *et al.* 2010, Torquati *et al.* 2005, Garrido-Sanchez *et al.* 2012, Mingrone *et al.* 2012).

In this audit FBG improvement was parallel with weight loss at one month post-operative. However, this improvement might be weight loss independent (Pournaras *et al.* 2010), because this observation was not reported immediately but was measured one month after the surgery. Moreover, Umeda *et al.,* (2011) note that the first improvement in BMI and FBG was observed one month after bariatric surgery, while a fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR) index was observed seven days after surgery (Umeda *et al.* 2011). In addition, the immediate improvement in blood glucose level in the post-operative period is weight loss independent, because immediately improved insulin secretion and reduced insulin resistance have been observed between the second and seventh day after a gastric

bypass (Pournaras *et al.* 2010). This increase was associated with an improved GLP-1 response (Pournaras *et al.* 2010), which may partly be explained by L-cell stimulation from bile acids (Pournaras *et al.* 2012). Furthermore, the results reveal prolonged improvements (six month post-operative) in FBG for most of the audit patients that underwent gastric sleeve or gastric bypass, and only two patients who were diagnosed with T2DM underwent a gastric bypass. However, these prolonged improvements could be explained by the substantial and maintained weight loss. A reduced appetite may be partly explained by enhanced satiety gut hormones from the endocrine L cell, such as GLP-1 (Le Roux *et al.* 2006). Moreover, Pournaras *et al.,* (2012) suggest that the changed anatomy after bariatric surgery (not gastric band) affects bile delivery to the terminal ileum and leads to elevated plasma bile acids resulting in increased satiety gut hormone responses, reduced food intake, and weight loss (Pournaras *et al.* 2012).

4.2.5.2 HbA1c

As previously presented in 4.2.5.1, the data shown in section 3.2.8 of HbA1c reveals a significant improvement within one month post-operative in the ED and NO-ED groups. This improvement in HbA1c is compatible with some of the literature (Proczko-Markuszewska *et al.* 2011, Umeda *et al.* 2011), but not all (Wickremesekera *et al.* 2005, Basso *et al.* 2011, Rizzello *et al.* 2010).

In this audit, a significant improvement in HbA1c was parallel to weight loss at one month post-operative. However, this improvement might be weight loss independent; Pournaras *et al.* (2010) reported an improvement of HbA1c at one week post-operative independent of weight loss (Pournaras *et al.* 2010). The audit cannot guarantee that the improvement is independent of weight loss due to the HbA1c results not being measured immediately but measured one month after surgery.

4.2.6 Limitation of the audit

There are several limitations to this audit that need to be addressed; mainly concerned with conducting a new method to assess the early effect of bariatric surgery on sexual and urological functions.

The small sample size of the audit groups might have overestimated the significant correlations between variables. Another important consideration is that the audit patients may not be a random sample of the male morbidly obese population due to the lack of randomisation. However, the groups (ED and NO-ED) were well matched for pre-operative patient characteristics.

In addition, bariatric surgery is more common in women (5,047 hospital incidents between 2009 to 2010) than in men (1,473 hospital incidents in the same years), and all the audit patients were male (National Obesity Observatory 2010). Most patients who listed for bariatric surgery in the UK are aged between 40 and 54 years, followed by those aged between 25 and 39 years (National Obesity Observatory 2010); while the age range of the audit participants was mostly patients with the age between 40 and 49 years, followed by those with the age between 50 and 59 years.

This audit was a small-scale single centre study set up at the UCLH. While single centre trials provide the flexibility of approach necessary for healthcare providers, using only a small number of participants carries a considerable risk of failing to demonstrate a treatment difference when one is really present, for example type II errors. While multicentre studies are an accepted way of evaluating a new intervention, a large number of participants and a multi-investigator design would provide a better basis for the success of the research and would give better clinical judgement regarding the value of the research (Copeland 2005). Since the audit was established in a single -centre with prospective experience, it represents a high number of tertiary care hospital patients who may not be representative of those in the general community.

Moreover, the audit results were limited to six months follow-up and based on a small number of participants. The evidence at longer than six months follow-up, in particular on the adverse events of bariatric surgery and mortality, remains unclear (Gloy *et al.* 2013).

Since urogenital function was assessed by using self-administered questionnaires, the data could have been influenced by patient recall bias due to the nature of self-administered questionnaires, and also regarding the time elapsed and amount of weight loss when reporting the post-operative severity of sexual and urological function.

The audit might have under estimated the severity of urinary dusfunction by substituting the answers in the IPSS questionnaire with those from the IIEF, and the length of the questionnaires might have contributed towards the poor response rate as there were two sets of questionnaires to complete. Therefore, it is important that urodynamic studies[17] are undertaken as a part of this audit (NICE 2015).

The audit also could not investigate the effect of bariatric surgery on cardiovascular morbidity and mortality, and did not analyse the severity or duration of diseases, such as cardiovascular disease, hypertension or diabetes as a function of domain scores.

No information was available on ethnicities and marital status, but the results might be different for specific subgroups. However, the limited number of published studies prohibited researchers from finding out differential effects due to sex or age (Gloy *et al.* 2013).

[17] Urodynamic studies assess the function of the bladder and urethra and are often useful in the assessment and diagnosis of patients presenting with lower urinary tract symptoms (LUTS) (NICE 2015).

Although no medical history was included to identify any medication or surgery that might affect urinary or sexual function, there may be other factors that affected the results such as parity and hormone levels.

A number of participants expressed (but did not report) some previous history of tobacco abuse, but control of this important variable is difficult. Patients often stopped (pre-operative) and restarted (post-operative over a two month period) tobacco use. Some were active tobacco users; others had remote histories. The amount of tobacco products consumed over time also varied within patients (but this was not reported). Some participants were successful at post-operative smoking cessation; others renewed tobacco use at variable times after surgery. Because of the lack of documentation and the complexity of tobacco consumption and limitations in the statistical calculation, the researcher chose not to include this important predictor variable in the statistical results.

Of note is the fact that waist circumference was not used to assess central obesity in the audit participants. According to NICE recommendations, the use of BMI in combination with waist circumference as a method for measuring overweight and obesity and determining health risks is important; specifically, the guidance currently states that assessment of health risks associated with being overweight and obese should be based on both BMI and waist circumference for those with a BMI of less than 35 kg/m^2 (NHS Information Centre 2014).

Additionally, testosterone has not been examined to assess sexual function or other hormone levels such as SHBG before and after weight loss. This is because testosterone is not part of the routine check for patients who are listed for bariatric surgery, the same as other hormones which are very important in this audit and have a significant role with regard to obesity (Esposito *et al.* 2005). Pasquali *et al.,* (1991) examined 52 obese men and found decreased free and total serum testosterone concentrations and a decrease in SHBG levels (Pasquali *et al.* 1991). Also, Reis *et al.,* (2009) noted the levels of these hormones increased significantly with BMI reduction (Reis *et al.* 2010).

Another important limitation that was not measured is bile acids. Studies suggested there is a link between bile acids and blood glucose level and these studies showed an improvement, especially with T2DM. Gastric bypass surgery is being used as a treatment for T2DM, although the mechanism of action remains unclear (Pournaras *et al.* 2010, Pournaras *et al.* 2012).

Also, aromatase enzyme levels were not measured in the audit. Aromatase is the enzyme responsible for converting androgens to oestrogens, and is widely distributed in several tissues such as testicular Ley-dig cells, adipose tissue, liver and reproductive tissue (Ho 2004). In men, oestrogen production occurs mainly by extra testicular aromatization of androstenedione to oestrone and testosterone to oestradiol (Ho 2004). Moreover, morbidly obese males have demonstrated the presence of decreased free and total testosterone levels with increased aromatase (Cohen 1999). Since waist circumference is shown to be an accurate predictor and abdominal fat contains aromatase, including this variable in future work would be beneficial.

Furthermore, it is well recognised that bariatric surgery is effective in improving insulin resistance and T2DM (Wickremesekera *et al.* 2005, Pournaras *et al.* 2010, Pournaras *et al.* 2012). These findings should be confirmed in the audit by measuring HOMA-IR and fasting insulin. The previous studies suggest these improvements can be achieved within one week post operation before any apparent weight loss and the suggested mechanisms are due to caloric restriction (Pournaras *et al.* 2010, Isbell *et al.* 2010). Another suggestion is that the instant improvements in insulin sensitivity after bariatric surgery could have been a result of the associated stress or inflammatory responses to surgery, thus masking a greater improvement in insulin sensitivity with RYGB than with caloric restriction (Isbell *et al.* 2010). Moreover, the majority of these limitations were expected from the beginning of the audit and will be addressed in future work.

The results presented in this thesis were obtained from two ongoning audits which aimed to increase the patient care quality and improve the outcomes and it was also used to confirm improvement in healthcare delivery. Although a plan

was made with the audits there was still a need for assistance in the implementation to reach a higher research level. The audits aimed to provide future assistance, by providing an initial practical overview to the structures and processes necessary to deliver a clinical audit at a higher research level. Additionally the parameters and blood tests measured were all useful to enrich the audit. However, they were inconclusive and the recommendation is to add the following testes; renal function, liver function, thyroid function, prolactin, SHBG, free and total testosterone level, aromatase levels, HOMA-IR and fasting insulin. Also, waist circumference is needed to assess central obesity. Notably, results of the audit recommend that the questionnaires (IIEF and IPSS) should be a standard for all patients undergoing bariatric surgery.

Generally, one of the possible benefits of the audit is to improve hospital cost-efficiencies (Gordon *et al.* 2010). The aim of these audits as described before was to evaluate the baseline characteristics of patients with erectile dysfunction and to determine the impact of bariatric surgery on erectile and urological function in morbidly obese men. Moreover, more aims will be added in future work to estimate the possible cost-savings for a study at certain medical centers from improved surgical performance for bariatric surgery in presence of urological dysfunction. The current audits were limited to the availability of data estimated for each test and measures were used in the audits. The published studies for example provids estimates on weight measuring techniques were inconsistent in the use of standard definitions and methods used to measure the weight loss (Ariyarathenam *et al.* 2012). This appears to be a common problem internationally as confirmed in a large UK review on the topic of monitoring weight (Ariyarathenam *et al.* 2012). The lack of evidence on the effectiveness level of the audit parameters for surgery and urological function was also a limitation for measuring the cost. This is possibly due to, the challenging nature of the topic, the possible legal and social difficulties and lack of time.

5 CONCLUSION

The aim of this study, as set out in section 1.5.2, was to evaluate the baseline characteristics of patients with erectile dysfunction and to determine the impact of bariatric surgery on erectile and urological function in morbidly obese men by conducting two separate clinical audits. This evaluation has then been used to investigate the hypothesis that surgical weight reduction is the hidden mechanism responsible for the association between obesity and erectile dysfunction. The impact of bariatric surgery was also used to investigate that effect on urological function.

These objectives were proposed to achieve the aim of the study:

1. To conduct an audit to investigate the baseline characteristics of men over 18 years of age and attending the urological clinic at UCLH using IIEF and IPSS questionnaires (results covered in section 3.1and discussed in section 4.1);

2. Perform an audit the effect of BMI on urogenital function in men over 18 years of age and attending the urological clinic at UCLH using IIEF and IPSS questionnaires (results covered in sections 3.1.7.1, 3.1.7.2 and discussed in sections 4.1.1);
3. To collate and analyse other baseline characteristics such as age, smoking status, and medical history (results covered in section 3.1.7 and discussed in sections 4.1.1);
4. To conduct a second audit to investigate the effect of bariatric surgery on the urogenital function and BMI of morbidly obese men over 30 years of age and BMI of 35 and over (results covered in section 3.2 and discussed in section 4.2);
5. To analyse the urogenital function and biomarker data acquired in the second audit to assess the effect of bariatric surgery on urogenital function and recommend further work based on these analyses (results covered in section 3.2.8 and discussed in section 4.2.4 and 4.2.5); (results covered in Chapter 3 and discussed in sections 4.1.2 and 4.2.6).

The results presented in section 3.1 and discussed in section 4.1 show that the methods used in selecting, recruiting and collecting information from the audit participants have successfully been established, which is reflected in the amount of data gained compared to the data from the literature review (according to Objective 1). Furthermore, this information has revealed an important database model of patient characteristics which can be used in future studies.

The results presented in section 3.1.7.1 and discussed in section 4.1.1 suggest, in parallel with other epidemiological studies, that obesity could be one of the causes of sexual dysfunction in men. However, the results presented in section 3.1.7.2 and discussed in section 4.1.1 demonstrate dissimilarities with other studies in that no correlation has been detected between obesity and LUTS (Objective 2).

The results presented in section 3.1.7 and discussed in sections 4.1.1 show that age has a negative influence on sexual function, and many significant correlations were presented between biomarkers, ED and LUTS, that were compatible with previous studies (Objective 3).

The results presented in section 3.2 and discussed in section 4.1 have shown that the method used in selecting, recruiting, observing and collecting information from audit participants has successfully been established, which is reflected in the observed effect of bariatric surgery for the ED group compared to the NO-ED group (Objective 4). Moreover, the present audit model has created an important initial database to be used in future studies.

The results presented in section 3.2.8 and discussed in section 4.2.5 show a significant improvement within one month post-operative for fasting blood glucose and HbA1c. Furthermore, the results reveal prolonged improvements (six month post-operative) in fasting blood glucose levels and HbA1c. The results presented in Chapter 3 and discussed in sections 4.1.2 and 4.2.6 highlight the limitations of the audits and addressing these difficulties in future work (Objective 5).

In summary, these audits have successfully achieved all the stated objectives, and a huge area for further research and development has arisen from the results gained.

5.1 Future works

In The work will be divided into two phases; phase one will consist of using baseline characteristics to help improve the decision making for male patients with obesity and urological dysfunction.

In addition, it will include using baseline factors that allow the assessment of specific patient risks for clinical development and the benefits of medical therapy.

A novel clinical decision tool based on these analyses will permit clinicians to evaluate specific patient benefits against possible risks from adverse effects on a given patient.

There is a need for more studies, such as longitudinal, cross-sectional studies to investigate the associations between baseline characteristics. For example, a cross-sectional study of sexual function, and a longitudinal study exploring the associations between changes in LUTS and sexual function among men with obesity and of different ethnicities. Phase two will consist of the following:

1. Creating a better understanding of the mechanisms of action for each variable to enable optimum information gathering from the surgery and follow up.
2. Patient data management should be a mandatory item. Bariatric surgical procedures should be incorporated into local and national clinical registries to enable objective assessment of the risks and benefits across the community. This does not apply in the UK, but does in other countries such as Saudi Arabia.
3. There is a need for more studies such as randomised controlled trials with a large sample size and different ethnicities to define the benefits of weight loss on the comorbidities of obesity.

4. Further randomised control studies are needed specifically for patients with ED, LUTS, T2DM, hypertension, non-alcoholic fatty liver, liver transplant, psychological disorders and obstructive sleep apnoea.
5. Additional essential information is needed to find out more about the most safe and efficient pathways for assessment, surgery and follow up of ED patients.
6. Further knowledge is needed to cost-effectively evaluate the bariatric surgical approach to disease management for ED and LUTS in comparison with current options.

However, as previously noted, bariatric surgery could be one of the most significant treatments for obesity, sexual and urological dysfunctions. This approach has been realised through good science, wide-ranging data management and high quality clinical care.

Specifically, the future work will be designed to be applied in one of the biggest hospitals in Saudi Arabia- King Faisal Specialist Hospital and Research Centre.

There are some considerations that need to be addressed based on the thesis audits recommendations.

First, as urinary incontinence is common in the morbidly obese population, an appropriate questionnaire to assess urinary incontinence such as the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) (Gotoh *et al.* 2009) should be added to the IPSS and IIEF questionnaires to be completed by the participants.

Second, there is a need to consider a large sample size from the study population to enhance the reliability of the findings and enhance the power of the results. This can be done by using different approaches to increase patient recruitment, including private and governmental sectors, and involving more bariatric surgeons from different hospitals.

Third, the work will include a comprehensive history of the lifestyle, psychological condition and medical status of the participants and their partners. Focusing on lifestyle, the psychological condition of the partners will be examined by giving them, for example, a quality of life questionnaire. This

will provide a broad and clear view of the indirect factors affecting the lifestyle, physical and psychological well-being of the participants.

Fourth, a detailed history of PDE5 inhibitor use as prescribed or non-prescribed (personal use of PDE5 inhibitors with no medical direction) should be included for each participant. Oral PDE5-Is are considered as the first-line treatment for erectile dysfunction (Costabile *et al.* 2003, Konstantinos *et al.* 2009). The daily administration of PDE5 inhibitors produced desirable effects in previous clinical studies (Corbin 2004, McMahon 2006, Bella *et al.* 2007). Both daily and on-demand PDE5-Is improved efficacy outcomes and were well-tolerated (McMahon 2006). However, the change in the IIEF domain score and the successful completion of sexual intercourse were higher with daily dosing (McMahon 2006). The improvement in the erectile response proposed most likely related to improved endothelial function (Corbin 2004, McMahon 2006, Bella *et al.* 2007) and the higher satisfaction in the daily use of PDE5-Is were described by the patient and his partner. The primary outcome measures included changes from baseline (first visit) in the erectile function domain of the International Index of Erectile Function (IIEF) and the proportion of “yes” responses to questions 2 (successful penetration) and 3 (successful completion of intercourse) (McMahon 2006). This information can be retrieved through adequate and comprehensive sexual history taking from the patient and his partner and also, through the Ministry of Health (MOH) database in Saudi Arabia.

Fifth, certain biomarkers should be measured such as testosterone, prolactin and aromatase enzyme at each time point of the research. Meanwhile, prolactin levels have been neglected in the hormonal studies of morbidly obese patients (Reis *et al.* 2010). Reis *et al.* (2010) highlighted an association between weight loss and prolactin levels decrease. Also, aromatase enzyme is concentrated in fat cells and decreases testosterone levels (Cohen 1999, Cohen 2001). Furthermore, the exact molecular mechanism of androgen action in EF remains unknown and testosterone imbalance recovery in morbidly obese men after

surgical weight loss could justify the erectile function improvement independently by acting at different sites (Reis *et al.* 2010).

Sixth, waist circumference measurements combined with BMI will be used as a measure of the central obesity; this can be done by the clinic nurse at each visit to the participants. Also, waist circumference may represent an easy diagnostic tool to elucidate the presence of occult voiding dysfunction. Waist circumference has shown to be an accurate predictor and abdominal fat contains aromatase and is needed to assess central obesity (Lee *et al.* 2012). According to NICE recommendations; the guidance currently states that assessment of health risks associated with being overweight and obese should be based on both BMI and waist circumference for those with a BMI of less than 35 kg/m^2 (NICE 2014). Furthermore, waist circumference being heavily linked to various prostate related problems and associated with worsened voiding function and pelvic dysfunction (Lee *et al.* 2012).

Finally, to strengthen the study, there should be a short term post-operative follow-up within one week and a long term follow-up period of up to two years. A short term post-operative follow-up should differentiate if the recovery of erectile function occurs early before weight loss in parallel with normalised blood glucose. The measurement of the long term effectiveness of weight loss surgeries on sexual function and the long term complications once patients have maintained a plateau weight for several months.

To conclude, there are only a few studies focusing on EF in morbidly obese patient, and very few are focusing on EF after weight loss. The underlying mechanism of obesity-related sexual dysfunction is probably multi-factorial. ED should be considered one of the numerous potentially reversible complications of obesity (Reis *et al.* 2010). There is still an excessive need for more effective studies that can provide long-lasting improvement for urogenital dysfunction in morbidly obese men following bariatric surgery.

REFERENCES

Abrams, P., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten, U., Van Kerrebroeck, P., Victor, A. and Wein, A., 2003. The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. *Urology*, 61(1), pp. 37-49.

Aills, L., Blankenship, J., Buffington, C., Furtado, M., Parrott, J. and Allied Health Sciences Section Ad Hoc Nutrition Committee, 2008. ASMBS allied health nutritional guidelines for the surgical weight loss patient. *Surgery for obesity and related diseases*, 4(5), pp. S73-S108.

Akbas, F., Gasteyger, C., Sjödin, A., Astrup, A. and Larsen, T.M., 2009. A critical review of the cannabinoid receptor as a drug target for obesity management. *Obesity reviews*, 10(1), pp. 58-67.

Altman, D.G., 1990. Practical statistics for medical research. *CRC Press.*

Amigo, I. and Fernández, C., 2007. Effects of diets and their role in weight control. *Psychology, Health & Medicine*, 12(3), pp. 321-327.

Andersen, I., Heitman, B.L. and Wagner, G., 2008. Obesity and sexual dysfunction in Younger Danish Men. *Journal of Sexual Medicine*, 5(9), pp. 2053-2060.

Anderson, B., Gill, R.S., de Gara, C.J., Karmali, S. and Gagner, M., 2013. Biliopancreatic Diversion: The Effectiveness of Duodenal Switch and Its Limitations. *Gastroenterology research and practice*, (article ID 9747762), 8 pages.

Anderson, W.A., Greene, G.W., Forse, R.A., Apovian, C.M. and Istfan, N.W., 2007. Weight loss and health outcomes in African Americans and whites after gastric bypass surgery. *Obesity*, 15(6), pp. 1455-1463.

Andersson, K., de Groat, W.C., McVary, K.T., Lue, T.F., Maggi, M., Roehrborn, C.G., Wyndaele, J.J., Melby, T. and Viktrup, L., 2011. Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism (s) of action. *Neurourology and urodynamics*, 30(3), pp. 292-301.

Andersson, K.E. and Arner, A., 2004. Urinary bladder contraction and relaxation: physiology and pathophysiology. *Physiological Reviews*, 84(3), pp. 935-986.

Ariyarathenam, A., Pournaras, D., Tham, J., Finlay, I. and Cota, A., 2012. Need for standardization of the measurement of preoperative weight in bariatric surgical patients in the UK: A survey of British Obesity and Metabolic Surgery Society (BOMSS) members. *International Journal of Surgery*, 10(10), pp. 598-600.

Aytaç, I.A., Mckinlay, J.B. and Krane, R.J., 1999. "The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences". *BJU International*, 84(1), pp. 50-56.

Bacon, C.G., Mittleman, M.A., Kawachi, I., Giovannucci, E., Glasser, D.B. and Rimm, E.B., 2003. Sexual Function in Men Older Than 50 Years of Age: Results from the Health Professionals Follow-up Study. *Annals of Internal Medicine*, 139(3), pp. 161-168.

Badlani, G.H., Davila, G.W., Michel, M.C. and Rosette, J.J., 2008. "*Continence: current concepts and treatment strategies".* Springer Science & Business Media.

Baltasar, A., Perez, N., Serra, C., Bou, R., Bengochea, M. and Borrás, F., 2011. Weight loss reporting: predicted body mass index after bariatric surgery. *Obesity Surgery*, 21(3), pp. 367-372.

Bansal, T.C., Guay, A.T., Jacobson, J., Woods, B.O. and Nesto, R.W., 2005. Incidence of metabolic syndrome and insulin resistance in a population with organic erectile dysfunction. *Journal of Sexual Medicine*, 2(1), pp. 96-103.

Barrett-Connor, E., von Mühlen, D.G. and Kritz-Silverstein, D., 1999. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. *The Journal of Clinical Endocrinology & Metabolism*, 84(2), pp. 573-577.

Barry, M.J., Fowler Jr., F.J., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L., Mebust, W.K., Cockett, A.T.K., Blaivas, J.G. and Wein, A.J., 1992. The American Urological Association symptom index for benign prostatic hyperplasia. *Journal of Urology*, 148(5 I), pp. 1549-1557.

Basso, N., Capoccia, D., Rizzello, M., Abbatini, F., Mariani, P., Maglio, C., Coccia, F., Borgonuovo, G., De Luca, M.L., Asprino, R., Alessandri, G., Casella, G. and Leonetti, F., 2011. First-phase insulin secretion, insulin sensitivity, ghrelin, GLP-1, and PYY changes 72 h after sleeve gastrectomy in obese diabetic patients: The gastric hypothesis. *Surgical Endoscopy and Other Interventional Techniques*, 25(11), pp. 3540-3550.

Bella, A.J., DeYoung, L.X., al-Numi, M. and Brock, G.B., 2007. Daily administration of phosphodiesterase type 5 inhibitors for urological and nonurological indications. *European urology*, 52(4), pp. 990-1005.

Bibel, B.M., 2012. "The Whole Life Prostate Book: Everything that Every Man-at Every Age-Needs To Know About Maintaining Optimal Prostate Health".

Birder, L.A., Nealen, M.L., Kiss, S., De Groat, W.C., Caterina, M.J., Wang, E., Apodaca, G. and Kanai, A.J., 2002. β-adrenoceptor agonists stimulate endothelial nitric oxide synthase in rat urinary bladder urothelial cells. *Journal of Neuroscience*, 22(18), pp. 8063-8070.

Blanker, M.H., Bohnen, A.M., Groeneveld, F.P.M.J., Bernsen, R.M.D., Prins, A., Thomas, S. and Ruud Bosch, J.L.H., 2001. Correlates for erectile and ejaculatory dysfunction in older Dutch Men: A community-based study. *Journal of the American Geriatrics Society*, 49(4), pp. 436-442.

Bond, D.S., Phelan, S., Leahey, T.M., Hill, J.O. and Wing, R.R., 2009. Weight-loss maintenance in successful weight losers: surgical vs non-surgical methods. *International journal of obesity*, 33(1), pp. 173-180.

Borges, R., Temido, P., Sousa, L., Azinhais, P., Conceição, P., Pereira, B., Leão, R., Retroz, E., Brandão, T., Cristo, L. and Sobral, F., 2009. Metabolic syndrome and sexual dysfunction. *Journal of Sexual Medicine*, 6(11), pp. 2958-2975.

Bose, M., Oliván, B., Teixeira, J., Pi-Sunyer, F.X. and Laferrère, B., 2009. Do incretins play a role in the remission of type 2 diabetes after gastric bypass surgery: what are the evidence? *Obesity Surgery*, 19(2), pp. 217-229.

Boyle, P., Robertson, C., Mazzetta, C., Keech, M., Hobbs, R., Fourcade, R., Kiemeney, L. and Lee, C., 2003. The association between lower urinary tract symptoms and erectile dysfunction in four centres: the UrEpik study. *BJU International*, 92(7), pp. 719-725.

Brand, J.S., Rovers, M.M., Yeap, B.B., Schneider, H.J., Tuomainen, T., Haring, R., Corona, G., Onat, A., Maggio, M. and Bouchard, C., 2014. Testosterone, sex hormone-binding globulin and the metabolic

syndrome in men: an individual participant data meta-analysis of observational studies, *Circulation*, 125 (10), A020.

Braun, M., Wassmer, G., Klotz, T., Reifenrath, B., Mathers, M. and Engelmann, U., 2000. Epidemiology of erectile dysfunction: Results of the 'Cologne Male Survey'. *International Journal of Impotence Research*, 12(6), pp. 305-311.

Brethauer, S.A., Hammel, J.P. and Schauer, P.R., 2009. Systematic review of sleeve gastrectomy as staging and primary bariatric procedure. *Surgery for Obesity and Related Diseases*, 5(4), pp. 469-475.

Buchwald, H. and Oien, D.M., 2009. Metabolic/bariatric surgery worldwide 2008. *Obesity Surgery*, 19(12), pp. 1605-1611.

Buchwald, H., Avidor, Y., Braunwald, E., Jensen, M.D., Pories, W., Fahrbach, K. and Schoelles, K., 2004. Bariatric surgery: A systematic review and meta-analysis. *Journal of the American Medical Association*, 292(14), pp. 1724-1737.

Buchwald, H., Estok, R., Fahrbach, K., Banel, D., Jensen, M.D., Pories, W.J., Bantle, J.P. and Sledge, I., 2009. Weight and Type 2 Diabetes after Bariatric Surgery: Systematic Review and Meta-analysis. *American Journal of Medicine*, 122(3), pp. 248-256.e5.

Bump, R.C., Sugerman, H.J., Fantl, J.A. and McClish, D.K., 1992. Obesity and lower urinary tract function in women: effect of surgically induced weight loss. *American Journal of Obstetrics and Gynecology*, 167(2), pp. 392-399.

Burgio, K.L., Richter, H.E., Clements, R.H., Redden, D.T. and Goode, P.S., 2007. Changes in urinary and fecal incontinence symptoms with weight loss surgery in morbidly obese women. *Obstetrics and gynecology*, 110(5), pp. 1034-1040.

Burke, J.P., Rhodes, T., Jacobson, D.J., McGree, M.E., Roberts, R.O., Girman, C.J., Lieber, M.M. and Jacobsen, S.J., 2006. Association of anthropometric measures with the presence and progression of benign prostatic hyperplasia. *American Journal of Epidemiology*, 164(1), pp. 41-46.

Bushmakin, A.G., Cappelleri, J.C., Symonds, T. and Stecher, V.J., 2014. Enhanced understanding of the relationship between erection and satisfaction in ED treatment: Application of a longitudinal mediation model. *International Journal of Impotence Research*, 26(1), pp. 20-23.

Calle, E.E., Rodriguez, C., Walker-Thurmond, K. and Thun, M.J., 2003. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *New England Journal of Medicine*, 348(17), pp. 1625-1638.

Camacho, E.M., Huhtaniemi, I.T., O'Neill, T.W., Finn, J.D., Pye, S.R., Lee, D.M., Tajar, A., Bartfai, G., Boonen, S., Casanueva, F.F., Forti, G., Giwercman, A., Han, T.S., Kula, K., Keevil, B., Lean, M.E., Pendleton, N., Punab, M., Vanderschueren, D., Wu, F.C. and EMAS Group, 2013. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. *European journal of endocrinology / European Federation of Endocrine Societies*, 168(3), pp. 445-455.

Cappelleri, J. and Rosen, R., 2005. The Sexual Health Inventory for Men (SHIM): a 5-year review of research and clinical experience. *International Journal of Impotence Research*, 17(4), pp. 307-319.

Cappelleri, J.C., Rosen, R.C., Smith, M.D., Mishra, A. and Osterloh, I.H., 1999. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology*, 54(2), pp. 346-351.

Cellek, S., Cameron, N.E., Cotter, M.A., Fry, C.H. and Ilo, D., 2014. Microvascular dysfunction and efficacy of PDE5 inhibitors in BPH-LUTS. *Nature Reviews Urology,* 11(4), pp. 231-241.

Cersosimo, E. and DeFronzo, R.A., 2006. Insulin resistance and endothelial dysfunction: The road map to cardiovascular diseases. *Diabetes/metabolism research and reviews,* 22(6), pp. 423-436.

Chakaroun, R., Raschpichler, M., Klöting, N., Oberbach, A., Flehmig, G., Kern, M., Schön, M.R., Shang, E., Lohmann, T., Dreßler, M., Fasshauer, M., Stumvoll, M. and Blüher, M., 2012. Effects of weight loss and exercise on chemerin serum concentrations and adipose tissue expression in human obesity. *Metabolism: Clinical and Experimental,* 61(5), pp. 706-714.

Chan, J.M., Rimm, E.B., Colditz, G.A., Stampfer, M.J. and Willett, W.C., 1994. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes care,* 17(9), pp. 961-969.

Cheng, J.Y.W. and Ng, E.M.L., 2007. Body mass index, physical activity and erectile dysfunction: An U-shaped relationship from population-based study. *International journal of obesity,* 31(10), pp. 1571-1578.

Choi, Y.S., Lee, S.K., Bae, W.J., Kim, S.J., Cho, H.J., Hong, S., Lee, J.Y., Hwang, T. and Kim, S.W., 2014. Bariatric Surgery Improves the Cavernosal Neuronal, Vasorelaxation, and Contraction Mechanisms for Erectile Dysfunction As Result of Amelioration of Glucose Homeostasis in a Diabetic Rat Model. *PloS one,* 9(8), pp. e104042.

Chung, E. and Brock, G., 2013. Sexual Rehabilitation and Cancer Survivorship: A State of Art Review of Current Literature and Management Strategies in Male Sexual Dysfunction Among Prostate Cancer Survivors. *Journal of Sexual Medicine,* 10(SUPPL.), pp. 102-111.

Chung, S.-., Chen, Y.-., Lin, H.-. and Lin, H.-., 2011. Increased Risk of Stroke among Men with Erectile Dysfunction: A Nationwide Population-based Study. *Journal of Sexual Medicine,* 8(1), pp. 240-246.

Çinar, A., Hall, S.A., Link, C.L., Kaplan, S.A., Kopp, Z.S., Roehrborn, C.G. and Rosen, R.C., 2008. Cluster analysis and lower urinary tract symptoms in men: findings from the Boston Area Community Health Survey. *BJU international,* 101(10), pp. 1247-1256.

Clark, N.G., Fox, K.M. and Grandy, S., 2007. Symptoms of diabetes and their association with the risk and presence of diabetes: Findings from the study to help improve early evaluation and management of risk factors leading to diabetes (SHIELD). *Diabetes care,* 30(11), pp. 2868-2873.

Cohen, P., 2001. Aromatase, adiposity, aging and disease. The hypogonadal-metabolic-atherogenic-disease and aging connection. *Medical hypotheses,* 56(6), pp. 702-708.

Cohen, P., 1999. The hypogonadal–obesity cycle: role of aromatase in modulating the testosterone–estradiol shunt–a major factor in the genesis of morbid obesity. *Medical hypotheses,* 52(1), pp. 49-51.

Colditz, G.A., Willett, W.C., Rotnitzky, A. and Manson, J.E., 1995. Weight gain as a risk factor for clinical diabetes mellitus in women. *Annals of Internal Medicine,* 122(7), pp. 481-486.

Copeland, G., 2005. A practical handbook for clinical audit. *NHS Clinical Governance Support Team,* .

Corbin, J., 2004. Mechanisms of action of PDE5 inhibition in erectile dysfunction. *International Journal of Impotence Research,* 16, pp. S4-S7.

Corder, G.W. and Foreman, D.I., 2014. Nonparametric statistics: A step-by-step approach. *John Wiley & Sons.*

Cornicelli, M., Noli, G., Marinari, G.M. and Adami, G.F., 2010. Dietary habits and body weight at long-term following biliopancreatic diversion. *Obesity Surgery,* 20(9), pp. 1278-1280.

Corona, G., Mannucci, E., Forti, G. and Maggi, M., 2009. Hypogonadism, ED, metabolic syndrome and obesity: a pathological link supporting cardiovascular diseases. *International journal of andrology,* 32(6), pp. 587-598.

Corona, G. and Maggi, M., 2010. The role of testosterone in erectile dysfunction. *Nature Reviews Urology,* 7(1), pp. 46-56.

Costabile, R.A., Steers, W., Andersson, K.-. and Goldstein, I., 2003. Optimizing treatment for diabetes mellitus induced erectile dysfunction. *Journal of Urology,* 170(2 II), pp. S35-S39.

Gotoh, M., Homma, Y., Funahashi, Y., Matsukawa, Y. and Kato, M., 2009. Psychometric validation of the Japanese version of the International Consultation on Incontinence Questionnaire-Short Form. *International journal of urology,* 16(3), pp. 303-306

Courtenay, M., 2002. Male sexual function: a guide to clinical management John J Mulcahy. *Family practice,* 19(1), pp. 117-118.

Coyne, K.S., Sexton, C.C., Thompson, C.L., Milsom, I., Irwin, D., Kopp, Z.S., Chapple, C.R., Kaplan, S., Tubaro, A., Aiyer, L.P. and Wein, A.J., 2009. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: Results from the epidemiology of LUTS (EpiLUTS) study. *BJU international,* 104(3), pp. 352-360.

Cummings, J. and Rodning, C., 2000. Urinary stress incontinence among obese women: review of pathophysiology therapy. *International Urogynecology Journal,* 11(1), pp. 41-44.

Dallal, R.M., Chernoff, A., O'Leary, M.P., Smith, J.A., Braverman, J.D. and Quebbemann, B.B., 2008. Sexual Dysfunction Is Common in the Morbidly Obese Male and Improves after Gastric Bypass Surgery. *Journal of the American College of Surgeons,* 207(6), pp. 859-864.

Dandona, P. and Rosenberg, M., 2010. A practical guide to male hypogonadism in the primary care setting. *International journal of clinical practice,* 64(6), pp. 682-696.

de Ronde, W., van der Schouw, Y.T., Pols, H.A., Gooren, L.J., Muller, M., Grobbee, D.E. and de Jong, F.H., 2006. Calculation of bioavailable and free testosterone in men: a comparison of 5 published algorithms. *Clinical chemistry,* 52(9), pp. 1777-1784.

Dean, R.C. and Lue, T.F., 2005. Physiology of penile erection and pathophysiology of erectile dysfunction. *Urologic Clinics of North America,* 32(4), pp. 379-395.

Deitel, M., Gawdat, K. and Melissas, J., 2007. Reporting weight loss 2007. *Obesity Surgery,* 17(5), pp. 565-568.

Deitel, M. and Shikora, S.A., 2002. The development of the surgical treatment of morbid obesity. *Journal of the American College of Nutrition,* 21(5), pp. 365-371.

Demaria, E.J., Winegar, D.A., Pate, V.W., Hutcher, N.E., Ponce, J. and Pories, W.J., 2010. Early postoperative outcomes of metabolic surgery to treat diabetes from sites participating in the ASMBS bariatric surgery center of excellence program as reported in the Bariatric Outcomes Longitudinal Database. *Annals of Surgery,* 252(3), pp. 559-66.

Demir, O., Akgul, K., Akar, Z., Cakmak, O., Ozdemir, I., Bolukbasi, A., Can, E. and Gumus, B.H., 2009. Association between severity of lower urinary tract symptoms, erectile dysfunction and metabolic syndrome. *Aging Male,* 12(1), pp. 29-34.

Demir, T., Demir, O., Kefi, A., Comlekci, A., Yesil, S. and Esen, A., 2006. Erratum: Prevalence of erectile dysfunction in patients with metabolic syndrome (International Journal of Urology 13, (385-388)). *International Journal of Urology,* 13(9), pp. 1264.

Després, J.-., 2006. Is visceral obesity the cause of the metabolic syndrome? *Annals of Medicine,* 38(1), pp. 52-63.

di Frega, A.S., Dale, B., Di Matteo, L. and Wilding, M., 2005. Secondary male factor infertility after Roux-en-Y gastric bypass for morbid obesity: Case report. *Human Reproduction,* 20(4), pp. 997-998.

Dixon, J.B., McPhail, T. and O'brien, P.E., 2005. Minimal reporting requirements for weight loss: current methods not ideal. *Obesity Surgery,* 15(7), pp. 1034-1039.

Dixon, J.B., Dixon, M.E. and O'Brien, P.E., 2002. Body image: Appearance orientation and evaluation in the severely obese. Changes with weight loss. *Obesity Surgery,* 12(1), pp. 65-71.

Dixon, J.B., Le Roux, C.W., Rubino, F. and Zimmet, P., 2012. Bariatric surgery for type 2 diabetes. *The Lancet,* 379(9833), pp. 2300-2311.

Dixon, J.B., Pories, W.J., O'Brien, P.E., Schauer, P.R. and Zimmet, P., 2005. Surgery as an effective early intervention for diabesity: Why the reluctance? *Diabetes care,* 28(2), pp. 472-474.

Dixon, J.B., Straznicky, N.E., Lambert, E.A., Schlaich, M.P. and Lambert, G.W., 2012. Laparoscopic adjustable gastric banding and other devices for the management of obesity. *Circulation,* 126(6), pp. 774-785.

Dong, J.-., Zhang, Y.-. and Qin, L.-., 2011. Erectile dysfunction and risk of cardiovascular disease: Meta-analysis of prospective cohort studies. *Journal of the American College of Cardiology,* 58(13), pp. 1378-1385.

Drake, M., Mills, I. and Gillespie, J., 2001. Model of peripheral autonomous modules and a myovesical plexus in normal and overactive bladder function. *The Lancet,* 358(9279), pp. 401-403.

Drucker, D.J. and Nauck, M.A., 2006. New Drug Class. *Lancet,* 368, pp. 1696-1705.

Efthymiou, V., Hyphantis, T., Karaivazoglou, K., Gourzis, P., Alexandrides, T.K., Kalfarentzos, F. and Assimakopoulos, K., 2014. The effect of bariatric surgery on patient HRQOL and sexual health during a 1-year postoperative period. *Obesity Surgery,* 25(2), pp. 310-318.

Elliott, S.P., Gulati, M., Pasta, D.J., Spitalny, G.M., Kane, C.J., Yee, R. and Lue, T.F., 2004. Obstructive lower urinary tract symptoms correlate with erectile dysfunction. *Urology,* 63(6), pp. 1148-1152.

Engström, G., Henningsohn, L., Steineck, G. and Leppert, J., 2005. Self-assessed health, sadness and happiness in relation to the total burden of symptoms from the lower urinary tract. *BJU international,* 95(6), pp. 810-815.

Esposito, K., Ciotola, M., Giugliano, F., De Sio, M., Giugliano, G., D'Armiento, M. and Giugliano, D., 2006. Mediterranean diet improves erectile function in subjects with the metabolic syndrome. *International Journal of Impotence Research,* 18(4), pp. 405-410.

Esposito, K. and Giugliano, D., 2005. Obesity, the metabolic syndrome, and sexual dysfunction. *International Journal of Impotence Research*, 17(5), pp. 391-398.

Esposito, K., Giugliano, F., Di Palo, C., Giugliano, G., Marfella, R., D'Andrea, F., D'Armiento, M. and Giugliano, D., 2004. Effect of lifestyle changes on erectile dysfunction in obese men: A randomized controlled trial. *Journal of the American Medical Association*, 291(24), pp. 2978-2984.

Esposito, K., Giugliano, F., Martedì, E., Feola, G., Marfella, R., D'Armiento, M. and Giugliano, D., 2005. High proportions of erectile dysfunction in men with the metabolic syndrome. *Diabetes care*, 28(5), pp. 1201-1203.

Faintuch, J., Matsuda, M., Cruz, M.E.L., Silva, M.M., Teivelis, M.P., Garrido Jr, A.B. and Gama-Rodrigues, J., 2004. Severe protein-calorie malnutrition after bariatric procedures. *Obesity Surgery*, 14(2), pp. 175-181.

Favretti, F., O'Brien, P.E. and Dixon, J.B., 2002. Patient management after LAP-BAND placement. *The American journal of surgery*, 184(6), pp. S38-S41.

Fedele, D., 2005. Therapy insight: Sexual and bladder dysfunction associated with diabetes mellitus. *Nature Clinical Practice Urology*, 2(6), pp. 282-290.

Feldman, H.A., Longcope, C., Derby, C.A., Johannes, C.B., Araujo, A.B., Coviello, A.D., Bremner, W.J. and McKinlay, J.B., 2002. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *The Journal of Clinical Endocrinology & Metabolism*, 87(2), pp. 589-598.

Feldman, H.A., Goldstein, I., Hatzichristou, D.G., Krane, R.J. and McKinlay, J.B., 1994. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *The Journal of urology*, 151(1), pp. 54-61.

Feldman, H.A., Johannes, C.B., Derby, C.A., Kleinman, K.P., Mohr, B.A., Araujo, A.B. and McKinlay, J.B., 2000. Erectile dysfunction and coronary risk factors: Prospective results from the Massachusetts Male Aging Study. *Preventive medicine*, 30(4), pp. 328-338.

Fenske, W.K., Bueter, M., Miras, A.D., Ghatei, M.A., Bloom, S.R. and Le Roux, C.W., 2012. Exogenous peptide YY3-36 and Exendin-4 further decrease food intake, whereas octreotide increases food intake in rats after Roux-en-Y gastric bypass. *International journal of obesity*, 36(3), pp. 379-384.

Flum, D.R. and Dellinger, E.P., 2004. Impact of gastric bypass operation on survival: a population-based analysis. *Journal of the American College of Surgeons*, 199(4), pp. 543-551.

Frankel, S., Donovan, J., Peters, T., Abrams, P., Dabhoiwala, N., Osawa, D. and Lin, A.T.L., 1998. Sexual dysfunction in men with lower urinary tract symptoms. *Journal of clinical epidemiology*, 51(8), pp. 677-685.

Franz, M.J., VanWormer, J.J., Crain, A.L., Boucher, J.L., Histon, T., Caplan, W., Bowman, J.D. and Pronk, N.P., 2007. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *Journal of the American Dietetic Association*, 107(10), pp. 1755-1767.

Friedman, J.M. and Halaas, J.L., 1998. Leptin and the regulation of body weight in mammals. *Nature*, 395(6704), pp. 763-770.

Fritschi, L., Tabrizi, J., Leavy, J., Ambrosini, G. and Timperio, A., 2007. Risk factors for surgically treated benign prostatic hyperplasia in Western Australia. *Public health*, 121(10), pp. 781-789.

Fujimoto, W.Y., 2000. The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus. *The American Journal of Medicine,* 108(6), pp. 9-14.

Gacci, M., Eardley, I., Giuliano, F., Hatzichristou, D., Kaplan, S.A., Maggi, M., McVary, K.T., Mirone, V., Porst, H. and Roehrborn, C.G., 2011. Critical analysis of the relationship between sexual dysfunctions and lower urinary tract symptoms due to benign prostatic hyperplasia. *European urology,* 60(4), pp. 809-825.

GAESSER, G.A., 2013. *Big fat lies: The truth about your weight and your health.* Gurze Books.

Gan, E.H., Pattman, S., Pearce, S. and Quinton, R., 2012. Many men are receiving unnecessary testosterone prescriptions. *BMJ (Clinical research ed.),* 345, pp. e5469.

Gan, S.S.H., Talbot, M.L. and Jorgensen, J.O., 2007. Efficacy of surgery in the management of obesity-related type 2 diabetes mellitus. *ANZ Journal of Surgery,* 77(11), pp. 958-962.

Garcia, F.J., Violette, P.D., Matsumoto, E.D., Brock, G.B. and Paulter, S.E., 2014. Nerve-sparing prostatectomy benefits men with poor preoperative erectile dysfunction. *Journal of Robotic Surgery,* 8(4), pp. 299-304.

Garrido-Sanchez, L., Murri, M., Rivas-Becerra, J., Ocaa-Wilhelmi, L., Cohen, R.V., Garcia-Fuentes, E. and Tinahones, F.J., 2012. Bypass of the duodenum improves insulin resistance much more rapidly than sleeve gastrectomy. *Surgery for Obesity and Related Diseases,* 8(2), pp. 145-150.

Ghasemi, A. and Zahediasl, S., 2012. Normality tests for statistical analysis: a guide for non-statisticians. *International journal of endocrinology and metabolism,* 10(2), pp. 486.

Ginsberg, H.N. and Huang, L.-., 2000. The insulin resistance syndrome: Impact on lipoprotein metebolism and atherothrombosis. *Journal of cardiovascular risk,* 7(5), pp. 325-331.

Giovannucci, E., Rimm, E.B., Chute, C.G., Kawachi, I., Colditz, G.A., Stampfer, M.J. and Willett, W.C., 1994. Obesity and benign prostatic hyperplasia. *American Journal of Epidemiology,* 140(11), pp. 989-1002.

Glasser, D.B., Carson III, C., Kang, J.-. and Laumann, E.O., 2007. Prevalence of storage and voiding symptoms among men aged 40 years and older in a US population-based study: Results from the Male Attitudes Regarding Sexual Health study. *International journal of clinical practice,* 61(8), pp. 1294-1300.

Gloy, V.L., Briel, M., Bhatt, D.L., Kashyap, S.R., Schauer, P.R., Mingrone, G., Bucher, H.C. and Nordmann, A.J., 2013. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ (Clinical research ed.),* 347, pp. f5934.

Goldman, H.B. and Appell, R.A., 1999. Voiding dysfunction in women with diabetes mellitus. *International urogynecology journal and pelvic floor dysfunction,* 10(2), pp. 130-133.

Goldstraw, M.A., Kirby, M.G., Bhardwa, J. and Kirby, R.S., 2007. Diabetes and the urologist: A growing problem. *BJU international,* 99(3), pp. 513-517.

Gontero, P. and Kirby, R., 2004a. Early rehabilitation of erectile function after nerve-sparing radical prostatectomy: what is the evidence? *BJU international,* 93(7), pp. 916-918.

Gontero, P. and Kirby, R., 2004b. Proerectile pharmacological prophylaxis following nerve-sparing radical prostatectomy (NSRP). *Prostate cancer and prostatic diseases,* 7(3), pp. 223-226.

Gordon, L.G. and Obermair, A., 2010. Potential hospital cost-savings attributed to improvements in outcomes for colorectal cancer surgery following self-audit. *BMC surgery,* 10, pp. 4-2482-10-4.

Gotoh, M., Homma, Y., Funahashi, Y., Matsukawa, Y. and Kato, M., 2009. Psychometric validation of the Japanese version of the International Consultation on Incontinence Questionnaire-Short Form. *International journal of urology,* 16(3), pp. 303-306.

Griffen, W.O.,Jr, Bivins, B.A. and Bell, R.M., 1983. The decline and fall of the jejunoileal bypass. *Surgery, gynecology & obstetrics,* 157(4), pp. 301-308.

Groeneveld, R.A. and Meeden, G., 1984. Measuring skewness and kurtosis. *The Statistician,* , pp. 391-399.

Guariguata, L., Whiting, D., Hambleton, I., Beagley, J., Linnenkamp, U. and Shaw, J., 2014. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes research and clinical practice,* 103(2), pp. 137-149.

Gurevich-Panigrahi, T., Panigrahi, S., Wiechec, E. and Los, M., 2009. Obesity: pathophysiology and clinical management. *Current medicinal chemistry,* 16(4), pp. 506-521.

Hackett, G., Kell, P., Ralph, D., Dean, J., Price, D., Speakman, M. and Wylie, K., 2008. British Society for Sexual Medicine guidelines on the management of erectile dysfunction. *The journal of sexual medicine,* 5(8), pp. 1841-1865.

Hall, J.C., Watts, J.M., O'Brien, P.E., Dunstan, R.E., Walsh, J.F., Slavotinek, A.H. and Elmslie, R.G., 1990. Gastric surgery for morbid obesity. The Adelaide Study. *Annals of Surgery,* 211(4), pp. 419-427.

Hammarsten, J. and Peeker, R., 2011. Urological aspects of the metabolic syndrome. *Nature Reviews Urology,* 8(9), pp. 483-494.

Hammoud, A., Gibson, M., Hunt, S.C., Adams, T.D., Carrell, D.T., Kolotkin, R.L. and Meikle, A.W., 2009. Effect of Roux-en-Y gastric bypass surgery on the sex steroids and quality of life in obese men. *Journal of Clinical Endocrinology & Metabolism,* 94(4), pp. 1329-1332.

Hammoud, A.O., Gibson, M., Peterson, C.M., Hamilton, B.D. and Carrell, D.T., 2006. Obesity and male reproductive potential. *Journal of andrology,* 27(5), pp. 619-626.

Hatzimouratidis, K. and Hatzichristou, D., 2009. Erectile dysfunction and diabetes mellitus. *Insulin,* 4(2), pp. 114-122.

Hidalgo-Tamola, J. and Chitaley, K., 2009. Type 2 diabetes mellitus and erectile dysfunction. *Journal of Sexual Medicine,* 6(4), pp. 916-926.

Ho, S., 2004. Estrogens and anti-estrogens: Key mediators of prostate carcinogenesis and new therapeutic candidates. *Journal of cellular biochemistry,* 91(3), pp. 491-503.

Horasanli, K., Boylu, U., Kendirci, M. and Miroglu, C., 2008. Do lifestyle changes work for improving erectile dysfunction? *Asian Journal of Andrology,* 10(1), pp. 28-35.

Humbles, A.A., Lloyd, C.M., McMillan, S.J., Friend, D.S., Xanthou, G., McKenna, E.E., Ghiran, S., Gerard, N.P., Yu, C., Orkin, S.H. and Gerard, C., 2004. A critical role for eosinophils in allergic airways remodeling. *Science (New York, N.Y.),* 305(5691), pp. 1776-1779.

Inman, B.A., St Sauver, J.L., Jacobson, D.J., McGree, M.E., Nehra, A., Lieber, M.M., Roger, V.L. and Jacobsen, S.J., 2009. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. *Obstetrical and Gynecological Survey*, 64(7), pp. 459-460.

Ioannides-Demos, L.L., Proietto, J., Tonkin, A.M. and McNeil, J.J., 2006. Safety of drug therapies used for weight loss and treatment of obesity. *Drug Safety*, 29(4), pp. 277-302.

Irwin, D.E., Milsom, I., Hunskaar, S., Reilly, K., Kopp, Z., Herschorn, S., Coyne, K., Kelleher, C., Hampel, C., Artibani, W. and Abrams, P., 2006. Population-Based Survey of Urinary Incontinence, Overactive Bladder, and Other Lower Urinary Tract Symptoms in Five Countries: Results of the EPIC Study. *European urology*, 50(6), pp. 1306-1315.

Isbell, J.M., Tamboli, R.A., Hansen, E.N., Saliba, J., Dunn, J.P., Phillips, S.E., Marks-Shulman, P.A. and Abumrad, N.N., 2010. The importance of caloric restriction in the early improvements in insulin sensitivity after Roux-en-Y gastric bypass surgery. *Diabetes care*, 33(7), pp. 1438-1442.

Isidori, A.M., Giannetta, E., Gianfrilli, D., Greco, E.A., Bonifacio, V., Aversa, A., Isidori, A., Fabbri, A. and Lenzi, A., 2005. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clinical endocrinology*, 63(4), pp. 381-394.

Jackson, S., 1999. Lower urinary tract symptoms and nocturia in men and women: Prevalence, aetiology and diagnosis. *BJU International, Supplement*, 84(1), pp. 5-8.

Jesmin, S., Sakuma, I., Salah-Eldin, A., Nonomura, K., Hattori, Y. and Kitabatake, A., 2003. Diminished penile expression of vascular endothelial growth factor and its receptors at the insulin-resistant stage of a type II diabetic rat model: A possible cause for erectile dysfunction in diabetes. *Journal of Molecular Endocrinology*, 31(3), pp. 401-418.

Johannes, C.B., Araujo, A.B., Feldman, H.A., Derby, C.A., Kleinman, K.P. and McKINLAY, J.B., 2000. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. *The Journal of urology*, 163(2), pp. 460-463.

Jones, C., Hill, J. and Chapple, C., 2010. Management of lower urinary tract symptoms in men: Summary of NICE guidance. *BMJ (Online)*, 340(7759), pp. 1300-1301.

Kalejaiye, O. and Persad, R., 2014. Erectile dysfunction associated with surgery for prostate and colorectal cancer. *Trends in Urology & Men's Health*, 5(1), pp. 35-39.

Kang, J.G. and Park, C., 2012. Anti-obesity drugs: a review about their effects and safety. *Diabetes & metabolism journal*, 36(1), pp. 13-25.

Kaplan, S.A., Te, A.E., Blaivas, J.G. and McGuire, E.J., 1995. Urodynamic findings in patients with diabetic cystopathy. *Journal of Urology*, 153(2), pp. 342-344.

Karamanakos, S.N., Vagenas, K., Kalfarentzos, F. and Alexandrides, T.K., 2008. Weight loss, appetite suppression, and changes in fasting and postprandial ghrelin and peptide-YY levels after Roux-en-Y gastric bypass and sleeve gastrectomy: a prospective, double blind study. *Annals of Surgery*, 247(3), pp. 401-407.

Karra, E., Yousseif, A. and Batterham, R.L., 2010. Mechanisms facilitating weight loss and resolution of type 2 diabetes following bariatric surgery. *Trends in Endocrinology and Metabolism*, 21(6), pp. 337-344.

Kaya, E., Sikka, S.C. and Gur, S., 2015. A Comprehensive Review of Metabolic Syndrome Affecting Erectile Dysfunction. *Journal of Sexual Medicine*, 12(4), pp. 856-875.

Keddie, A.M., 2011. Associations between severe obesity and depression: results from the National Health and Nutrition Examination Survey, 2005-2006. *Preventing chronic disease,* 8(3), pp. A57.

Kendirci, M., Tanriverdi, O., Trost, L. and Hellstrom, W.J., 2006. Management of sildenafil treatment failures. *Current opinion in urology,* 16(6), pp. 449-459.

Kim, G.W., Doo, S.W., Yang, W.J. and Song, Y.S., 2010. Effects of obesity on prostate volume and lower urinary tract symptoms in Korean men. *Korean journal of urology,* 51(5), pp. 344-347.

Kirby, M., Chapple, C., Jackson, G., Eardley, I., Edwards, D., Hackett, G., Ralph, D., Rees, J., Speakman, M., Spinks, J. and Wylie, K., 2013. Erectile dysfunction and lower urinary tract symptoms: A consensus on the importance of co-diagnosis. *International journal of clinical practice,* 67(7), pp. 606-618.

Kirby, M.G., White, I.D., Butcher, J., Challacombe, B., Coe, J., Grover, L., Hegarty, P., Jackson, G., Lowndes, A., Payne, H., Rees, J., Sangar, V. and Thompson, A., 2014. Development of UK recommendations on treatment for post-surgical erectile dysfunction. *International journal of clinical practice,* 68(5), pp. 590-608.

Kirby, R.S., Kirby, M.G., Amoroso, P., Dean, J. and Gould, D., 2006. Steps by which better overall health for men could be achieved. *BJU international,* 98(2), pp. 285-288.

Klok, M., Jakobsdottir, S. and Drent, M., 2007. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obesity reviews,* 8(1), pp. 21-34.

Knoops, K.T., de Groot, L.C., Kromhout, D., Perrin, A., Moreiras-Varela, O., Menotti, A. and Van Staveren, W.A., 2004. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *Jama,* 292(12), pp. 1433-1439.

Kokoska, S. and Zwillinger, D., 2000. Standard Probability and Statistics Tables: Student Edition. *Boca Raton, FL: CRC*.

Kolotkin, R.L., Crosby, R.D., Pendleton, R., Strong, M., Gress, R.E. and Adams, T., 2003. Health-related quality of life in patients seeking gastric bypass surgery vs non-treatment-seeking controls. *Obesity Surgery,* 13(3), pp. 371-377.

Konstantinos, G. and Petros, P., 2009. Phosphodiesterase-5 inhibitors: future perspectives. *Current pharmaceutical design,* 15(30), pp. 3540-3551.

Kratzik, C.W., Schatzl, G., Lunglmayr, G., Rücklinger, E. and Huber, J., 2005. The impact of age, body mass index and testosterone on erectile dysfunction. *The Journal of urology,* 174(1), pp. 240-243.

Kristal, A.R., Arnold, K.B., Schenk, J.M., Neuhouser, M.L., Weiss, N., Goodman, P., Antvelink, C.M., Penson, D.F. and Thompson, I.M., 2007. Race/ethnicity, obesity, health related behaviors and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *The Journal of urology,* 177(4), pp. 1395-1400.

Kubin, M., Wagner, G. and Fugl-Meyer, A.R., 2003. Epidemiology of erectile dysfunction. *International Journal of Impotence Research,* 15(1), pp. 63-71.

Kuo, H., 2007. Differential diagnosis of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia and non-benign prostatic hyperplasia. *Incont Pelvic Floor Dysfunct,* 1(Suppl 1), pp. 3-6.

Kuo, H.C., 2000. Pathophysiology of lower urinary tract symptoms in aged men without bladder outlet obstruction. *Urologia internationalis,* 64(2), pp. 86-92.

Kupelian, V., Wei, J.T., O'Leary, M.P., Kusek, J.W., Litman, H.J., Link, C.L. and McKinlay, J.B., 2006. Prevalence of lower urinary tract symptoms and effect on quality of life in a racially and ethnically diverse random sample: The Boston Area Community Health (BACH) survey. *Archives of Internal Medicine,* 166(21), pp. 2381-2387.

Kurbatov, D., Kuznetsky, J. and Traish, A., 2008. Testosterone improves erectile function in hypogonadal patients with venous leakage. *Journal of andrology,* 29(6), pp. 630-637.

Kuruba, R., Almahmeed, T., Martinez, F., Torrella, T.A., Haines, K., Nelson, L.G., Gallagher, S.F. and Murr, M.M., 2007. Bariatric surgery improves urinary incontinence in morbidly obese individuals. *Surgery for Obesity and Related Diseases,* 3(6), pp. 586-590.

Laaksonen, D.E., Niskanen, L., Punnonen, K., Nyyssonen, K., Tuomainen, T., Valkonen, V. and Salonen, J.T., 2005. The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: a prospective cohort study. *The Journal of Clinical Endocrinology & Metabolism,* 90(2), pp. 712-719.

Laungani, R.G., Seleno, N. and Carlin, A.M., 2009. Effect of laparoscopic gastric bypass surgery on urinary incontinence in morbidly obese women. *Surgery for Obesity and Related Diseases,* 5(3), pp. 334-338.

Le Roux, C.W., Aylwin, S.J.B., Batterham, R.L., Borg, C.M., Coyle, F., Prasad, V., Shurey, S., Ghatei, M.A., Patel, A.G. and Bloom, S.R., 2006. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. *Annals of Surgery,* 243(1), pp. 108-114.

Lean, M., 2000. Pathophysiology of obesity. *Proceedings of the Nutrition Society,* 59(03), pp. 331-336.

Lee, R.K., Chung, D., Chughtai, B., Te, A.E. and Kaplan, S.A., 2012. Central obesity as measured by waist circumference is predictive of severity of lower urinary tract symptoms. *BJU international,* .

Li, Y.R., 2015. *Cardiovascular Diseases: From Molecular Pharmacology to Evidence-Based Therapeutics.* John Wiley & Sons.

Li, Z., Maglione, M., Tu, W., Mojica, W., Arterburn, D., Shugarman, L.R., Hilton, L., Suttorp, M., Solomon, V. and Shekelle, P.G., 2005a. Meta-analysis: pharmacologic treatment of obesity. *Annals of Internal Medicine,* 142(7), pp. 532-546.

Li, M., Garcia, L.A. and Rosen, R., 2005b. Lower urinary tract symptoms and male sexual dysfunction in Asia: A survey of ageing men from five Asian countries. *BJU international,* 96(9), pp. 1339-1354.

Llorente, C., 2010. New Concepts in Epidemiology of Lower Urinary Tract Symptoms in Men. *European Urology, Supplements,* 9(4), pp. 477-481.

Lue, T.F., Giuliano, F., Montorsi, F., Rosen, R.C., Andersson, K.-., Althof, S., Christ, G., Hatzichristou, D., Hirsch, M., Kimoto, Y., Lewis, R., McKenna, K., MacMahon, C., Morelas, A., Mulcahy, J., Padman-Nathan, H., Pryor, J., Saenz de Tejada, I., Shabsigh, R. and Wagner, G., 2004. Summary on the recommendations on sexual dysfunctions in men. *Journal of Sexual Medicine,* 1(1), pp. 6-23.

Lukacs, B., Leplege, A., Thibault, P. and Jardin, A., 1996. Prospective study of men with clinical benign prostatic hyperplasia treated with alfuzosin by general practitioners: 1-year results. *Urology,* 48(5), pp. 731-740.

Luke, S., Addison, B., Broughton, K., Masters, J., Stubbs, R. and Kennedy-Smith, A., 2015. Effects of bariatric surgery on untreated lower urinary tract symptoms: a prospective multicentre cohort study. *BJU international,* 115(3), pp. 466-472.

MacDonald, A.A., Herbison, G.P., Showell, M. and Farquhar, C.M., 2010. The impact of body mass index on semen parameters and reproductive hormones in human males: a systematic review with meta-analysis. *Human reproduction update,* 16(3), pp. 293-311.

Maggard, M.A., Shugarman, L.R., Suttorp, M., Maglione, M., Sugarman, H.J., Livingston, E.H., Nguyen, N.T., Li, Z., Mojica, W.A., Hilton, L., Rhodes, S., Morton, S.C. and Shekelle, P.G., 2005. Meta-analysis: Surgical treatment of obesity. *Annals of Internal Medicine,* 142(7), pp. 547-559.

Matthews, D.R., Hosker, J.P. and Rudenski, A.S., 1985. Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia,* 28(7), pp. 412-419.

Mauro, M., Taylor, V., Wharton, S. and Sharma, A.M., 2008. Barriers to obesity treatment. *European journal of internal medicine,* 19(3), pp. 173-180.

McConnell, J.D., Roehrborn, C.G., Bautista, O.M., Andriole Jr., G.L., Dixon, C.M., Kusek, J.W., Lepor, H., McVary, K.T., Nyberg Jr., L.M., Clarke, H.S., Crawford, E.D., Diokno, A., Foley, J.P., Foster, H.E., Jacobs, S.C., Kaplan, S.A., Kreder, K.J., Lieber, M.M., Lucia, M.S., Miller, G.J., Menon, M., Milam, D.F., Ramsdell, J.W., Schenkman, N.S., Slawin, K.M. and Smith, J.A., 2003. The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. *New England Journal of Medicine,* 349(25), pp. 2387-2398.

McIntyre, R.S., Mancini, D., Eisfeld, B.S., Soczynska, J.K., Grupp, L., Konarski, J.Z. and Kennedy, S.H., 2006. Calculated bioavailable testosterone levels and depression in middle-aged men. *Psychoneuroendocrinology,* 31(9), pp. 1029-1035.

McMahon, C.G., 2006. Treatment of erectile dysfunction with chronic dosing of tadalafil. *European urology,* 50(2), pp. 215-217.

McQuigg, M., Brown, J., Broom, J., Laws, R.A., Reckless, J.P., Noble, P.A., Kumar, S., McCombie, E.L., Lean, M.E., Lyons, G.F., Frost, G.S., Quinn, M.F., Barth, J.H., Haynes, S.M., Finer, N., Ross, H.M., Hole, D.J. and Counterweight Project Team, 2005. Empowering primary care to tackle the obesity epidemic: the Counterweight Programme. *European journal of clinical nutrition,* 59 Suppl 1, pp. S93-100; discussion S101.

Mehraban, D., Naderi, G.H., Yahyazadeh, S.R. and Amirchaghmaghi, M., 2008. Sexual dysfunction in aging men with lower urinary tract symptoms. *Urology journal,* 5(4), pp. 260-264.

Mikhail, N., 2006. Does testosterone have a role in erectile function? *The American Journal of Medicine,* 119(5), pp. 373-382.

Miller, T.A., 2000. Diagnostic evaluation of erectile dysfunction. *American Family Physician,* 61(1), pp. 95-104, 109-10.

Miner, M., Seftel, A.D., Nehra, A., Ganz, P., Kloner, R.A., Montorsi, P., Vlachopoulos, C., Ramsey, M., Sigman, M., Tilkemeier, P. and Jackson, G., 2012. Prognostic utility of erectile dysfunction for cardiovascular disease in younger men and those with diabetes. *American Heart Journal,* 164(1), pp. 21-28.

Mingrone, G. and Castagneto-Gissey, L., 2009. Mechanisms of early improvement / resolution of type 2 diabetes after bariatric surgery. *Diabetes and Metabolism,* 35(6 PART II), pp. 518-523.

Mingrone, G., Panunzi, S., De Gaetano, A., Guidone, C., Iaconelli, A., Leccesi, L., Nanni, G., Pomp, A., Castagneto, M., Ghirlanda, G. and Rubino, F., 2012. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *New England Journal of Medicine,* 366(17), pp. 1577-1585.

Mithieux, G., 2012. Comment about intestinal gluconeogenesis after gastric bypass in human in relation with the paper by Hayes et al., 2011. *Obesity Surgery,* 22(12), pp. 1920-1922.

Mokdad, A.H., Ford, E.S., Bowman, B.A., Dietz, W.H., Vinicor, F., Bales, V.S. and Marks, J.S., 2003. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA: the journal of the American Medical Association,* 289(1), pp. 76-79.

Montero, P.N., Stefanidis, D., Norton, H.J., Gersin, K. and Kuwada, T., 2011. Reported excess weight loss after bariatric surgery could vary significantly depending on calculation method: a plea for standardization. *Surgery for Obesity and Related Diseases,* 7(4), pp. 531-534.

Mora, M., Aranda, G.B., De Hollanda, A., Flores, L., Puig-Domingo, M. and Vidal, J., 2013. Weight loss is a major contributor to improved sexual function after bariatric surgery. *Surgical Endoscopy and Other Interventional Techniques,* 27(9), pp. 3197-3204.

Mydlo, J.H., 2004. The impact of obesity in urology. *The Urologic clinics of North America,* 31(2), pp. 275.

Nandipati, K.C., Raina, R., Agarwal, A. and Zippe, C.D., 2006. Erectile dysfunction following radical retropubic prostatectomy: Epidemiology, pathophysiology and pharmacological management. *Drugs and Aging,* 23(2), pp. 101-117.

National Institutes of Health, 1993. Consensus Development conference statement. Impotence. *International Journal of Impotence Research,* 5(1), pp. 181-284.

National Obesity Observatory, 2010-last update, Trends in obesity prevalence. Available: http://www.noo.org.uk/NOO_about_obesity/trends ,(02/05/2015).

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., Mullany, E.C., Biryukov, S., Abbafati, C. and Abera, S.F., 2014. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet,* 384(9945), pp. 766-781.

Nguyen, C.P., Hirsch, M.S., Moeny, D., Kaul, S., Mohamoud, M. and Joffe, H.V., 2015. Testosterone and "age-related hypogonadism"FDA Concerns", *The New England journal of medicine,* 373(8), pp. 689-691.

NHS Choices, 2015a-last update, Obesity Medication information "Orlistat". Available: http://services.medicines.org.uk/assethosting/assets/printable/o/r/orlistat/printable.1294_933_6848.pdf ,(15/06/2015).

NHS Choices, 2015b-last update, What is a Mediterranean diet?. Available: http://www.nhs.uk/Livewell/Goodfood/Pages/what-is-a-Mediterranean-diet.aspx ,(01/10/2015).

NHS Choices information, 2013-last update, Body Mass Index: BMI for adult. Available: http://www.nhs.uk/Tools/Pages/Healthyweightcalculator.aspx ,(10/31/2015).

NHS Information Centre, 2014-last update, Statistics on obesity, physical activity and diet. Available: https://catalogue.ic.nhs.uk/publications/public-health/obesity/obes-phys-acti-diet-eng-2013/obes-phys-acti-diet-eng-2013-rep.pdf ,(30/09/2014).

NHS- Services, 2015-last update, The UCLH centre for weight loss, metabolic and endocrine surgery. Available: https://www.uclh.nhs.uk/OurServices/ServiceA-Z/GI/BARI/Pages/Home.aspx ,(06/02/2015).

NICE, 2015-last update, Lower urinary tract symptoms in men: assessment and management. Available: https://www.nice.org.uk/guidance/cg97/resources/guidance-lower-urinary-tract-symptoms-in-men-assessment-and-management-pdf ,(23/09/2015).

NICE, 2014-last update, Obesity: identification, assessment and management. Available: https://www.nice.org.uk/guidance/cg189/chapter/introduction ,(03/05/2015).

Nijamkin, M.P., Campa, A., Sosa, J., Baum, M., Himburg, S. and Johnson, P., 2012. Comprehensive Nutrition and Lifestyle Education Improves Weight Loss and Physical Activity in Hispanic Americans Following Gastric Bypass Surgery: A Randomized Controlled Trial. *Journal of the Academy of Nutrition and Dietetics*, 112(3), pp. 382-390.

Ning, Y., Wang, L. and Giovannucci, E., 2010. A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies. *Obesity Reviews*, 11(1), pp. 19-30.

Nunes, K.P. and Webb, R.C., 2012. Mechanisms in erectile function and dysfunction: an overview. *Erectile Dysfunction–Disease-associated Mechanisms and Novel Insights into Therapy*. pp. 3-22.

Oberbach, A., Schlichting, N., Heinrich, M., Lehmann, S., Till, H., Mohr, F., Mannello, F., Stolzenburg, J. and Neuhaus, J., 2014. Weight loss surgery improves the metabolic status in an obese rat model but does not affect bladder fibrosis associated with high fat diet feeding. *International journal of obesity*, 38(8), pp. 1061-1067.

O'Brien, P.E., 2010. Bariatric surgery: Mechanisms, indications and outcomes. *Journal of gastroenterology and hepatology*, 25(8), pp. 1358-1365.

Oelke, M., Burger, M., Castro-Diaz, D., Chartier-Kastler, E., Cidre, M.A.J., McNicholas, T., Radziszewski, P. and Kirby, M., 2012. Diagnosis and medical treatment of lower urinary tract symptoms in adult men: Applying specialist guidelines in clinical practice. *BJU international*, 110(5), pp. 710-718.

Olbers, T., Björkman, S., Lindroos, A., Maleckas, A., Lönn, L., Sjöström, L. and Lönroth, H., 2006. Body composition, dietary intake, and energy expenditure after laparoscopic Roux-en-Y gastric bypass and laparoscopic vertical banded gastroplasty: A randomized clinical trial. *Annals of Surgery*, 244(5), pp. 715-722.

O'Leary, M.P., Fowler, F.J., Lenderking, W.R., Barber, B., Sagnier, P.P., Guess, H.A. and Barry, M.J., 1995. A brief male sexual function inventory for urology. *Urology*, 46(5), pp. 697-706.

Ozayar, A., Zumrutbas, A.E. and Yaman, O., 2008. The relationship between lower urinary tract symptoms (LUTS), diagnostic indicators of benign prostatic hyperplasia (BPH), and erectile dysfunction in patients with moderate to severely symptomatic BPH. *International urology and nephrology*, 40(4), pp. 933-939.

Padwal, R., Li, S. and Lau, D., 2003. Long-term pharmacotherapy for obesity and overweight. *Cochrane Database System Review*, 4(4).

Padwal, R., Klarenbach, S., Wiebe, N., Birch, D., Karmali, S., Manns, B., Hazel, M., Sharma, A.M. and Tonelli, M., 2011. Bariatric surgery: A systematic review and network meta-analysis of randomized trials. *Obesity Reviews*, 12(8), pp. 602-621.

Palleschi, G., Pastore, A.L., Rizzello, M., Cavallaro, G., Silecchia, G. and Carbone, A., 2015. Laparoscopic sleeve gastrectomy effects on overactive bladder symptoms. *Journal of Surgical Research*, 196(2), pp. 307-312.

Papamargaritis, D., Miras, A. and Le Roux, C.W., 2013. Influence of diabetes surgery on gut hormones and incretins. *Nutr Hosp*, 28(2), pp. 95-103.

Papamargaritis, D., Panteliou, E., Miras, A.D. and Le Roux, C.W., 2012. Mechanisms of weight loss, diabetes control and changes in food choices after gastrointestinal surgery. *Current atherosclerosis reports*, 14(6), pp. 616-623.

Parazzini, F., Menchini Fabris, F., Bortolotti, A., Calabro, A., Chatenoud, L., Colli, E., Landoni, M., Lavezzari, M., Turchi, P., Sessa, A. and Mirone, V., 2000. Frequency and determinants of erectile dysfunction in Italy. *European urology*, 37(1), pp. 43-49.

Parsons, J.K., Sarma, A.V., McVary, K. and Wei, J.T., 2013. Obesity and benign prostatic hyperplasia: clinical connections, emerging etiological paradigms and future directions. *The Journal of urology*, 189(1), pp. S102-S106.

Parsons, J.K., 2010. Benign Prostatic Hyperplasia and Male Lower Urinary Tract Symptoms: Epidemiology and Risk Factors. *Current Bladder Dysfunction Reports*, 5(4), pp. 212-218.

Pasquali, R., Casimirri, F., Cantobelli, S., Melchionda, N., Labate, A.M.M., Fabbri, R., Capelli, M. and Bortoluzzi, L., 1991. Effect of obesity and body fat distribution on sex hormones and insulin in men. *Metabolism*, 40(1), pp. 101-104.

Penna, G., Fibbi, B., Amuchastegui, S., Cossetti, C., Aquilano, F., Laverny, G., Gacci, M., Crescioli, C., Maggi, M. and Adorini, L., 2009. Human benign prostatic hyperplasia stromal cells as inducers and targets of chronic immuno-mediated inflammation. *Journal of Immunology*, 182(7), pp. 4056-4064.

Petrie, A. and Sabin, C., 2013. Medical statistics at a glance. *John Wiley & Sons.*

Pitteloud, N., Hardin, M., Dwyer, A.A., Valassi, E., Yialamas, M., Elahi, D. and Hayes, F.J., 2013. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *The Journal of Clinical Endocrinology & Metabolism*.

Plante, M., Corcos, J., Gregoire, I., Belanger, M.F., Brock, G. and Rossingol, M., 1996. The International Prostate Symptom Score: Physician versus self- administration in the quantification of symptomatology. *Urology*, 47(3), pp. 326-328.

Polivy, J. and Herman, C.P., 2002. If at first you don't succeed: False hopes of self-change. *American Psychologist*, 57(9), pp. 677.

Popenţiu, A., Moga, D., Sabău, A., Dumitra, A., Barb, I. and Sabău, D., 2011. Mixed techniques in bariatric surgery. *Acta Medica Transilvanica*, 16(3).

Porcellati, F., Pampanelli, S., Rossetti, P., Cordoni, C., Marzotti, S., Scionti, L., Bolli, G.B. and Fanelli, C.G., 2003. Counterregulatory hormone and symptom responses to insulin-induced hypoglycemia in the postprandial state in humans. *Diabetes*, 52(11), pp. 2774-2783.

Pories, W.J. and Albrecht, R.J., 2001. Etiology of type II diabetes mellitus: Role of the foregut. *World journal of surgery*, 25(4), pp. 527-531.

Pories, W.J., Swanson, M.S., MacDonald, K.G., Long, S.B., Morris, P.G., Brown, B.M., Barakat, H.A., DeRamon, R.A., Israel, G., Dolezal, J.M., Dohm, L., MacLean, L.D., Sugerman, H.J. and Mason, E., 1995. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Annals of Surgery*, 222(3), pp. 339-352.

Pournaras, D.J., Glicksman, C., Vincent, R.P., Kuganolipava, S., Alaghband-Zadeh, J., Mahon, D., Bekker, J.H., Ghatei, M.A., Bloom, S.R. and Walters, J.R., 2012. The role of bile after Roux-en-Y gastric bypass in promoting weight loss and improving glycaemic control. *Endocrinology*, 153(8), pp. 3613-3619.

Pournaras, D.J., Osborne, A., Hawkins, S.C., Vincent, R.P., Mahon, D., Ewings, P., Ghatei, M.A., Bloom, S.R., Welbourn, R. and Le Roux, C.W., 2010. Remission of type 2 diabetes after gastric bypass and banding: Mechanisms and 2 year outcomes. *Annals of Surgery*, 252(6), pp. 966-971.

Prins, J., Blanker, M.H., Bohnen, A.M., Thomas, S. and Bosch, J.L., 2002. Prevalence of erectile dysfunction: a systematic review of population-based studies. *International Journal of Impotence Research*, 14(6), pp. 422-432.

Proczko-Markuszewska, M., Stefaniak, T., Kaska, Ł. and Śledziński, Z., 2011. Early results of Roux-en-Y gastric by-pass on regulation of diabetes type 2 in patients with BMI above and below 35 Kg/m 2. *Polski Przeglad Chirurgiczny/ Polish Journal of Surgery*, 83(2), pp. 81-86.

Public Health England, 2015-last update, "Child and adult slide sets", Available: www.noo.org.uk/slid_sets ,(26/06/2015).

Ranasinghe, W.K.B., Wright, T., Attia, J., McElduff, P., Doyle, T., Bartholomew, M., Hurley, K. and Persad, R.A., 2011. Effects of bariatric surgery on urinary and sexual function. *BJU international*, 107(1), pp. 88-94.

Randall, J., Slater, M., Stewart, A., Pugh, G., Lewis, K., Levy, C. and Alessandri-Gray, P., 2014. The Effectiveness of Non-Surgical Weight Management Interventions for Obesity in the UK: A Review and Meta-Regression Analysis. *Open Journal of Medical Psychology*, 3(03), pp. 235.

Reis, L.O., Favaro, W.J., Barreiro, G.C., De Oliveira, L.C., Chaim, E.A., Fregonesi, A. and Ferreira, U., 2010. Erectile dysfunction and hormonal imbalance in morbidly obese male is reversed after gastric bypass surgery: A prospective randomized controlled trial. *International journal of andrology*, 33(5), pp. 736-744.

Rhoden, E.L., Teloken, C., Sogari, P.R. and Souto, C.A.V., 2002. The relationship of serum testosterone to erectile function in normal aging men. *The Journal of urology*, 167(4), pp. 1745-1748.

Riedner, C.E., Rhoden, E.L., Ribeiro, E.P. and Fuchs, S.C., 2006. Central Obesity is an Independent Predictor of Erectile Dysfunction in Older Men. *Journal of Urology*, 176(4), pp. 1519-1523.

Rizzello, M., Abbatini, F., Casella, G., Alessandri, G., Fantini, A., Leonetti, F. and Basso, N., 2010. Early postoperative insulin-resistance changes after sleeve gastrectomy. *Obesity Surgery*, 20(1), pp. 50-55.

Roehrborn, C.G., Boyle, P., Bergner, D., Gray, T., Gittelman, M., Shown, T., Melman, A., Bracken, R.B., White, R.D., Taylor, A., Wang, D. and Waldstreicher, J., 1999. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: Results of a four-year, randomized trial comparing finasteride versus placebo. *Urology*, 54(4), pp. 662-669.

Rohrmann, S., Smit, E., Giovannucci, E. and Platz, E.A., 2004. Associations of obesity with lower urinary tract symptoms and noncancer prostate surgery in the Third National Health and Nutrition Examination Survey. *American Journal of Epidemiology*, 159(4), pp. 390-397.

Rolls, E.T., 2012. Taste, olfactory and food texture reward processing in the brain and the control of appetite. *Proceedings of the Nutrition Society*, 71(4), pp. 488-501.

Roosen, A., Chapple, C.R., Dmochowski, R.R., Fowler, C.J., Gratzke, C., Roehrborn, C.G., Stief, C.G. and Andersson, K.-., 2009. A Refocus on the Bladder as the Originator of Storage Lower Urinary Tract Symptoms: A Systematic Review of the Latest Literature. *European urology*, 56(5), pp. 810-820.

Rosen, R.C., 2001. Psychogenic erectile dysfunction: classification and management. *Urologic Clinics of North America*, 28(2), pp. 269-278.

Rosen, R.C. and Breyer, B.N., 2014. Lower urinary tract symptoms and benign prostatic hyperplasia: epidemiology, correlates, and risk factors. *Male Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia* Boca Raton: Wiley, pp. 10-21.

Rosen, R.C., Catania, J., Pollack, L., Althof, S., O'Leary, M. and Seftel, A.D., 2004. Male Sexual Health Questionnaire (MSHQ): scale development and psychometric validation. *Urology*, 64(4), pp. 777.

Rosen, R., Altwein, J., Boyle, P., Kirby, R.S., Lukacs, B., Meuleman, E., O'Leary, M.P., Puppo, P., Robertson, C. and Giuliano, F., 2003. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *European urology*, 44(6), pp. 637-649.

Rosen, R. and Seftel, A., 2008. Validated questionnaires for assessing sexual dysfunction and BPH/LUTS: solidifying the common pathophysiologic link. *International Journal of Impotence Research*, 20, pp. S27-S32.

Rosen, R.C., 1999. The process of care model for evaluation and treatment of erectile dysfunction. *International Journal of Impotence Research*, 11(2), pp. 59-74.

Rosen, R.C., Riley, A., Wagner, G., Osterloh, I.H., Kirkpatrick, J. and Mishra, A., 1997. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology*, 49(6), pp. 822-830.

Rosen, R.C., Wing, R., Schneider, S. and Gendrano III, N., 2005. Epidemiology of erectile dysfunction: The role of medical comorbidities and lifestyle factors. *Urologic Clinics of North America*, 32(4), pp. 403-417.

Rosen, R.O., Fisher, W.A., Eardley, I., Niederberger, C., Nadel, A. and Sand, M., 2004. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. *Current medical research and opinion*, 20(5), pp. 607-617.

Rothenberg, M.E. and Hogan, S.P., 2006. The eosinophil. *Immunology*, 24(1), pp. 147.

Rubino, F., Kaplan, L.M., Schauer, P.R. and Cummings, D.E., 2010a. The diabetes surgery summit consensus conference: Recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 diabetes mellitus. *Annals of Surgery*, 251(3), pp. 399-405.

Rubino, F., R'Bibo, S.L., Del Genio, F., Mazumdar, M. and McGraw, T.E., 2010b. Metabolic surgery: The role of the gastrointestinal tract in diabetes mellitus. *Nature Reviews Endocrinology*, 6(2), pp. 102-109.

Ruxton, G.D., 2006. The unequal variance t-test is an underused alternative to Student's t-test and the Mann–Whitney U test. *Behavioral Ecology*, 17(4), pp. 688-690.

Saber, T.P., Ng, C., Renard, G., Lynch, B.M., Pontifex, E., Walsh, C.A., Grier, A., Molloy, M., Bresnihan, B. and FitzGerald, O., 2010. Research article Remission in psoriatic arthritis: is it possible and how can it be predicted?, Arthritis Research and Therapy, 12(3), R94.

Sáenz de Tejada, I., Angulo, J., Cellek, S., González-Cadavid, N., Heaton, J., Pickard, R. and Simonsen, U., 2004. Physiology of erectile function. *The journal of sexual medicine*, 1(3), pp. 254-265.

Sariyildiz, M.A., Batmaz, I., Dilek, B., İnanir, A., Bez, Y., Tahtasiz, M., Em, S. and Çevik, R., 2013. Relationship of the sexual functions with the clinical parameters, radiological scores and the quality of life in male patients with ankylosing spondylitis. *Rheumatology international*, 33(3), pp. 623-629.

Sarwer, D.B., Lavery, M. and Spitzer, J.C., 2012. A review of the relationships between extreme obesity, quality of life, and sexual function. *Obesity Surgery*, 22(4), pp. 668-676.

Schauer, P.R., Burguera, B., Ikramuddin, S., Cottam, D., Gourash, W., Hamad, G., Eid, G.M., Mattar, S., Ramanathan, R., Barinas-Mitchel, E., Rao, R.H., Kuller, L., Kelley, D., Saar, M.G., Meguid, M.A. and Buchwald, H., 2003. Effect of Laparoscopic Roux-En Y Gastric Bypass on Type 2 Diabetes Mellitus. *Annals of Surgery*, 238(4), pp. 467-485.

Schouten, R., van Dijke, J., van't Hof, G. and Feskens, P., 2013. Prevalence and Risk Factors of Urinary Incontinence and Bladder Retention in Gastric Bypass Surgery: a Cross-Sectional Study. *Obesity Surgery*, 23(6), pp. 760-763.

Schwartz, B.G. and Kloner, R.A., 2011. Clinical cardiology: physician update: erectile dysfunction and cardiovascular disease. *Circulation*, 123(1), pp. 98-101.

Scopinaro, N., Gianetta, E., Civalleri, D., Bonalumi, U. and Bachi, V., 1979. Bilio-pancreatic bypass for obesity: II. Initial experience in man. *British Journal of Surgery*, 66(9), pp. 618-620.

Seftel, A., 2006. Male hypogonadism. Part II: Etiology, pathophysiology, and diagnosis. *International Journal of Impotence Research*, 18(3), pp. 223-228.

Seftel, A.D., Rosen, R.C., Rosenberg, M.T. and Sadovsky, R., 2008. Benign prostatic hyperplasia evaluation, treatment and association with sexual dysfunction: Practice patterns according to physician specialty. *International journal of clinical practice*, 62(4), pp. 614-622.

Shamloul, R. and Ghanem, H., 2013. Erectile dysfunction. *The Lancet*, 381(9861), pp. 153-165.

Shen, R., Dugay, G., Rajaram, K., Cabrera, I., Siegel, N. and Ren, C.J., 2004. Impact of patient follow-up on weight loss after bariatric surgery. *Obesity Surgery*, 14(4), pp. 514-519.

Shiri, R., Häkkinen, J., Koskimäki, J., Hakama, M., Tammela, T.L.J. and Auvinen, A., 2007. Erectile dysfunction influences the subsequent incidence of lower urinary tract symptoms and bother. *International Journal of Impotence Research*, 19(3), pp. 317-320.

Shores, M.M., Smith, N.L., Forsberg, C.W., Anawalt, B.D. and Matsumoto, A.M., 2012. Testosterone treatment and mortality in men with low testosterone levels. *The Journal of Clinical Endocrinology & Metabolism*, 97(6), pp. 2050-2058.

Singh, D., Laya, A.S., Clarkston, W.K. and Allen, M.J., 2009. Jejunoileal bypass: a surgery of the past and a review of its complications. *World journal of gastroenterology*, 15(18), pp. 2277-2279.

Sjöholm, Å., 2009. Impact of glucagon-like peptide-1 on endothelial function. *Diabetes, Obesity and Metabolism, Supplement*, 11(SUPPL. 3), pp. 19-25.

St Sauver, J.L., Jacobsen, S.J., Jacobson, D.J., McGree, M.E., Girman, C.J., Nehra, A., Roger, V.L. and Lieber, M.M., 2011. Statin use and decreased risk of benign prostatic enlargement and lower urinary tract symptoms. *BJU international*, 107(3), pp. 443-450.

Stylopoulos, N., Hoppin, A.G. and Kaplan, L.M., 2009. Roux-en-Y gastric bypass enhances energy expenditure and extends lifespan in diet-induced obese rats. *Obesity*, 17(10), pp. 1839-1847.

Subak, L.L., Wing, R., West, D.S., Franklin, F., Vittinghoff, E., Creasman, J.M., Richter, H.E., Myers, D., Burgio, K.L. and Gorin, A.A., 2009. Weight loss to treat urinary incontinence in overweight and obese women. *New England Journal of Medicine*, 360(5), pp. 481-490.

Suzuki, K., Jayasena, C.N. and Bloom, S.R., 2011. The gut hormones in appetite regulation. *Journal of obesity*, 2011.

Tack, J., Arts, J., Caenepeel, P., De Wulf, D. and Bisschops, R., 2009. Pathophysiology, diagnosis and management of postoperative dumping syndrome. *Nature Reviews Gastroenterology and Hepatology*, 6(10), pp. 583-590.

Tadross, J.A. and Le Roux, C.W., 2009. The mechanisms of weight loss after bariatric surgery. *International journal of obesity*, 33(SUPPL. 1), pp. S28-S32.

Tam, C.S., Berthoud, H.-., Bueter, M., Chakravarthy, M.V., Geliebter, A., Hajnal, A., Holst, J., Kaplan, L., Pories, W., Raybould, H., Seeley, R., Strader, A. and Ravussin, E., 2011. Could the mechanisms of bariatric surgery hold the key for novel therapies?: Report from a Pennington Scientific Symposium. *Obesity Reviews*, 12(11), pp. 984-994.

Teloken, P., Mulhall, J., Brock, G. and Kim, E., 2006. Obesity, dyslipidemias and erectile dysfunction: A report of a subcommittee of the sexual medicine society of North America. *Journal of Sexual Medicine*, 3(5), pp. 778-786.

Tham, J.C., Howes, N. and Le Roux, C.W., 2014. The role of bariatric surgery in the treatment of diabetes. *Therapeutic advances in chronic disease*, , pp. 204-206.

The American Heritage® Stedman's Medical Dictionary, 26 February 2014, 2014-last update, bariatrics." The American Heritage® Stedman's Medical Dictionary [Homepage of Houghton Mifflin Company], [Online] ,(26 /02/2014).

The medical biochemistry page, 2015-last update, Role of intestinal gluconeogenesis and control of feeding behaviours . Available: http://themedicalbiochemistrypage.org/gluconeogenesis.php#intro ,(25/06/2015).

Thomson PDR, 2006. *Physicians' Desk Reference (PDR).*

Thrower, S.L. and Ahmad, B., 2013. Testosterone deficiency in the ageing man: is the 'male menopause'an entity? *Trends in Urology & Men's Health*, 4(4), pp. 19-22.

Torquati, A., Lutfi, R., Abumrad, N. and Richards, W.O., 2005. Is Roux-en-Y gastric bypass surgery the most effective treatment for type 2 diabetes mellitus in morbidly obese patients? *Journal of Gastrointestinal Surgery*, 9(8), pp. 1112-1118.

Traish, A.M., Feeley, R.J. and Guay, A., 2009. Mechanisms of obesity and related pathologies: Androgen deficiency and endothelial dysfunction may be the link between obesity and erectile dysfunction. *FEBS Journal*, 276(20), pp. 5755-5767.

Troy, S., Soty, M., Ribeiro, L., Laval, L., Migrenne, S., Fioramonti, X., Pillot, B., Fauveau, V., Aubert, R., Viollet, B., Foretz, M., Leclerc, J., Duchampt, A., Zitoun, C., Thorens, B., Magnan, C., Mithieux, G. and Andreelli, F., 2008. Intestinal Gluconeogenesis Is a Key Factor for Early Metabolic Changes after Gastric Bypass but Not after Gastric Lap-Band in Mice. *Cell Metabolism*, 8(3), pp. 201-211.

Tsao, C.-., Cha, T.-., Lee, S.-., Tang, S.-., Wu, S.-., Tsui, K.-. and Sun, G.-., 2008. Association between lower urinary tract symptoms and sexual dysfunction in Taiwanese men. *Andrologia*, 40(6), pp. 387-391.

UCL Library Services, 2015-last update, UCL- Protecting information . Available: http://www.ucl.ac.uk/library/about/records-office/infoprotect-res ,(06/04/2015).

Ulrich, P. and Cerami, A., 2001. Protein glycation, diabetes, and aging. *Recent progress in hormone research*, 56, pp. 1-21.

Umeda, L.M., Silva, E.A., Carneiro, G., Arasaki, C.H., Geloneze, B. and Zanella, M.T., 2011. Early improvement in glycemic control after bariatric surgery and its relationships with insulin, GLP-1, and glucagon secretion in type 2 diabetic patients. *Obesity Surgery*, 21(7), pp. 896-901.

Vallancien, G., Emberton, M., Harving, N., van Moorselaar, R Jeroen A and Alf-One Study Group, 2003. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. *The Journal of urology*, 169(6), pp. 2257-2261.

Verhamme, K., Dieleman, J., Bleumink, G., Bosch, J., Stricker, B.C. and Sturkenboom, M., 2003. Treatment strategies, patterns of drug use and treatment discontinuation in men with LUTS suggestive of benign prostatic hyperplasia: the Triumph project. *European urology*, 44(5), pp. 539-545.

Vidal, J., Ibarzabal, A., Nicolau, J., Vidov, M., Delgado, S., Martinez, G., Balust, J., Morinigo, R. and Lacy, A., 2007. Short-term effects of sleeve gastrectomy on type 2 diabetes mellitus in severely obese subjects. *Obesity Surgery*, 17(8), pp. 1069-1074.

Vidal, J., Ibarzabal, A., Romero, F., Delgado, S., Momblán, D., Flores, L. and Lacy, A., 2008. Type 2 diabetes mellitus and the metabolic syndrome following sleeve gastrectomy in severely obese subjects. *Obesity Surgery*, 18(9), pp. 1077-1082.

Virtual Medical Centre, 2015-last update, The male urogenital system. Available: http://www.myvmc.com/anatomy/male-reproductive-system-male-urogenital-system/ ,(05/05/2015).

Wang, Y., Beydoun, M.A., Liang, L., Caballero, B. and Kumanyika, S.K., 2008a. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. *Obesity*, 16(10), pp. 2323-2330.

Wang, Y., Sun, G.F., He, L.J., Meng, J., Wu, S.L., Xiao, Y.X., Li, X.S. and Na, Y.Q., 2008b. Correlation of lower urinary tract symptoms with erectile dysfunction in men aged 50 years and above. *Zhonghua nan ke xue = National journal of andrology*, 14(6), pp. 517-520.

Weiner, R.A., Weiner, S., Pomhoff, I., Jacobi, C., Makarewicz, W. and Weigand, G., 2007. Laparoscopic sleeve gastrectomy - Influence of sleeve size and resected gastric volume. *Obesity Surgery*, 17(10), pp. 1297-1305.

Weiss, N.S. and Koepsell, T.D., 2014. Epidemiologic methods: studying the occurrence of illness. *Oxford University Press*.

Welbourn, R., Fiennes, A., Kinsman, R. and Walton, P., 2010. The United Kingdom national bariatric surgery registry. *First registry report to March*, 2010.

Welbourn, R., Small, P., Finlay, I., Sareela, A., Somers, S., Mahawar, K., Walton, P. and Kinsman, R., 2014. The United Kingdom National Bariatric Surgery Registry. 2014.

Weller, P.F., Lim, K., Wan, H.C., Dvorak, A.M., Wong, D.T., Cruikshank, W.W., Kornfeld, H. and Center, D.M., 1996. Role of the eosinophil in allergic reactions. *The European respiratory journal.Supplement*, 22, pp. 109s-115s.

Wespes, E., Amar, E., Hatzichristou, D., Montorsi, F., Pryor, J. and Vardi, Y., 2002. Guidelines on erectile dysfunction. *European urology*, 41(1), pp. 1-5.

Wickremesekera, K., Miller, G., DeSilva Naotunne, T., Knowles, G. and Stubbs, R.S., 2005. Loss of insulin resistance after Roux-en-Y gastric bypass surgery: A time course study. *Obesity Surgery*, 15(4), pp. 474-481.

Wilson, T.D., Lindsey, S. and Schooler, T.Y., 2000. A model of dual attitudes. *Psychological review*, 107(1), pp. 101.

World Health Organisation, 2000. *Obesity: preventing and managing the global epidemic.* 894. Technical Report Series-WHO, 894.

Wortley, K.E., Anderson, K.D., Garcia, K., Murray, J.D., Malinova, L., Liu, R., Moncrieffe, M., Thabet, K., Cox, H.J., Yancopoulos, G.D., Wiegand, S.J. and Sleeman, M.W., 2004. Genetic deletion of ghrelin does not decrease food intake but influences metabolic fuel preference. *Proceedings of the National Academy of Sciences of the United States of America*, 101(21), pp. 8227-8232.

Wylie, K., Rees, M., Hackett, G., Anderson, R., Bouloux, P., Cust, M., Goldmeier, D., Kell, P., Terry, T. and Trinick, T., 2010. Androgens, health and sexuality in women and men. *Human Fertility*, 13(4), pp. 277-297.

Yanovski, J.A. and Yanovski, S.Z., 2003. Treatment of pediatric and adolescent obesity. *Jama*, 289(14), pp. 1851-1853.

Yassin, A.A., Saad, F. and Traish, A., 2006. Testosterone undecanoate restores erectile function in a subset of patients with venous leakage: A series of case reports. *Journal of Sexual Medicine*, 3(4), pp. 727-735.

Yoshimura, N., Chancellor, M.B., Andersson, K.-. and Christ, G.J., 2005. Recent advances in understanding the biology of diabetes-associated bladder complications and novel therapy. *BJU international*, 95(6), pp. 733-738.

Yule, M., Davison, J. and Brotto, L., 2011. The international index of erectile function: A methodological critique and suggestions for improvement. *Journal of Sex and Marital Therapy*, 37(4), pp. 255-269.

Zhiqing, W., Jing, W., Haili, X., Shaozhuang, L., Chunxiao, H., Haifeng, H., Hui, W. and Sanyuan, H., 2014. Renal function is ameliorated in a diabetic nephropathy rat model through a duodenal-jejunal bypass. *Diabetes research and clinical practice*, 103(1), pp. 26-34.

Ziemens, B., Wallaschofski, H., Volzke, H., Rettig, R., Dorr, M., Nauck, M., Keevil, B.G., Brabant, G. and Haring, R., 2013. Positive association between testosterone, blood pressure, and hypertension in women: longitudinal findings from the Study of Health in Pomerania. *Journal of hypertension*, 31(6), pp. 1106-1113.

Zimmet, P., Alberti, K.G.M., Rubino, F. and Dixon, J.B., 2011. IDF's view of bariatric surgery in type 2 diabetes. *The Lancet*, 378(9786), pp. 108-110.

Zohdy, W., Kamal, E.E. and Ibrahim, Y., 2007. Androgen deficiency and abnormal penile duplex parameters in obese men with erectile dysfunction. *Journal of Sexual Medicine*, 4(3), pp. 797-808.

APPENDICES

This section provides relevant supplementary information to project, including questionnaires used in audits, additional data not presented in the main body of this report and all information relating to the ethical approval of this project.

Appendix A: Supplementary information to Chapter 2 – Methods.

This appendix section presents the questionnaires that were used to obtain the majority of the data presented in chapter 3, as well as chapter 1and 2.

A.1 IIEF questionnaire

INTERNATIONAL INDEX
OF ERECTILE FUNCTION
(IIEF)

Patient Questionnaire

These questions ask about the effects that your erection problems have had on your sex life over the last four weeks. Please try to answer the questions as honestly and as clearly as you are able. Your answers will help your doctor to choose the most effective treatment suited to your condition. In answering the questions, the following definitions apply:

- **sexual activity** includes intercourse, caressing, foreplay & masturbation
- **sexual intercourse** is defined as sexual penetration of your partner
- **sexual stimulation** includes situation such as foreplay, erotic pictures etc.
- **ejaculation** is the ejection of semen from the penis (or the feeling of this)
- **orgasm** is the fulfilment or climax following sexual stimulation or intercourse

---

	Over the past 4 weeks:	*Please check one box only*
☐ Q1	How often were you able to get an erection during sexual activity?	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q3	When you attempted intercourse, how often were you able to penetrate (enter) your partner?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q4	During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q5	During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0 Did not attempt intercourse 1 Extremely difficult 2 Very difficult 3 Difficult 4 Slightly difficult 5 Not difficult

☐ Q6	How many times have you attempted sexual intercourse?	0 No attempts 1 One to two attempts 2 Three to four attempts 3 Five to six attempts 4 Seven to ten attempts 5 Eleven or more attempts
☐ Q7	When you attempted sexual intercourse, how often was it satisfactory for you?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q8	How much have you enjoyed sexual intercourse?	0 No intercourse 1 No enjoyment at all 2 Not very enjoyable 3 Fairly enjoyable 4 Highly enjoyable 5 Very highly enjoyable
☐ Q9	When you had sexual stimulation or intercourse, how often did you ejaculate?	0 No sexual stimulation or intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q10	When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q11	How often have you felt sexual desire?	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q12	How would you rate your level of sexual desire?	1 Very low or none at all 2 Low 3 Moderate 4 High 5 Very high
☐ Q13	How satisfied have you been with your overall sex life?	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q14	How satisfied have you been with your sexual relationship with your partner?	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q15	How do you rate your confidence that you could get and keep an erection?	1 Very low 2 Low 3 Moderate 4 High 5 Very high

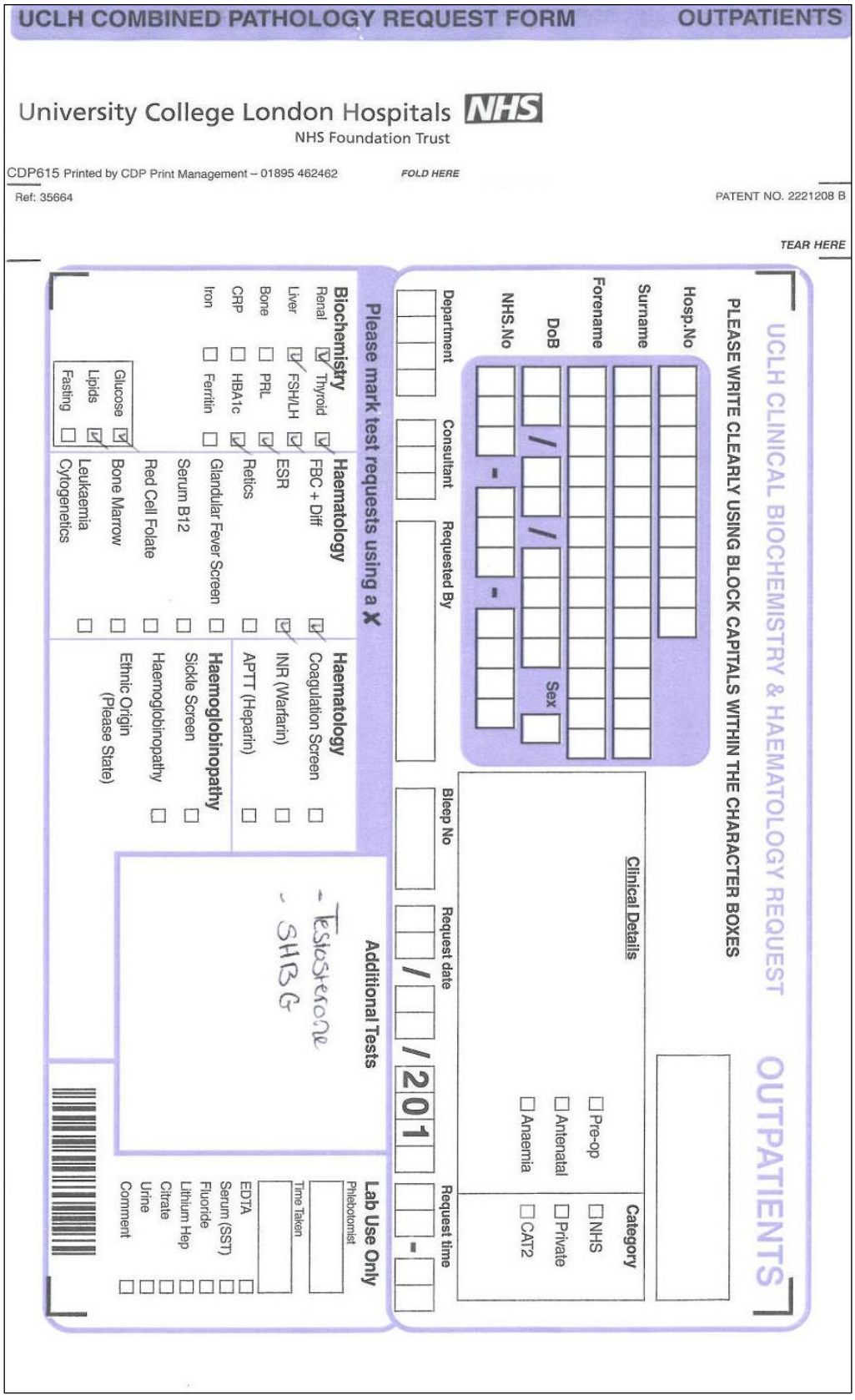
A.2 IPSS questionnaire

International Prostate Symptom Score (I-PSS)

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

A.3 UCLH biochemistry and haematology request



Appendix B: Documentation relating to the ethical approval of this project.

B.1 Baseline characteristics of urogenital function audit protocol submitted for ethics board approval.

STUDY PROTOCOL
Version 1, 3rd April 2014

Cranfield Investigator:
Dr Selim Cellek, Reader in Translational Medicine,
Cranfield University, Bedfordshire, MK43 0AL
Phone: 01234 758319
E-mail: s.cellek@cranfield.ac.uk

Clinical investigators:
Mr David Ralph and Mr Asif Muneer
Urology Department
University College Hospital
Ground Floor Central
250 Euston Road
London, NW1 2PG
Phone: 020 3447 9280
E-mail:
dralph@andrology.co.uk
asif.muneer@uclh.nhs.uk

Estimated start date: 1st May 2014
Estimate duration: 1 year

1. **Study Title:** Audit of baseline characteristics of urogenital function

2. **Project Background:**
   Erectile dysfunction (ED) is a disease that affects generally men aged 40 years or more. Lower urinary tract symptoms, diabetes mellitus, obesity, inactive lifestyle and hypertension are the risk factors for ED. ED is a strong predictor for cardiovascular and coronary artery diseases.
   ED is one of the multifactorial aetiology diseases, many organs interact in the erection process. Generally, ED can be of psychogenic and organic origin. And because of this multifactorial aetiology it may be hard to define the factors involved in the problem. Although the baseline characteristics of patients with ED are well characterised, particularly the effect of obesity on the incidence of ED has not been clarified. Therefore

our aim is to investigate the effect of BMI on urogenital function of men over 30 years of age and to collate and analyse other baseline characteristics (age, smoking, medical history etc.). The erectile function and urological function will be evaluated using validated and widely used questionnaires (International Index of Erectile Function [IIEF] and International Prostate Symptom Score [IPSS]). If successful, this study will be the first assess the baseline characteristics of patients with ED at UCLH. The questionnaires will be totally anonymised. There will no additional intervention or change to the surgical procedure/patient care.

3. Study Aims:

Aim:

To assess the baseline characteristics of patients with erectile dysfunction

Objectives:

- To investigate the effect of BMI on urogenital function of men over 30 years of age and attending urological clinic using IIEF and IPSS questionnaires.
- To collate and analyse other baseline characteristics (age, smoking, medical history etc.)
- Analyse and present the above data.
- Recommend further work based on the above analysis.

4. Recruitment and Consent:

a. **Study population:** Prospective study of patients who have been listed to attend urological clinic for treatment of ED. We are hoping to recruit 30 patients within this audit.

b. Specific Inclusion and Exclusion Criteria:

i. Inclusion criteria:

a. Age 30 years old and above.
b. Listed for attending urological clinic at UCLH
c. No other serious illness for example cancer or neurodegenerative disease.

ii. Exclusion criteria:

a. Age less than 30 years old
b. Not listed for attending urological clinic at UCLH
c. Other serious illness such as cancer or neurodegenerative disease

a. Recruitment:

Those patients who have been seen or listed for attending UCLH urological and meet the inclusion and exclusion criteria will be given included in the audit. Mr Asif Muneer and Mr David Ralph will be responsible for the recruitment process.

b. Anonymisation:

The patients will be asked not to put their names or any other personal information on the questionnaires. The study will be totally anonymised. The only data that will be transferred to Cranfield University are: two completed questionnaires (IIEF, IPSS), age, BMI, smoking, medical history and blood chemistry values. No subject identifiable data will be transferred.

c. Sponsorship:

This study is sponsored by UCLH.

5. Study Methodology

This study will not change the surgical or medical care the patients receive in anyway. No additional tests or procedures are required.

As soon as collected at the clinic, the questionnaire will be placed in a folder and kept in the secured drawer at the Urology Department, Ground Floor, University College London Hospital. Each questionnaire will be accompanied by a brief note with date, age, BMI, IIEF and IPSS scores, blood chemistry values (see Appendix I). The questionnaires will then be transferred to Cranfield University within 24 hours. On arrival at Cranfield University, the questionnaire will be given a unique subject number and the data on the accompanying note will be recorded electronically.

The questionnaires will be processed for data analysis by using statistical tests that will be performed by using SPSS version 19. The questionnaires will be destroyed at the completion of the study.

Dr Selim Cellek will be responsible for recording of the data on the accompanying note, the questionnaires storage and disposal at Cranfield University.

6. Data analysis:

Appropriate statistical tests which we commonly use for these types of experiments will be utilised throughout the study. When/if necessary, professional statistician will be consulted.

7. Dissemination of information:

The results of the study will be disseminated by:

a. Presentation at international meetings such as, but not limited to European Society for Sexual Medicine, European Association of Urology and American Urological Association.
b. Publication in peer reviewed journals such as but not limited to Journal of Sexual Medicine, Journal of Urology and British Journal of Urology.

The only patient-related data that will be used in these publications are patient's age, BMI, scores of IPSS and IIEF. No subject identifiable data will be published.

8. Ethical Issues Arising:

Since this is an audit, patient consent is not required. Therefore the patients will be given an information sheet but they will not be asked for their consent.

Based on our previous experience with the use of questionnaires in basic research, we do not envisage any ethical issues arising. In previous similar studies, we have observed that the majority of the patients are comfortable in giving consent to such studies since no extra test will be taken and the study is totally anonymised. We will exclude patients who do not understand the information sheet which is based again on our previous experience with patients who had difficulty comprehending the information sheet usually due to language barriers.

9. Data Protection:

No subject identifiable information will be transferred with the questionnaires. Only data that will be transferred are (see Appendix I):

a. Date of the questionnaire
b. Age of the patient
c. BMI of the patient
d. Questionnaires (IIEF, IPSS) scores
e. Testosterone level

f. Prolactin level
g. Fasting blood glucose level
h. Thyroid function
i. Kidney function
j. Liver function
k. Full blood count (number of red cells, white cells and platelets)
l. HbA1c level
m. Diabetes status
n. Medical History
o. Smoking

These data will be recorded and kept electronically in a password-protected computer at Cranfield University. Dr Selim Cellek will be responsible for these data.

B.2 Patient information sheet of baseline characteristics of urogenital function audit

University College London Hospitals NHS
NHS Foundation Trust

Patient Information Sheet, version 1
Date: 3rd April 2014

Audit of baseline characteristics urogenital function

You are being invited to take part in a clinical audit. Before you decide it is important for you to understand why the audit is being done and what it will involve. Please take time to decide whether or not you wish to take part. Whether or not you choose to take part will in no way influence the care that you receive.

What is the purpose of this audit?

This audit is being carried out by the urology unit at University College London Hospitals.

The aim of this audit is to assess the baseline characteristics of patients with urogenital dysfunction. This will help our understanding the factors involved in the urogenital dysfunction.

Why have I been chosen?

We are approaching all male patients who are attending urology clinic. You will be invited to complete two questionnaires called IIEF (International Index for Erectile Function) and IPSS (International Prostate Symptom Score) before the appointment. IIEF measures erectile function while IPSS measures bladder and urological function.

You will not be asked to put your name or personal details on the questionnaires. The data will be kept anonymised and a study number will be allocated. At the end of the audit, the questionnaires will be destroyed.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep. If you decide to take part, you are free to withdraw at any time and without giving a reason. Your decision to take part, not to take part, or to withdraw will not affect the standard of care you receive.

1

What are the possible benefits of taking part?

You will not receive any direct benefit from participating in this audit, but the results from this audit may contribute towards a better understanding the urogenital function and the effect of weight loss on urogenital function. This in turn may form a basis for future studies on obesity related illnesses and their treatments.

Will my taking part in this audit be kept confidential?

All information which is collected about you during the course of this audit will be kept strictly confidential.

What will happen to the results of the audit?

The results from this audit may be used in internal NHS publications, external scientific publications or in a student research thesis. You will not be personally identified in any publication. Because of the exploratory nature of the work, none of the results will be provided to you.

Who is organising this audit?

This is an audit for Urology Speciality at University College London Hospitals, and is managed by Urology Department.

Contact details for further information:

Mr David Ralph and Mr Asif Muneer
Urology Department
Ground Floor Central
250 Euston Road
London, NW1 2PG
Phone: 020 3447 9280
E-mail: dralph@andrology.co.uk
asif.muneer@uclh.nhs.uk

B.3 Copy of approval letter from ethics board (Cranfield University Health Research Ethics Committee; CUHREC)

Cranfield UNIVERSITY

Cranfield, Bedfordshire,
MK43 0AL, England
Tel +44 (0) 1234 758349
Fax +44 (0) 1234 758380
www.cranfield.ac.uk

Date 13.06.14

Dear Selim

Project Reference No 12/14: Title – Audit of baseline function characteristics of Urogenital Function

Thank you for undertaking the required amendments and submitting the revised approval form. I can confirm that your study now has ethical approval from the CUHREC Committee.

Subsequent to approval being given by the committee, applicants are responsible for:

- reporting of any adverse incidents occurring during the course of the study to the committee, even if the incident is not directly related to the study (e.g. a complaint by a participant);
- notifying the committee of any major changes to the protocol and obtaining further ethical approval as appropriate;
- notifying the committee when the study has ended.

The committee may revoke approval for a submission if they become aware of any unethical or other improper practices during the execution of the research.

Yours sincerely

Dr Ruth Bevan
Acting Chairman
Cranfield University Health Ethics Committee

B.4 Urogenital function following bariatric surgery audit protocol submitted for ethics board approval

STUDY PROTOCOL
Version 1, 23rd February 2013

Cranfield Investigator:
Dr Selim Cellek, Reader in Translational Medicine,
Cranfield Health, Cranfield University, Bedfordshire, MK43 0AL
Phone: 01234 758319
E-mail: s.cellek@cranfield.ac.uk

Clinical investigators:
Mr Majid Hashemi
University College Hospital
250 Euston Central
London, NW1 2PG
Phone: 0203 447 9202
E-mail: majid.hashemi@uclh.nhs.uk

Mr Asif Muneer
Urology Department
University College Hospital
Ground Floor Central
250 Euston Road
London, NW1 2PG
Phone: 020 3447 9280
E-mail: asif.muneer@uclh.nhs.uk

Estimated start date: 1st April 2013
Estimate duration: 2 years

10. **Study Title:** Urogenital function in morbidly obese men following bariatric surgery

11. **Project Background:**
    Bariatric surgery is a gastrointestinal surgery that is intended to achieve weight loss and has been shown to elicit remission in Type 2 diabetes mellitus. Recently it has been shown that insulin resistance is decreased dramatically within a week following the surgery much before the weight loss is observed. Although the mechanisms for this acute effect on insulin resistance of the bariatric surgery are unknown, this presents itself as an unprecedented opportunity as a model to study the effect of insulin resistance recovery on diabetic complications independent of weight loss. Therefore our aim is to investigate the effect of bariatric surgery on urogenital function in morbidly obese men with and without type 2 diabetes. The erectile and urological function will be evaluated before and after the surgery. The assessment will be performed using validated and widely used questionnaires (International Index of Erectile Function [IIEF] and International Prostate Symptom Score [IPSS]). The post-surgery assessment will be at 4 weeks, 3 and 6 months after the surgery to distinguish the effect of the weight loss. We are seeking approval to utilise these two questionnaires (IIEF, IPSS). Moreover, the questionnaires will be totally anonymised. There will no additional intervention or change to the surgical procedure/patient care.

12. **Study Aims:**

Aim:
To investigate the impact of bariatric surgery on urogenital function in morbidly obese men.

Objective:

- Utilise and mine urogenital function and biomarker data from the research project on morbidly obese men undergoing elective bariatric surgery.
- Analyse and present the above data.
- Recommend further work based on the above analysis.

13. Recruitment and Consent:

c. **Study population:** Prospectively study for patients who have been listed for bariatric surgery for treatment of obesity and the patients are morbidly obese men with BMI more than 35. The populations will be recruited among patients who have been seen by Mr Majid Hashemi or one of his surgical team members at University College London Hospitals. We are hoping to recruit 30 patients per year.

d. Specific Inclusion and Exclusion Criteria:

iii. Inclusion criteria:

d. Age 30 years old and above.
e. Body Mass Index BMI 35 and above
f. Listed for bariatric surgery
g. No other serious illness for example cancer or neurodegenerative disease.

iv. Exclusion criteria:

d. Age less than 30 years old
e. Body Mass Index BMI less than 35
f. Not eligible for bariatric surgery
g. Other serious illness such as cancer or neurodegenerative disease

a. Recruitment and Consenting Process:

Those patients who have been seen and listed for surgery by Mr Hashemi or one of his surgical team and meet the inclusion and exclusion criteria will be given the patient information sheet and the consent form 4 weeks prior to the surgery and 4 weeks, 3 and 6 months after the surgery. After the pre-assessment clinics (4 weeks before the surgery), consent form will be collected from the patient, if unsigned. If it is signed, it will be countersigned by a member of the surgical team. A copy of the signed consent form will be kept in the patient's medical records, a copy will be given to the patient and a copy will be kept by the surgeon. Mr Majid Hashemi will be responsible for the recruitment and consenting process.

b. Anonymisation:

The study will be totally anonymised: The only data that will be transferred to Cranfield University are: two questionnaires (IIEF, IPSS), age of the patient, BMI of the patient and date of each questionnaire. No subject identifiable data will be transferred.

c. Sponsorship:

This study is sponsored by UCLH.

14. Study Methodology

This study will not change the surgical or medical care the patients receive in anyway. No additional tests or procedures are required. The questionnaires that will be collected would have been discarded otherwise.

As soon as collected at the clinic or the operating theatre, the questionnaire will be placed in a folder and kept in the secured drawer at urology department, ground floor central of university college hospital. Each questionnaire will be accompanied by a brief note with date, age, BMI, IIEF and IPSS scores, Testosterone level, C-peptide level, Fasting blood glucose, fasting insulin, HbA1c level and diagnosis of diabetes miletus (see Appendix I). The questionnaires will then be transferred to Cranfield University within 24 hours. On arrival at Cranfield Health, the questionnaire will be given a unique subject number and the data on the accompanying note will be recorded electronically.

The questionnaires will be processed for data analysis by using statistical tests that will be performed by using SPSS version 10. The questionnaires will be destroyed at the completion of the study.

All questionnaires at the end of the study will be discarded by using local procedures.

Dr Selim Cellek will be responsible for recording of the data on the accompanying note, the questionnaires storage and disposal at Cranfield University.

15. Data analysis:

Appropriate statistical tests which we commonly use for these types of experiments will be utilised throughout the study. When/if necessary, professional statistician will be consulted.

16. Dissemination of information:

The results of the study will be disseminated by:

a. Presentation at international meetings such as but not limited to European Society for Sexual Medicine, European Association of Urology and Americal Urological Association.
b. Publication in peer reviewed journals such as but not limited to Journal of Sexual Medicine, Journal of Urology and British Journal of Urology.

The only patient-related data that will be used in these publications are patient's age, BMI, scores of IPSS and IIEF. No subject identifiable data will be published.

17. Ethical Issues Arising:

Based on our previous experience with the use of questionnaires in basic research, we do not envisage any ethical issues arising. In previous similar studies, we have observed that the majority of the patients are comfortable in giving consent to such studies since no extra test will be taken and the study is totally anonymised. We will exclude patients who do not understand the information sheet which is based again on our previous experience with patients who had difficulty comprehending the information sheet usually due to language barriers.

18. Data Protection:

Consent forms will be scanned and the electronic copies will be stored in Mr Asif Muneer's password protected UCLH computer in his secure office. Mr Asif Muneer will be responsible for storage of the consent forms.

No subject identifiable information will be transferred with the questionnaires. Only data that will be transferred are (see Appendix I):

a. Date of the questionnaire
b. Age of the patient
c. BMI of the patient
d. Disease of the patient (Diabetic or not)
e. Questionnaires (IIEF, IPSS) scores
f. Testosterone level
g. Fasting blood glucose level
h. HbA1c level

These data will be recorded and kept electronically in a password-protected computer at Cranfield Health, Cranfield University. Dr Selim Cellek will be responsible for these data.

B.5 UCLH patient information sheet of urogenital function following bariatric surgery audit

University College London Hospitals NHS
NHS Foundation Trust

Patient Information Sheet, version 1
Date: 27th February 2013

Audit of urogenital function following bariatric surgery

You are being invited to take part in a clinical audit. Before you decide it is important for you to understand why the audit is being done and what it will involve. Please take time to decide whether or not you wish to take part. Whether or not you choose to take part will in no way influence the care that you receive.

What is the purpose of this audit?

This audit is being carried out by the urology and bariatric units at University College London Hospitals.

The aim of this audit is to understand the effects of bariatric surgery on urogenital function. This will help our understanding of the effects of excess weight on urogenital function and the effects on urogenital function of weight loss.

Why have I been chosen?

We are approaching all male patients who are due to have bariatric surgery. You are going to be operated for the treatment of obesity and as such you will be invited to complete two questionnaires called IIEF (International Index for Erectile Function) and IPSS (International Prostate Symptom Score) 4 weeks before surgery and then again at and 4 weeks, 3 months and 6 months after the surgery. IIEF measures erectile function while IPSS measures bladder and urological function.

You will not be asked to put your name or personal details on the questionnaires. The data will be kept anonymised and a study number will be allocated. At the end of the audit, the questionnaires will be destroyed.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep. If you decide to take part, you are free to withdraw at any time and without giving a reason. Your decision to take part, not to take part, or to withdraw will not affect the standard of care you receive.

1

What are the possible benefits of taking part?
You will not receive any direct benefit from participating in this audit, but the results from this audit may contribute towards a better understanding of the effects of obesity and in particular the way in which various systems in the body react to weight loss. This in turn may form a basis for future studies on obesity related illnesses and their treatments.

Will my taking part in this audit be kept confidential?
All information which is collected about you during the course of this audit will be kept strictly confidential.

What will happen to the results of the audit?
The results from this audit may be used in internal NHS publications, external scientific publications or in a student research thesis. You will not be personally identified in any publication. Because of the exploratory nature of the work, none of the results will be provided to you.

Who is organising this audit?
This is an audit for Surgical Specialities at University College London Hospitals, and is managed by UCLH Centre for Weight Loss and Urology Department.

Contact details for further information:

Mr Majid Hashemi
The UCLH Centre for Weight Loss
University College Hospital
Ground Floor Central
250 Euston Road
London, NW1 2PG
Phone: 0203 447 9202
E-mail: majid.hashemi@uclh.nhs.uk

Mr Asif Muneer
Urology Department
University College Hospital
Ground Floor Central
250 Euston Road
London, NW1 2PG
Phone: 020 3447 9280
E-mail: asif.muneer@uclh.nhs.uk

B.6 Copy of approval letter from ethics board (Cranfield University Health Research Ethics Committee; CUHREC)

Cranfield Health

Cranfield UNIVERSITY

Vincent Building
Cranfield University
Cranfield
Bedfordshire
MK43 0AL
England
T: +44 (0)1234 758300
F: +44 (0)1234 758380
www.cranfield.ac.uk/health

13th February 2013

Dear Selim

Project Reference No 03.13: Audit of urogenital function in morbidly obese men following bariatric surgery.

Thank you for undertaking the required amendments and submitting the revised approval form. I can confirm that your study now has ethical approval from the CUHREC Committee.

Subsequent to approval being given by the committee, applicants are responsible for:

- reporting of any adverse incidents occurring during the course of the study to the committee, even if the incident is not directly related to the study (e.g. a complaint by a participant);
- notifying the committee of any major changes to the protocol and obtaining further ethical approval as appropriate;
- notifying the committee when the study has ended.

The committee may revoke approval for a submission if they become aware of any unethical or other improper practices during the execution of the research.

Yours sincerely

Professor Paul Harrison
Chairman
Cranfield University Health Ethics Committee

REGISTERED

The Queen's Anniversary Prizes
2011

B.7 Copy of approval letter from Surgical Specialties at University College London Hospital

UCL HOSPITALS

University College London Hospitals NHS
NHS Foundation Trust

Department of Andrology
In association with the Institute of Urology

Specialists in
Genital Oncology, Genital Reconstruction,
Male Sexual Dysfunction & Infertility

Directorate of Urology

University College Hospital
235 Euston Road
London NW1 2PQ
0845 155 5000

Mail Address
Ground Floor Central
250 Euston Road
London
NW1 2PG

Administrative Enquiries
☎ 020 7380 9280
Fax: 020 7380 9303
Pathway Co-ordinator: e-mail: jane.bradley@uclh.nhs.uk
web: www.uclh.org

Dear Dr Cellek,

Audit titled "Audit of urogenital function in morbidly obese men following bariatric surgery"

As the Audit lead for Surgical Specialties at University College London Hospitals, I can confirm that the above project will be a part of a planned audit which we will be carrying out at our hospital jointly with the urology and bariatric units. I can also confirm that the Cranfield University PhD student, Mrs Maha Aleid who has an honorary contract at UCLH will be allowed to include anonymised data from this audit in her thesis and further joint publications without a need for patient consent. An Audit Project Assessment Tool (APAT form) is completed and there will be no personal patient information collected outside the trust IT system for which Maha has been given her own log in and password.

Mrs Aleid has now been given an honorary contract as an audit assistant at our hospital and we are ready to start the study. I look forward to hearing from you with a positive outcome from your institute's ethics committee.

Yours sincerely,

Mr Asif Muneer BSc MD FRCS (Urol)
Consultant Andrologist & Urological Surgeon

B.8 Copy of honorary contract from Surgical Specialties at University College London Hospital (page1)

University College London Hospitals NHS
NHS Foundation Trust

TERMS OF PLACEMENT AS HONORARY APPOINTEE

Name:	**Mrs Maha Aleid**
Address:	
Placement Title:	**Honorary Audit Assistant / PhD Student**
Place of Work or Main Base:	**Urology Department, Surgical Specialities University College London Hospitals**
Starting Date of Honorary Appointment:	**24th October 2012**
Honorary Appointment expires:	**23rd October 2013**
Responsible to:	**Dr Asif Muneer**

FURTHER CONDITIONS

1. This honorary appointment will enable you to undertake your role as an Honorary Audit Assistant based in the Urology Department for the Surgical Specialities under the UCL Hospitals NHS Foundation Trust.

2. Your honorary attachment to the Trust does not constitute employment and you will not be entitled to any form of payment on its cessation. For the avoidance of doubt, this appointment does not constitute an employment relationship.

3. **RESEARCH GOVERNANCE**

University College London Hospitals NHS Trust manages all research in accordance with the requirements of the Research Governance Framework. All research active appointees must familiarise themselves with the UCL Hospitals NHS Trust policies for research governance and be aware of the obligations this places on them. You must comply with all reporting requirements, systems and duties of action put in place by the Trust to deliver research governance. You are reminded that any breach in research governance policy will result in appropriate action. This may include discontinuation of your honorary appointment and cessation of your involvement with all research at UCL Hospitals NHS Trust.

4. **PROFESSIONAL REGISTRATION**

Dependent upon the nature of your role, you may be required to be registered with a relevant professional body eg GMC, NMC, CPSM.

A copy of confirmation of your professional registration should be attached and returned with this document.

A copy of your registration renewal document must also be provided to the Trust.

Failure to be registered with the appropriate professional body, and to maintain professional registration, may result in your honorary appointment being terminated.

B.9 Copy of honorary contract first extension from Surgical Specialties at University College London Hospital (page1)

University College London Hospitals NHS
NHS Foundation Trust

HONORARY CONTRACT EXTENSION

TERMS OF PLACEMENT AS HONORARY APPOINTEE

Name:	**Maha Aleid**
Address:	
Placement Title:	**Honorary Audit Assistant**
Place of Work or Main Base:	**Urology, Surgical Specialities, Surgery & Cancer Board, UCLH**
Starting Date of Honorary Appointment:	**25th October 2013**
Honorary Appointment expires:	**24th October 2014**
Responsible to:	**Mr Asif Muneer**

FURTHER CONDITIONS

This honorary appointment will enable you to undertake your role as an **Honorary Audit Assistant** within the **Urology Department** for the **UCL Hospitals NHS Foundation Trust.**

Your honorary attachment to the Trust does not constitute employment and you will not be entitled to any form of payment on its cessation. For the avoidance of doubt, this appointment does not constitute an employment relationship.

1. RESEARCH GOVERNANCE

University College London Hospitals NHS Trust manages all research in accordance with the requirements of the Research Governance Framework. All research active appointees must familiarise themselves with the UCL Hospitals NHS Trust policies for research governance and be aware of the obligations this places on them. You must comply with all reporting requirements, systems and duties of action put in place by the Trust to deliver research governance. You are reminded that any breach in research governance policy will result in appropriate action. This may include discontinuation of your honorary appointment and cessation of your involvement with all research at UCL Hospitals NHS Trust.

2. PROFESSIONAL REGISTRATION

Dependent upon the nature of your role, you may be required to be registered with a relevant professional body eg GMC, NMC, CPSM.

A copy of confirmation of your professional registration should be attached and returned with this document.

A copy of your registration renewal document must also be provided to the Trust.

Failure to be registered with the appropriate professional body, and to maintain professional registration, may result in your honorary appointment being terminated.

1

B.10 Copy of honorary contract of second extension from Surgical Specialties at University College London Hospital (page1)

University College London Hospitals NHS
NHS Foundation Trust

TERMS OF PLACEMENT AS HONORARY APPOINTEE

Mrs Maha Aleid

[redacted]

Placement Title: Honorary Researcher/ PhD Student

Place of Work or Main Base: University College Hospital (UCH)

Starting Date of Honorary Appointment: 7th November 2014

Honorary Appointment expires: 9th February 2015

Responsible to: Asif Muneer

FURTHER CONDITIONS

1. This honorary appointment will enable you to undertake your role visiting UCL Hospitals NHS Foundation Trust.

2. Your honorary attachment to the Trust does not constitute employment and you will not be entitled to any form of payment on its cessation. For the avoidance of doubt, this appointment does not constitute an employment relationship.

3. RESEARCH GOVERNANCE
University College London Hospitals NHS Trust manages all research in accordance with the requirements of the Research Governance Framework. All research active appointees must familiarise themselves with the UCL Hospitals NHS Trust policies for research governance and be aware of the obligations this places on them. You must comply with all reporting requirements, systems and duties of action put in place by the Trust to deliver research governance. You are reminded that any breach in research governance policy will result in appropriate action. This may include discontinuation of your honorary appointment and cessation of your involvement with all research at UCL Hospitals NHS Trust.

4. PROFESSIONAL REGISTRATION

Dependent upon the nature of your role, you may be required to be registered with a relevant professional body eg GMC, NMC, CPSM.

A copy of confirmation of your professional registration should be attached and returned with this document.

A copy of your registration renewal document must also be provided to the Trust.

1 of 5

B.11 Copy of honorary contract of third extension from Surgical Specialties at University College London Hospital

University College London Hospitals NHS
NHS Foundation Trust

TERMS OF PLACEMENT AS HONORARY APPOINTEE

Mrs Maha Aleid

Placement Title: Honorary Researcher - PHD Student

Place of Work or Main Base: University College Hospital

Starting Date of Honorary Appointment: 09th February 2015

Honorary Appointment expires: 01st October 2015

Responsible to: Asif Muneer

FURTHER CONDITIONS

1. This honorary appointment will enable you to undertake your role visiting UCL Hospitals NHS Foundation Trust.

2. Your honorary attachment to the Trust does not constitute employment and you will not be entitled to any form of payment on its cessation. For the avoidance of doubt, this appointment does not constitute an employment relationship.

3. RESEARCH GOVERNANCE
University College London Hospitals NHS Trust manages all research in accordance with the requirements of the Research Governance Framework. All research active appointees must familiarise themselves with the UCL Hospitals NHS Trust policies for research governance and be aware of the obligations this places on them. You must comply with all reporting requirements, systems and duties of action put in place by the Trust to deliver research governance. You are reminded that any breach in research governance policy will result in appropriate action. This may include discontinuation of your honorary appointment and cessation of your involvement with all research at UCL Hospitals NHS Trust.

4. PROFESSIONAL REGISTRATION

Dependent upon the nature of your role, you may be required to be registered with a relevant professional body eg GMC, NMC, CPSM.

A copy of confirmation of your professional registration should be attached and returned with this document.

1 of 6

Appendix C Supplementary data to Chapter 3 – Results

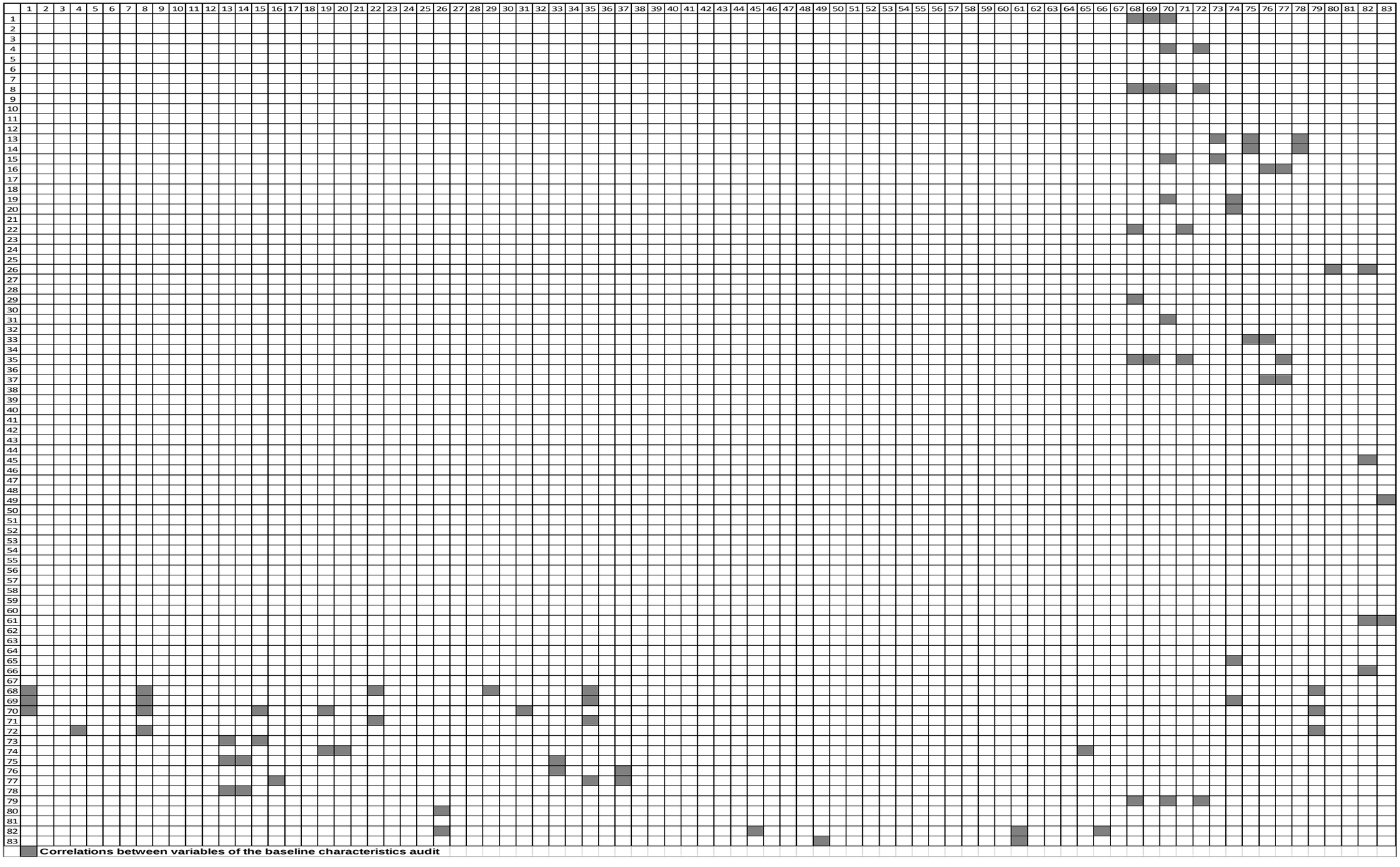
C.1 Supplementary data to Section 3.1.7

Table 5-1: List of definitions of the numbers in Figure 5-1

1	Age	22	Eosinophil	43	SHBG	64	Hydrocele testis
2	Weight (kg)	23	Basophils	44	T2DM	65	Smoker
3	Height (cm)	24	FSH	45	Psoriatic arthritis	66	Overweight BMI ≥25
4	BMI	25	TSH	46	Obstructive sleep apnoea	67	Morbidly Obese BMI ≥30
5	Fasting blood glucose	26	Free T4	47	Hypercholesterolemia	68	IIEF-EF
6	HbA1c level	27	Alkaline phosphate	48	Anxiety	69	IIEF-OF
7	Prolactin test	28	Alkaline transaminase	49	Depression	70	IIEF-SD
8	Testosterone level	29	Bilirubin total	50	Non-alcoholic fatty liver	71	IIEF- IS
9	WBC	30	Albumin	51	Gout	72	IIEF- OS
10	RBC	31	LH	52	Hyperlipidaemia	73	IPSS-Inc. emptying
11	Haemoglobin	32	Sodium	53	Irritable bowel syndrome	74	IPSS- Frequency
12	HCT	33	Potassium	54	Peyronie's disease	75	IPSS- Intermittency
13	MCV	34	Creatinine	55	Fertility problem	76	IPSS- Urgency
14	MCH	35	ESR	56	Proteinuria	77	IPSS- Weak stream
15	MCHC	36	Urea	57	Right testicular atrophy	78	IPSS- Straining
16	RDW	37	Estimated GFR	58	Left testicular atrophy	79	IPSS- Nocturia
17	Platelet count	38	Cholesterol	59	Klinefelter syndrome	80	IPSS- QoL
18	MPV	39	Triglyceride	60	AIDS	81	IPSS total score
19	Neutrophils	40	HDL	61	Hypertension		
20	Lymphocytes	41	LDL	62	Coughlan's syndrome		
21	Monocytes	42	Cholesterol HDL ratio	63	Asthma		

Figure 5-1: Table of correlations between variables of the baseline characteristics audit

(All correlations between variables are presented as grey dots where the p<0.05)



Pearson correlation coefficient between biochemistry tests and IIEF, IPSS (N=60)

IIEF/IPSS domains	Correlation	Prolactin	Bilirubin total	Sodium	Estimated GFR	HDL
IIEF- EF	Pearson correlation	-0.05	0.27	0.03	0.11	0.00
	p	0.71	**0.03***	0.84	0.41	0.98
IIEF-Orgasmic function	Pearson correlation	0.01	0.13	0.11	0.23	0.16
	p	0.96	0.31	0.41	0.07	0.24
IIEF- Sexual desire	Pearson correlation	0.00	0.24	0.14	0.15	-0.04
	p	0.97	0.07	0.29	0.24	0.79
IIEF- Intercourse satisfaction	Pearson correlation	-0.05	0.25	0.09	0.13	0.07
	p	0.73	0.05	0.51	0.31	0.62
IIEF- Overall satisfaction	Pearson correlation	0.09	0.23	0.11	0.12	-0.16
	p	0.51	0.08	0.42	0.36	0.22
IPSS- Incomplete emptying	Pearson correlation	0.16	0.14	-0.03	-0.17	-0.22
	p	0.23	0.30	0.79	0.20	0.09
IPSS- Frequency	Pearson correlation	0.11	0.01	0.04	-0.17	-0.02
	p	0.41	0.94	0.77	0.19	0.91
IPSS- Urgency	Pearson correlation	0.07	0.05	-0.12	-0.29	-0.07
	p	0.57	0.70	0.37	**0.02***	0.57
IPSS- Weak-stream	Pearson correlation	0.19	0.08	-0.10	-0.35	-0.23
	p	0.14	0.55	0.44	**0.01***	0.08
IPSS- Nocturia	Pearson correlation	0.01	0.22	-0.04	-0.08	0.02
	p	0.95	0.09	0.75	0.56	0.89
IPSS- QoL	Pearson correlation	0.15	-0.12	-0.11	-0.08	-0.02
	p	0.25	0.37	0.40	0.55	0.90
IPSS total score	Pearson correlation	0.17	0.13	-0.07	-0.22	-0.14
	p	0.21	0.33	0.59	0.10	0.29

IIEF/IPSS domains	Correlation	Prolactin	Bilirubin total	Sodium	Estimated GFR	HDL
Intermittency	Spearman's rho	0.07	0.24	-0.09	-0.15	-0.10
	p	0.59	0.06	0.46	0.22	0.42
Straining	Spearman's rho	0.21	0.12	-0.01	-0.09	-0.03
	p	0.10	0.35	0.91	0.47	0.81

Spearman's rho correlation coefficient between biochemistry tests and IIEF, IPSS (N=60)

Variables		IIEF-EF	IIEF-OF	IIEF-SD	IIEF-IS	IIEF-OS	IPSS-Incomplete emptying	Frequency	Intermittency	Urgency	Weak stream	Straining	Nocturia	QoL	IPSS total score
Fasting blood glucose	rho	-0.14	-0.18	-0.19	-0.14	0.06	0.05	0.08	-0.02	-0.10	0.20	-0.01	0.11	0.13	0.05
	p	0.29	0.17	0.16	0.29	0.66	0.71	0.53	0.90	0.43	0.12	0.94	0.39	0.32	0.68
HbA1c	rho	-0.24	-0.18	-0.06	-0.14	0.07	-0.12	-0.06	-0.19	-0.21	0.01	-0.12	-0.07	-0.03	-0.11
	p	0.07	0.18	0.65	0.28	0.58	0.36	0.63	0.15	0.11	0.93	0.34	0.59	0.80	0.38
Testosterone	rho	0.36	0.42	0.26	0.33	0.06	0.07	-0.08	0.09	0.17	0.00	0.08	-0.01	0.01	0.06
	p	**<0.001**	**<0.001**	**0.04**	**0.01**	0.65	0.59	0.55	0.49	0.20	0.98	0.55	0.91	0.93	0.66
Free testosterone	P	0.34	0.40	0.99	0.33	0.84	0.86	0.33	0.24	0.10	0.50	0.40	0.60	0.37	0.41
	rho	0.13	0.11	0.002	0.13	0.03	0.02	0.13	0.16	0.22	0.09	0.11	-0.07	0.12	0.11
Bioavailable testosterone	P	0.54	0.39	0.76	0.54	0.67	0.92	0.89	0.22	0.57	0.80	0.25	0.35	0.43	0.76
	rho	0.08	0.11	0.04	0.08	-0.06	-0.01	0.02	0.16	0.07	0.04	0.15	-0.12	0.10	0.04
FSH	rho	0.00	-0.06	-0.07	0.03	0.03	0.02	0.10	0.06	0.24	0.02	0.09	0.11	0.01	0.11
	p	0.97	0.64	0.57	0.83	0.85	0.91	0.46	0.67	0.06	0.86	0.49	0.40	0.97	0.41
TSH	rho	-0.11	0.01	-0.05	-0.08	0.04	-0.10	0.07	0.10	0.03	0.01	0.01	0.02	-0.14	0.01
	p	0.42	0.92	0.72	0.55	0.77	0.45	0.58	0.44	0.83	0.95	0.93	0.88	0.30	0.96
Free T4	rho	0.15	0.06	0.10	0.09	-0.06	0.21	0.00	0.25	0.14	0.05	0.20	0.06	0.31	0.14
	p	0.25	0.68	0.43	0.51	0.67	0.10	0.99	0.05	0.27	0.73	0.13	0.63	**0.02**	0.29

Variables		IIEF-EF	IIEF-OF	IIEF-SD	IIEF-IS	IIEF-OS	IPSS-Incomplete emptying	Frequency	Intermittency	Urgency	Weak stream	Straining	Nocturia	QoL	IPSS total score
Alkaline phosphate	rho	0.01	0.04	-0.07	-0.01	0.09	0.16	0.23	0.06	0.24	0.11	0.02	0.14	0.05	0.17
	p	0.93	0.74	0.57	0.93	0.51	0.21	0.07	0.65	0.07	0.41	0.87	0.30	0.70	0.20
Alkaline transaminase	rho	-0.12	-0.10	-0.05	-0.19	0.11	0.21	0.06	0.12	0.05	0.20	0.14	-0.06	-0.09	0.13
	p	0.37	0.45	0.68	0.14	0.41	0.11	0.66	0.36	0.73	0.13	0.29	0.63	0.49	0.34
Albumin	rho	-0.02	-0.23	0.00	0.05	-0.07	-0.13	-0.07	-0.13	-0.14	-0.24	-0.10	-0.14	0.03	-0.16
	p	0.87	0.08	0.99	0.70	0.57	0.33	0.58	0.33	0.30	0.06	0.46	0.28	0.82	0.22
LH	rho	0.19	0.08	0.29	0.19	0.10	-0.13	-0.08	0.04	0.06	-0.05	0.19	-0.11	-0.01	-0.02
	p	0.14	0.52	**0.02**	0.15	0.45	0.33	0.53	0.76	0.66	0.68	0.16	0.40	0.92	0.88
Potassium	rho	-0.02	0.05	0.09	-0.07	0.23	-0.17	-0.16	-0.31	-0.37	-0.07	-0.24	-0.25	-0.03	-0.25
	p	0.89	0.70	0.49	0.60	0.08	0.20	0.22	**0.01**	**<0.001**	0.60	0.07	0.05	0.83	0.06
Creatinine	rho	0.14	0.04	0.12	0.08	0.11	0.21	0.20	0.15	0.24	0.17	0.17	0.01	0.04	0.22
	p	0.28	0.78	0.38	0.55	0.42	0.11	0.13	0.24	0.07	0.18	0.20	0.92	0.76	0.09
ESR	rho	-0.26	-0.29	-0.21	-0.28	-0.01	-0.01	-0.05	0.04	-0.10	0.27	0.05	0.12	0.07	0.08
	p	**0.04**	**0.03**	0.11	**0.03**	0.91	0.94	0.70	0.74	0.44	**0.03**	0.69	0.36	0.57	0.53
Urea	rho	-0.11	-0.14	-0.02	-0.12	-0.06	-0.10	-0.02	-0.09	-0.14	0.01	-0.13	-0.20	-0.02	-0.11
	p	0.38	0.27	0.90	0.34	0.63	0.45	0.86	0.48	0.28	0.91	0.33	0.13	0.85	0.38
Cholesterol	rho	-0.12	-0.20	0.08	-0.11	-0.20	-0.10	-0.13	-0.23	-0.24	-0.20	-0.25	-0.03	0.01	-0.20
	p	0.35	0.13	0.55	0.40	0.12	0.44	0.34	0.07	0.06	0.12	0.06	0.82	0.92	0.13
Triglyceride	rho	-0.08	-0.02	-0.04	-0.11	0.21	0.03	-0.01	-0.12	0.02	0.14	-0.05	0.05	-0.03	0.02
	p	0.54	0.87	0.76	0.40	0.10	0.80	0.94	0.37	0.87	0.29	0.71	0.72	0.83	0.89
LDL	rho	-0.06	-0.22	0.11	-0.09	-0.19	0.03	-0.04	-0.23	-0.16	-0.07	-0.26	-0.05	-0.01	-0.11
	p	0.62	0.09	0.39	0.50	0.15	0.84	0.78	0.08	0.21	0.59	0.05	0.69	0.95	0.38
Cholesterol HDL ratio	rho	-0.02	-0.12	0.13	-0.05	0.05	0.13	0.01	-0.04	0.00	0.08	-0.14	0.05	0.00	0.04
	p	0.89	0.38	0.33	0.68	0.73	0.32	0.91	0.78	1.00	0.57	0.27	0.71	1.00	0.76
SHBG	rho	-0.03	0.09	-0.05	0.10	-0.10	-0.18	-0.15	0.01	-0.01	-0.17	0.17	-0.04	0.00	-0.09

Variables		IIEF-EF	IIEF-OF	IIEF-SD	IIEF-IS	IIEF-OS	IPSS-Incomplete emptying	Frequency	Intermittency	Urgency	Weak stream	Straining	Nocturia	QoL	IPSS total score
	p	0.82	0.48	0.73	0.45	0.47	0.18	0.26	0.95	0.93	0.20	0.20	0.75	0.98	0.48

Spearman's rho correlation coefficient between haematology tests and IIEF, IPSS (N=60)

Variables		IIEF-EF	IIEF-OF	IIEF-SD	IIEF-IS	IIEF-OS	IPSS-Inc. emptying	Frequency	Intermittency	Urgency	Weak stream	Straining	Nocturia	QoL	IPSS total score
WBC	rho	-0.21	-0.09	-0.20	-0.13	0.02	0.02	0.17	-0.04	-0.02	0.01	-0.01	0.04	-0.13	0.06
	p	0.11	0.51	0.13	0.34	0.90	0.86	0.21	0.75	0.91	0.92	0.97	0.76	0.33	0.66
RBC	rho	0.06	0.08	0.14	0.04	0.01	0.16	0.13	0.05	0.07	-0.06	0.07	0.00	0.00	0.05
	p	0.66	0.54	0.27	0.77	0.95	0.22	0.31	0.69	0.60	0.65	0.58	0.98	1.00	0.73
Haemoglobin	rho	0.07	0.11	0.12	0.03	0.01	0.13	0.11	-0.02	0.05	-0.15	-0.01	-0.13	-0.02	-0.02
	p	0.61	0.40	0.35	0.84	0.95	0.33	0.39	0.87	0.73	0.25	0.93	0.32	0.90	0.89
HCT	rho	0.00	0.16	0.09	-0.01	-0.05	0.02	0.09	-0.12	0.03	-0.18	-0.15	-0.10	-0.08	-0.08
	p	0.97	0.22	0.47	0.92	0.70	0.87	0.49	0.35	0.82	0.16	0.27	0.43	0.56	0.52
MCV	rho	-0.21	-0.09	-0.23	-0.18	-0.19	-0.33	-0.07	-0.32	-0.06	-0.21	-0.38	-0.17	-0.18	-0.25
	p	0.10	0.51	0.08	0.18	0.15	**0.01**	0.61	**0.01**	0.63	0.10	**<0.001**	0.21	0.17	0.06
MCH	rho	-0.18	-0.17	-0.15	-0.15	-0.13	-0.20	-0.06	-0.27	-0.09	-0.17	-0.29	-0.25	-0.10	-0.22
	p	0.18	0.20	0.27	0.24	0.32	0.12	0.65	**0.04**	0.50	0.20	**0.02**	0.06	0.44	0.09
MCHC	rho	0.12	0.08	0.30	0.07	0.14	0.29	0.08	0.06	-0.02	0.04	0.01	-0.20	-0.01	0.06
	p	0.36	0.56	**0.02**	0.59	0.29	**0.03**	0.55	0.67	0.90	0.76	0.93	0.14	0.92	0.65
RDW	rho	-0.20	-0.03	-0.22	-0.23	-0.23	0.21	0.15	0.11	0.09	0.38	0.23	0.15	0.17	0.22
	p	0.12	0.80	0.09	0.08	0.08	0.10	0.24	0.38	0.50	**<0.001**	0.08	0.25	0.20	0.09
Platelet	rho	0.11	0.24	0.12	0.05	0.09	-0.09	-0.03	-0.19	-0.18	-0.05	-0.15	-0.06	0.01	-0.11
	p	0.42	0.07	0.37	0.68	0.47	0.50	0.80	0.14	0.16	0.73	0.24	0.67	0.92	0.40

Variables		IIEF-EF	IIEF-OF	IIEF-SD	IIEF-IS	IIEF-OS	IPSS-Inc. emptying	Frequency	Intermittency	Urgency	Weak stream	Straining	Nocturia	QoL	IPSS total score
MPV	rho	0.23	0.15	0.02	0.17	0.11	0.22	0.06	0.17	0.19	0.22	0.17	0.09	0.00	0.18
	p	0.08	0.26	0.90	0.19	0.41	0.09	0.67	0.19	0.15	0.08	0.18	0.50	0.97	0.16
Neutrophils	rho	-0.17	0.09	-0.29	-0.20	-0.14	0.12	0.27	-0.01	0.24	0.05	-0.07	0.14	0.03	0.14
	p	0.19	0.51	**0.02**	0.13	0.30	0.38	**0.04**	0.97	0.06	0.71	0.60	0.29	0.84	0.27
Lymphocytes	rho	0.12	0.21	0.02	0.01	0.09	0.14	0.28	0.09	0.09	0.09	0.06	0.01	-0.24	0.16
	p	0.37	0.10	0.89	0.93	0.48	0.27	**0.03**	0.48	0.48	0.51	0.67	0.93	0.06	0.22
Monocytes	rho	0.09	0.03	0.08	0.05	0.11	0.03	0.08	-0.03	-0.03	-0.09	-0.09	-0.07	-0.14	0.01
	p	0.52	0.84	0.55	0.72	0.40	0.80	0.56	0.80	0.81	0.49	0.52	0.59	0.29	0.97
Eosinophil	rho	0.26	0.07	0.11	0.27	0.17	0.05	0.10	0.16	0.12	0.02	0.12	-0.05	-0.21	0.09
	p	**0.04**	0.59	0.40	**0.03**	0.20	0.72	0.45	0.22	0.37	0.88	0.36	0.69	0.10	0.51
Basophils	rho	0.06	-0.18	-0.17	0.16	0.12	0.02	0.16	0.05	0.17	0.07	0.11	0.00	-0.12	0.08
	p	0.63	0.17	0.19	0.22	0.37	0.88	0.23	0.70	0.18	0.57	0.38	0.97	0.35	0.53

The correlations between smoker and IIEF, IPSS (N=60)

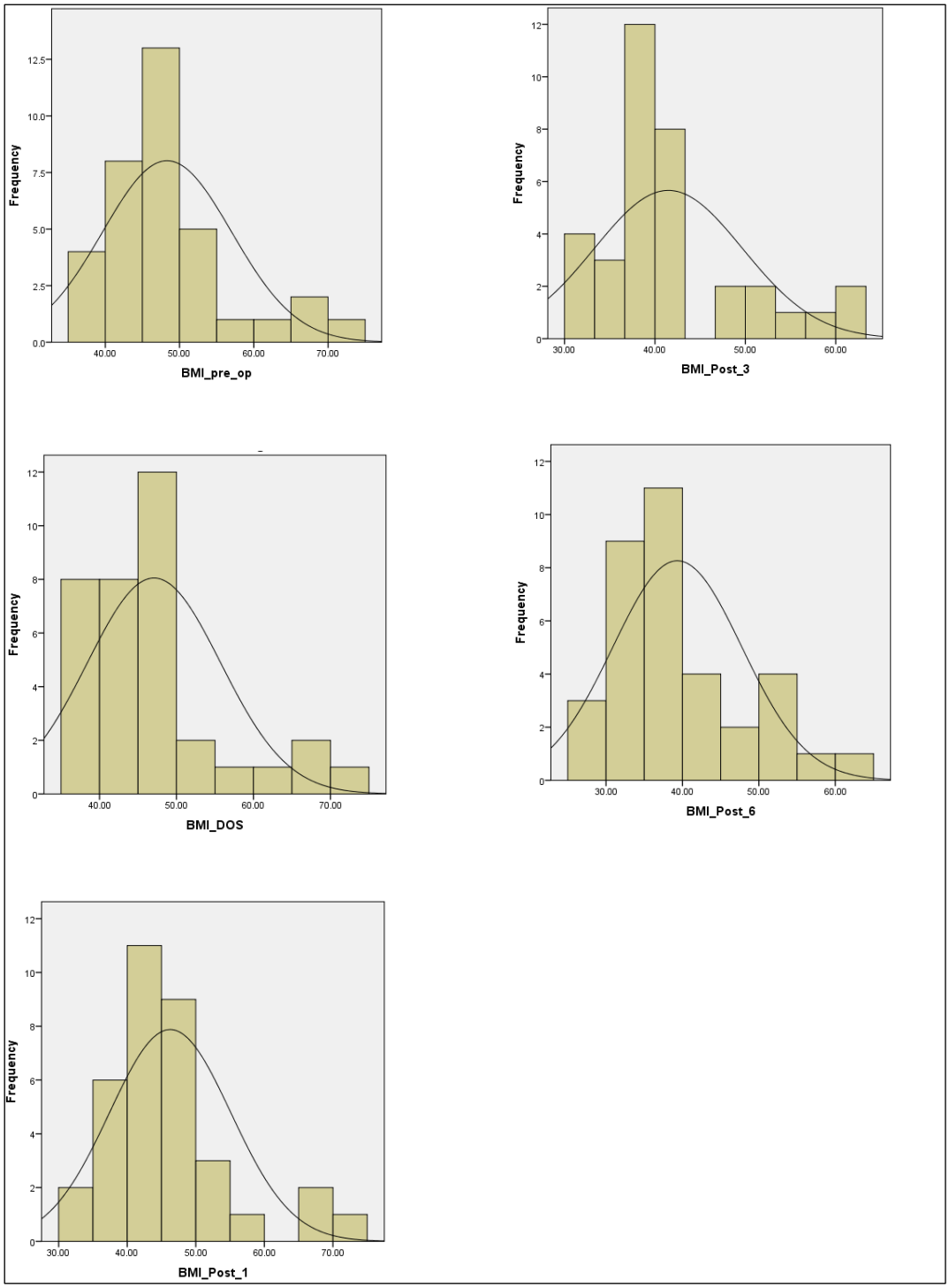
Variables	Correlation	
IIEF -Erectile function	r	-0.05
	p	0.72
IIEF Orgasmic function	r	-0.04
	p	0.74
IIEF Sexual desire	r	-0.06
	p	0.65
IIEF Intercourse satisfaction	r	-0.07
	p	0.57
IIEF Overall satisfaction	r	-0.03
	p	0.82
Incomplete emptying	r	0.00
	p	1.00
Frequency	r	0.26
	p	**0.04***
Intermittency	rho	0.01
	p	0.87
Urgency	r	0.06
	p	0.63
Weak stream	r	0.01
	p	0.95
Straining	rho	-0.05
	p	0.71
Nocturia	r	0.02
	p	0.89
QoL	r	-0.10
	p	0.43
IPSS total score	r	0.06
	p	0.66

* Pearson correlation was significant at the 0.05 level

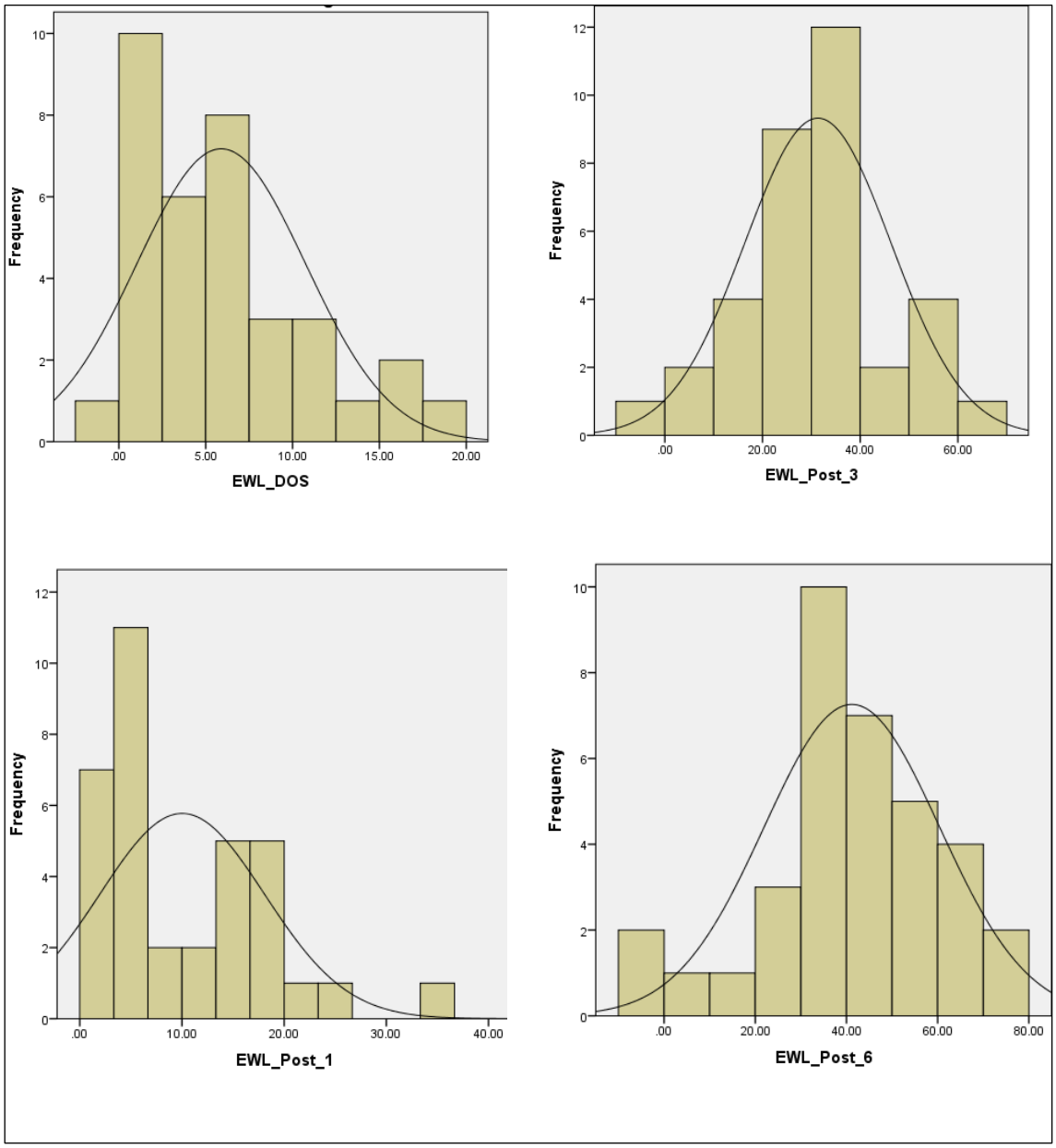
C.2 Supplementary data to section 3.2

Examples of normality checking by histogram of BMI and EWL

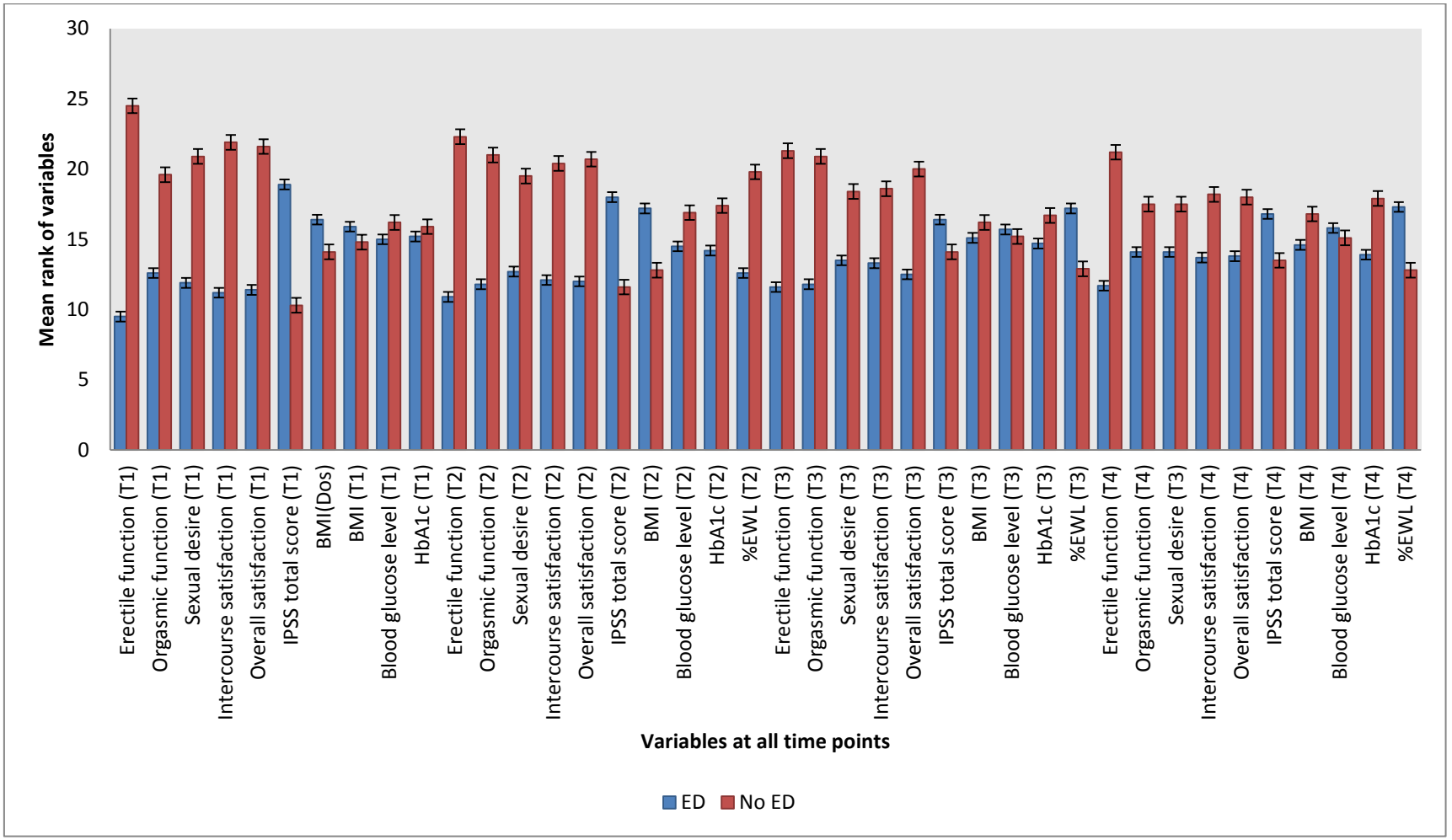
- **Example of BMI distributions with IPSS- frequency over time**



- **Example of EWL distributions with IPSS- frequency over time**



Changes in variables of ED and NO-ED groups across time



C.3 Supplement figures to section 3.2.8.

- **Time 1 (baseline)**

Table 5-2: Mann Whitney U test of all variables at baseline

Variable/Time	Mean rank		Mann Whitney U test	p
	ED	NO-ED		
Erectile function	9.5	24.5	0.0	**<0.001**
Orgasmic function	12.6	19.6	58.5	**0.03**
Sexual desire	11.9	20.9	42.5	**0.005**
Intercourse satisfaction	11.2	21.9	31.0	**0.001**
Overall Satisfaction	11.4	21.6	35.0	**0.002**
IPSS (total)	18.9	10.3	45.5	**0.008**
BMI(Dos)	16.4	14.1	91.0	0.47
BMI	15.9	14.8	100.0	0.73
Blood glucose level	15.0	16.2	99.5	0.71
HbA1c	15.2	15.9	102.5	0.81
%EWL (Dos)	14.0	17.7	81.0	0.25

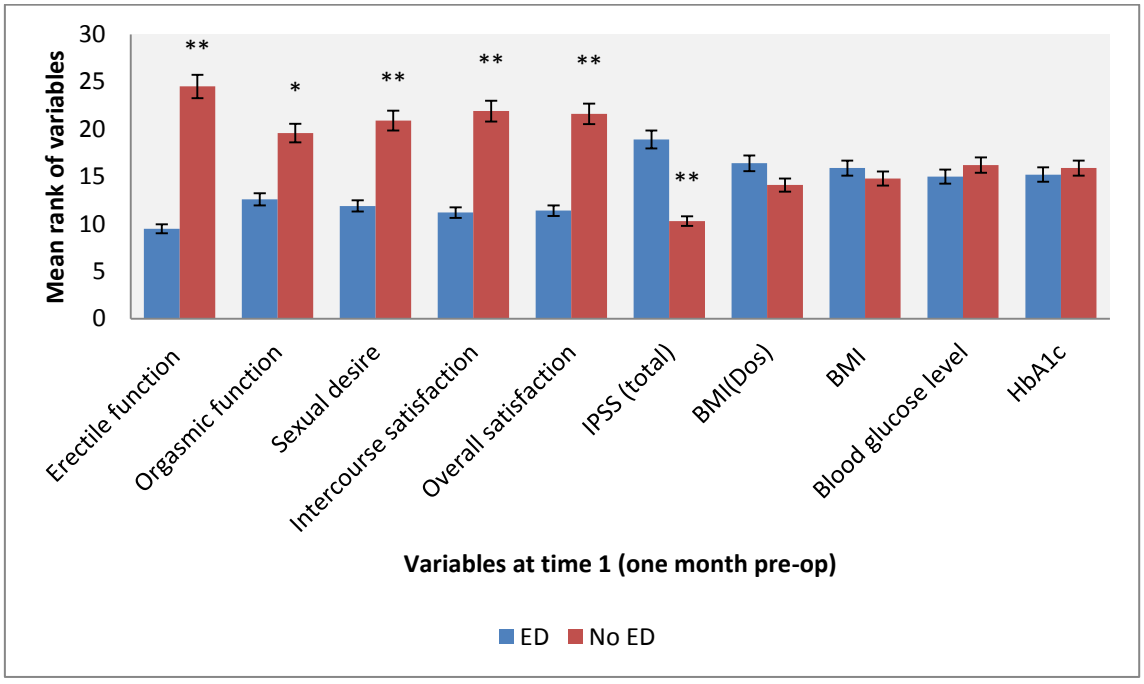


Figure 5-2: Differences between variables of ED and NO-ED groups at time 1 (baseline)

** Significant (p<0.01), * significant (p<0.05)

- **Time 2 (one month post-op)**

Table 5-3: Mann Whitney U test of all variables at time 2

Variable/Time	Mean rank		Mann Whitney U test	p
	ED	NO-ED		
Erectile function	10.9	22.3	26.0	**0.001**
Orgasmic function	11.8	21	42.0	**0.004**
Sexual desire	12.7	19.5	59.0	**0.035**
Intercourse satisfaction	12.1	20.4	48.5	**0.011**
Overall satisfaction	12.0	20.7	45.5	**0.007**
IPSS	18.0	11.6	61.5	**0.048**
BMI	17.2	12.8	76.0	0.176
Blood glucose level	14.5	16.9	90.5	0.457
HbA1c	14.2	17.4	85.0	0.328
%EWL	12.6	19.8	56.0	**0.028**

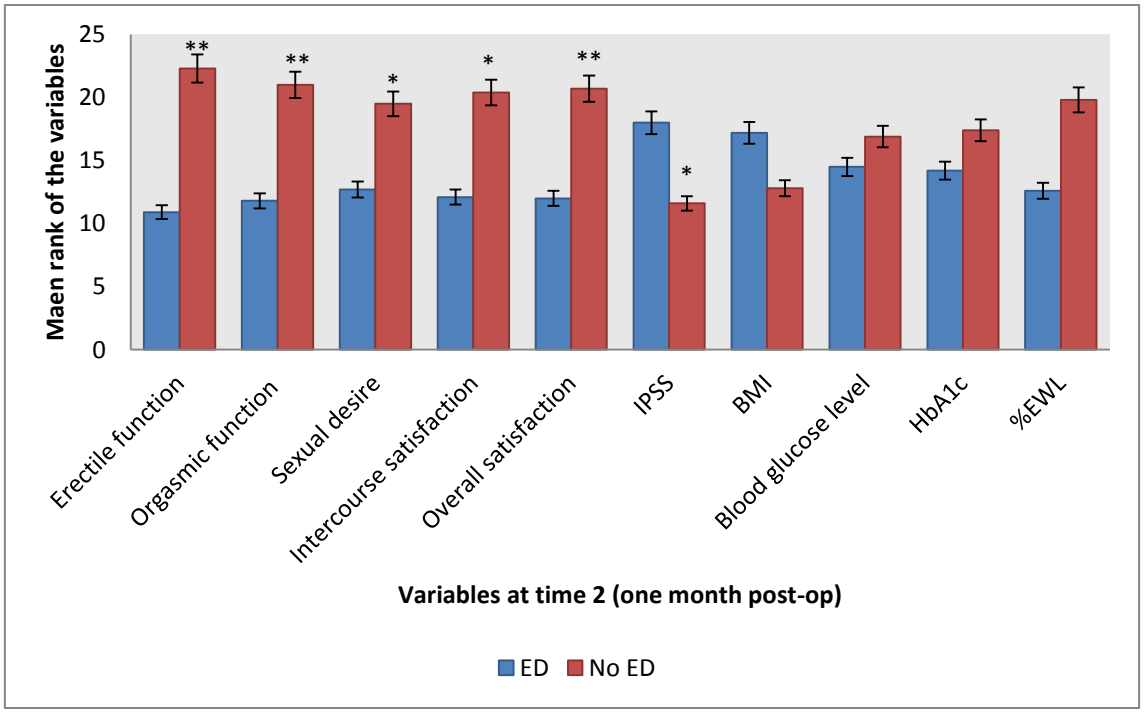


Figure 5-3: Differences between variables of ED and NO-ED groups at time 2

** Significant (p<0.01), * significant (p<0.05)

- **Time 3 (three month post-op)**

Table 5-4: Mann Whitney U test of all variables at time 3

Variable/Time	Mean rank		Mann Whitney U test	p
	ED	NO-ED		
Erectile function	11.6	21.3	38.5	**0.003**
Orgasmic function	11.8	20.9	43.0	**0.003**
Sexual desire	13.5	18.4	73.0	0.131
Intercourse satisfaction	13.3	18.6	70.0	.104
Overall satisfaction	12.5	20.0	54.0	**0.018**
IPSS (total)	16.4	14.1	91.5	0.483
BMI	15.1	16.2	100.0	0.735
Blood glucose level	15.7	15.2	104.0	0.865
HbA1	14.7	16.7	93.5	0.537
%EWL	17.2	12.9	77.0	0.189

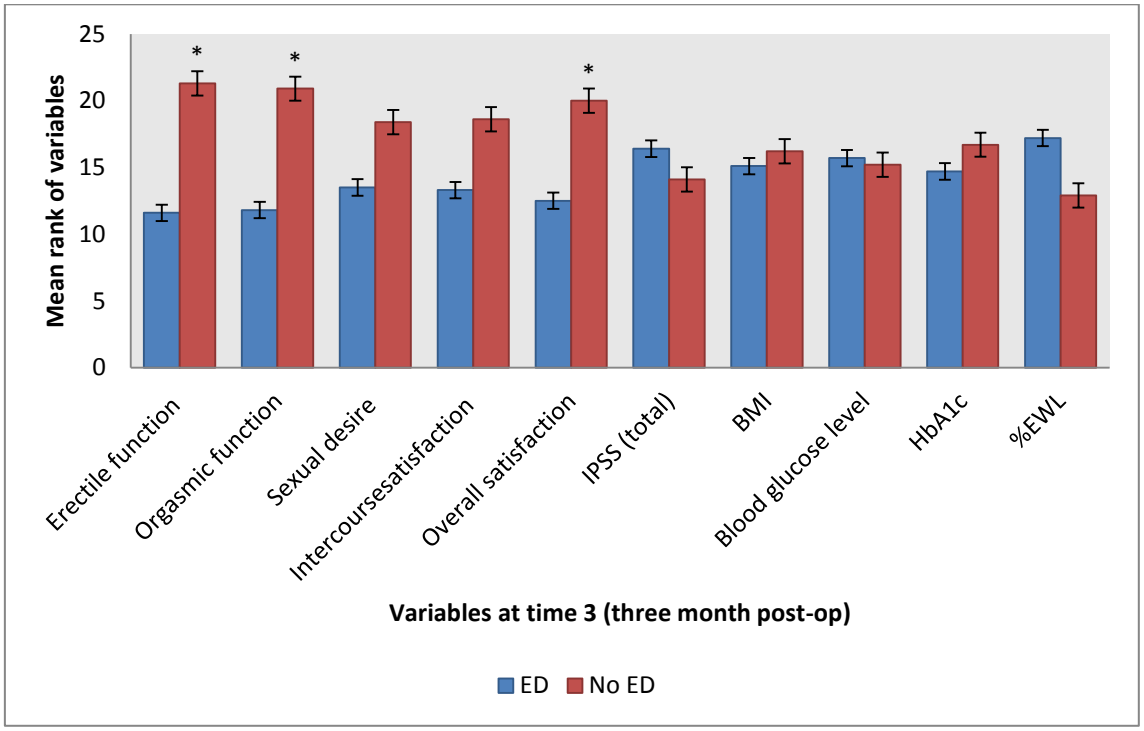


Figure 5-4: Differences between variables of ED and NO-ED groups at time 3

* Significant (p<0.02)

- **Time 4 (four month post-op)**

Table 5-5: Mann Whitney U test of all variables at time 4

Variable/Time	Mean rank		Mann Whitney U test	p
	ED	NO-ED		
Erectile function	11.7	21.2	39.5	**0.003**
Orgasmic function	14.1	17.5	83.0	0.25
Sexual desire	14.1	17.5	83.0	0.25
Intercourse satisfaction	13.7	18.2	75.0	0.14
Overall satisfaction	13.8	18.0	77.5	0.17
IPSS (total)	16.8	13.5	84.5	0.31
BMI	14.6	16.8	92.0	0.50
Blood glucose level	15.8	15.1	103.5	0.85
HbA1c	13.9	17.9	78.5	0.21
%EWL	17.3	12.8	76.0	0.18

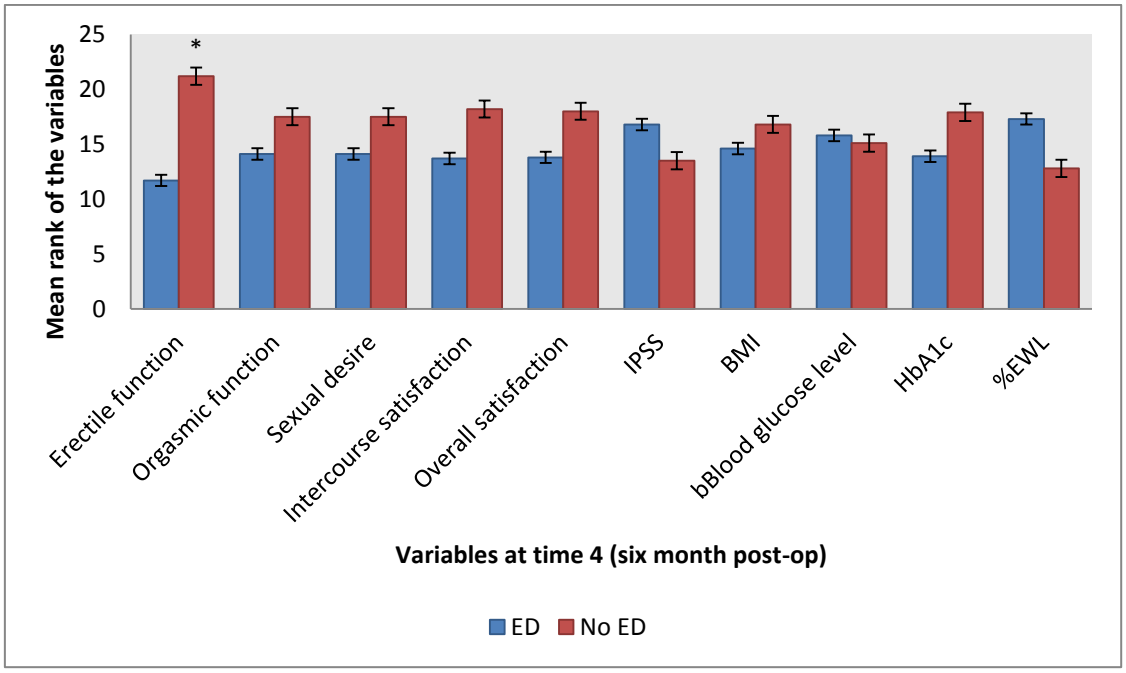


Figure 5-5: Differences between variables of ED and NO-ED groups at time 4

Appendix D List of publications

Aleid, M.; Renshaw, S; George, J, Muneer, A; Hashemi, M;. and Cellek, S. ": "Early effect of bariatric surgery on urogenital function in morbidly obese male patients: preliminary observations" Presented : 17th congress of the European Society for Sexual Medicine (ESSM) 5 - 7 Feb 2015, Denmark".
http://onlinelibrary.wiley.com/doi/10.1111/jsm.12872_2/epdf

Early effect of bariatric surgery on urogenital function in morbidly obese male patients: preliminary observations

Mrs Maha Aleid, Dr. Sara Renshaw, Mr. Jason George, Mr. Majid Hashemi, Mr. David Ralph, Mr. Asif Muneer, Prof. Selim Cellek and Dr. Nicola White

Cranfield UNIVERSITY

INTRODUCTION:

Obesity is a complex psycho-social and endocrine disorder that may have a negative impact on urinary and erectile function. Bariatric surgery promotes weight loss by changing the digestive system's anatomy. Previous studies have investigated the effect of bariatric surgery on urogenital function at late time points postoperatively. The aim of this study is to assess the early effects of bariatric surgery on urogenital function.

METHOD:

A prospective study investigating the urogenital function in obese men aged > 30 years with a body mass index (BMI) of >35 kg/m2 undergoing bariatric surgery. The assessment was performed using two questionnaires: International Index of Erectile Function (IIEF) and International Prostate Symptom Score (IPSS) which were completed before the surgery and four weeks, three months and six months after the surgery. The influence of bariatric surgery on urogenital function and BMI were analysed using non-parametric tests for paired samples. The data were obtained from an ongoing clinical audit at UCL Hospitals. The study is approved by Cranfield University Health Research Ethics Committee.

RESULTS:

Out of 24 patients who have completed the study so far, 14 reported erectile dysfunction (ED) before the operation (EF domain <25). The results shown here are derived from patients with ED. BMI decreased gradually after the surgery reaching significance at 3-months post-op (P<0.05, Figure A). There was a progressive improvement in EF score after the surgery reaching significance at 3-months post-op (P<0.05, Figure B). A trend towards improvement in the IPSS score was also observed which reached significance at 3-months post-op (P<0.05, Figure C). Fasting blood glucose and HbA1c improved at 1 month post-op (P<0.05, Figures D and E). A decrease in orgasmic function (OF) domain was observed 1 month post-op which returned to pre-op levels over the following 5 months (Figure F). Sexual desire (SD), intercourse satisfaction (IS) and overall satisfaction (OS) domain scores gradually improved, all reaching significance at 6 months post-op (P<0.05; Figure F).

CONCLUSIONS:

The preliminary findings indicate that bariatric surgery represents an effective surgical treatment for obesity, leading to a significant BMI reduction and improvement in erectile and urinary function within 3-months post operatively. The successful completion of the study will examine for the first time the short-term effect of bariatric surgery on urogenital function in morbidly obese men and will investigate the relationship between urogenital function, insulin resistance and obesity.

Table: Demographic and clinical data

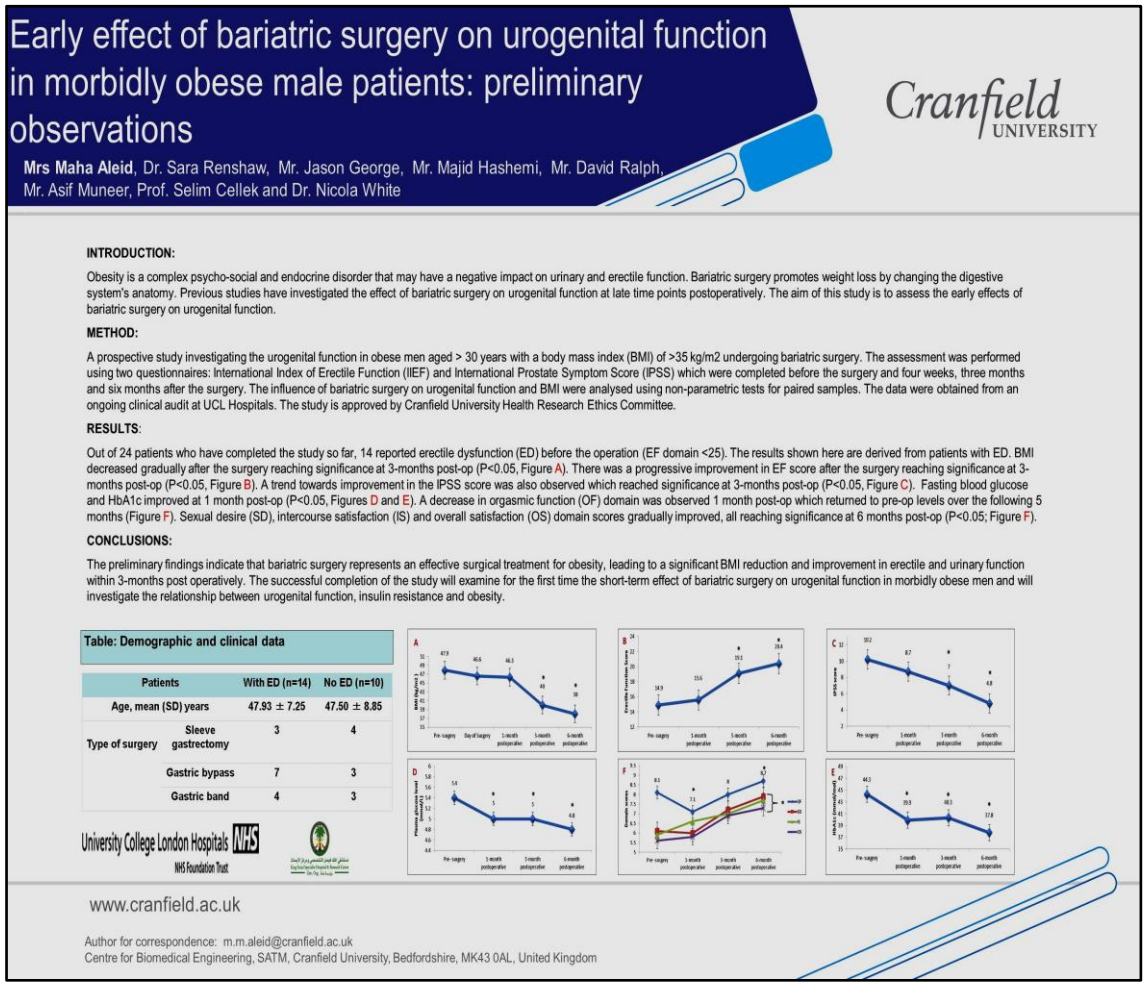
Patients		With ED (n=14)	No ED (n=10)
Age, mean (SD) years		47.93 ± 7.25	47.50 ± 8.85
Type to surgery	Sleeve gastrectomy	3	4
	Gastric bypass	7	3
	Gastric Band	4	3

University College London Hospitals NHS
NHS Foundation Trust

www.cranfield.ac.uk

Author for correspondence: m.m.aleid@cranfield.ac.uk
Centre for Biomedical Engineering, SATM, Cranfield University, Bedfordshire, MK43 0AL, United Kingdom

Aleid, M .; Renshaw, S; George, J, Muneer, A; Hashemi, M;. and Cellek, S. ": "Early effect of bariatric surgery on urogenital function in morbidly obese male patients: preliminary observations" Presented : 6th BOMSS Annual Scientific Meeting, 22 – 23 January 2015, Newcastle, UK
http://onlinelibrary.wiley.com/doi/10.1002/bjs.9794/epdf



Early effect of bariatric surgery on urogenital function in morbidly obese male patients: preliminary observations

Mrs Maha Aleid, Dr. Sara Renshaw, Mr. Jason George, Mr. Majid Hashemi, Mr. David Ralph, Mr. Asif Muneer, Prof. Selim Cellek and Dr. Nicola White

Cranfield UNIVERSITY

INTRODUCTION:

Obesity is a complex psycho-social and endocrine disorder that may have a negative impact on urinary and erectile function. Bariatric surgery promotes weight loss by changing the digestive system's anatomy. Previous studies have investigated the effect of bariatric surgery on urogenital function at late time points postoperatively. The aim of this study is to assess the early effects of bariatric surgery on urogenital function.

METHOD:

A prospective study investigating the urogenital function in obese men aged > 30 years with a body mass index (BMI) of >35 kg/m2 undergoing bariatric surgery. The assessment was performed using two questionnaires: International Index of Erectile Function (IIEF) and International Prostate Symptom Score (IPSS) which were completed before the surgery and four weeks, three months and six months after the surgery. The influence of bariatric surgery on urogenital function and BMI were analysed using non-parametric tests for paired samples. The data were obtained from an ongoing clinical audit at UCL Hospitals. The study is approved by Cranfield University Health Research Ethics Committee.

RESULTS:

Out of 24 patients who have completed the study so far, 14 reported erectile dysfunction (ED) before the operation (EF domain <25). The results shown here are derived from patients with ED. BMI decreased gradually after the surgery reaching significance at 3-months post-op (P<0.05, Figure A). There was a progressive improvement in EF score after the surgery reaching significance at 3-months post-op (P<0.05, Figure B). A trend towards improvement in the IPSS score was also observed which reached significance at 3-months post-op (P<0.05, Figure C). Fasting blood glucose and HbA1c improved at 1 month post-op (P<0.05, Figures D and E). A decrease in orgasmic function (OF) domain was observed 1 month post-op which returned to pre-op levels over the following 5 months (Figure F). Sexual desire (SD), intercourse satisfaction (IS) and overall satisfaction (OS) domain scores gradually improved, all reaching significance at 6 months post-op (P<0.05; Figure F).

CONCLUSIONS:

The preliminary findings indicate that bariatric surgery represents an effective surgical treatment for obesity, leading to a significant BMI reduction and improvement in erectile and urinary function within 3-months post operatively. The successful completion of the study will examine for the first time the short-term effect of bariatric surgery on urogenital function in morbidly obese men and will investigate the relationship between urogenital function, insulin resistance and obesity.

Table: Demographic and clinical data

Patients		With ED (n=14)	No ED (n=10)
Age, mean (SD) years		47.93 ± 7.25	47.50 ± 8.85
Type of surgery	Sleeve gastrectomy	3	4
	Gastric bypass	7	3
	Gastric band	4	3

University College London Hospitals NHS Foundation Trust

www.cranfield.ac.uk

Author for correspondence: m.m.aleid@cranfield.ac.uk
Centre for Biomedical Engineering, SATM, Cranfield University, Bedfordshire, MK43 0AL, United Kingdom

Presented (as poster presenter) in "8th Saudi Students Conference 31 January -1 February 2015" at Queen Elizabeth II conference centre, London, UK. "Early effect of bariatric surgery on urogenital function in morbidly obese male patients: preliminary observations" and Published in Saudi Students Conference in the UK, proceedings book. (see above)

Aleid, M .; Cellek, S; Muneer, A; Hashemi, M; George, J. “Urogenital function in morbidly obese men following bariatric surgery.Presented “16th ESSM 2014 joint by 12th EFS Congress 29 Jan - 1 Feb 2014” at the Istanbul Convention and Exhibition Centre, Istanbul, Turkey. Published in the Journal Of Sexual Medicine 2014;11(suppl 1):54-81
http://onlinelibrary.wiley.com/doi/10.1111/jsm.12415/epdf

Urogenital function in morbidly obese men following bariatric surgery

Maha Aleid[1,2,3*], Jason George[2], Sara Renshaw[2], Asif Muneer[2], Majid Hashemi[2] and Selim Cellek[1]
[1]Centre for Biomedical Engineering, Cranfield University, Bedfordshire, MK43 0AL, UK;
[2]Surgical Specialties, University College Hospital, London, NW1 2PG, UK;
[3]King Faisal Specialist Hospital & Research Centre, Riyadh 11211 , Saudi Arabia.
*author for correspondence: m.m.aleid@cranfield.ac.uk

INTRODUCTION:

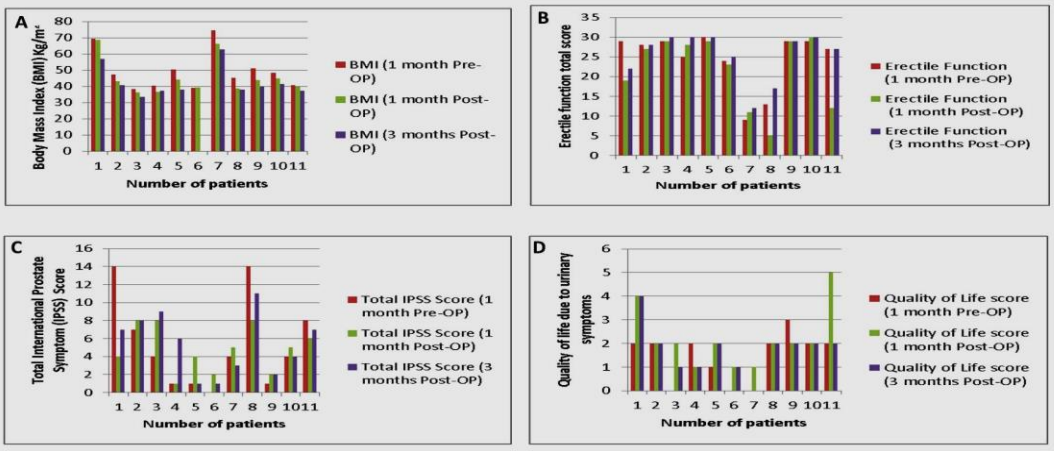
Obesity is a complex psycho-social and endocrine disorder that may have negative impact on urogenital function. Bariatric surgery promotes sustained weight loss by changing the digestive system's anatomy. The aim of this study is to understand the effects of bariatric surgery on urogenital function.

METHOD:

This is an ongoing prospective study of the urogenital function of obese men aged > 30 years with a Body Mass Index (BMI) of >35 kg/m^2 who undergo bariatric surgery. The assessment of urogenital function is performed using questionnaires: International Index of Erectile Function (IIEF) and International Prostate Symptom Score (IPSS). The two questionnaires are requested to be completed by the patients before the surgery, four weeks, three months and six months after the surgery.

RESULTS:

The data below are obtained from 11 patients so far who have reached the 3 month post-op follow-up. BMI (A), IIEF (B), IPSS (C) and QoL (D) scores of each individual patient are presented.



CONCLUSIONS:

The preliminary results suggest:

1. Study of urogenital function using the two questionnaires in patients undergoing bariatric surgery is feasible.
2. A decrease in BMI as early as 1 month after the surgery has been observed.
3. Most of the men have had high IIEF scores before the surgery.
4. The effect of the surgery on erectile and urological function is variable.
5. Further in-depth analysis is required for each patient.

www.cranfield.ac.uk

Presented (as poster presenter) in "7th Saudi Students Conference 1 - 2 Feb 2014" at Edinburgh International conference centre, Edinburgh, UK. "Urogenital function in morbidly obese men following bariatric surgery", (poster No. 113) and published in Saudi Students Conference in the UK, proceedings book, ISBN-14:9780956904522

Urogenital function in morbidly obese men following bariatric surgery

Maha Aleid[1,2,3*], Jason George[2], Sara Renshaw[2], Asif Muneer[2], Majid Hashemi[2] and Selim Cellek[1]

[1]Centre for Biomedical Engineering, Cranfield University, Bedfordshire, MK43 0AL, UK;
[2]Surgical Specialties, University College Hospital, London, NW1 2PG, UK;
[3]King Faisal Specialist Hospital & Research Centre, Riyadh 11211, Saudi Arabia.
*author for correspondence: m.m.aleid@cranfield.ac.uk

INTRODUCTION:

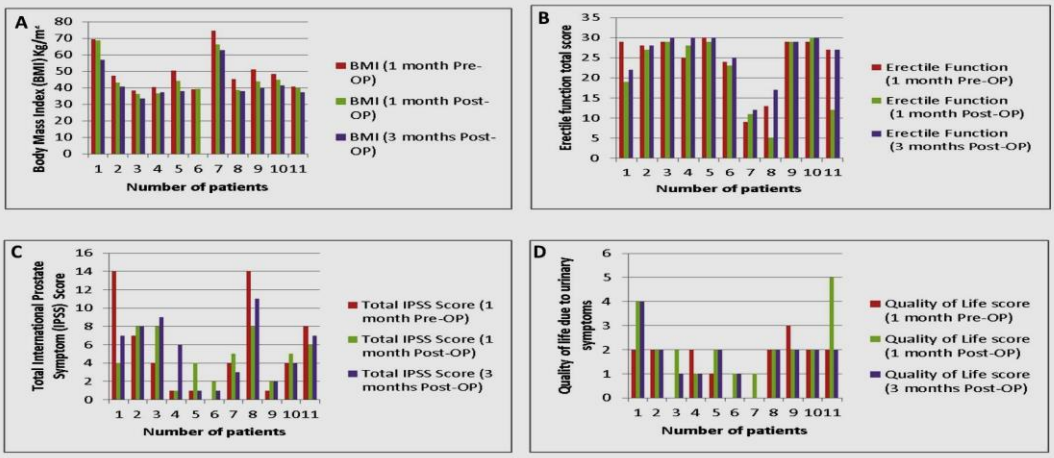
Obesity is a complex psycho-social and endocrine disorder that may have negative impact on urogenital function. Bariatric surgery promotes sustained weight loss by changing the digestive system's anatomy. The aim of this study is to understand the effects of bariatric surgery on urogenital function.

METHOD:

This is an ongoing prospective study of the urogenital function of obese men aged > 30 years with a Body Mass Index (BMI) of >35 kg/m^2 who undergo bariatric surgery. The assessment of urogenital function is performed using questionnaires: International Index of Erectile Function (IIEF) and International Prostate Symptom Score (IPSS). The two questionnaires are requested to be completed by the patients before the surgery, four weeks, three months and six months after the surgery.

RESULTS:

The data below are obtained from 11 patients so far who have reached the 3 month post-op follow-up. BMI (A), IIEF (B), IPSS (C) and QoL (D) scores of each individual patient are presented.



CONCLUSIONS:

The preliminary results suggest:

1. Study of urogenital function using the two questionnaires in patients undergoing bariatric surgery is feasible.
2. A decrease in BMI as early as 1 month after the surgery has been observed.
3. Most of the men have had high IIEF scores before the surgery.
4. The effect of the surgery on erectile and urological function is variable.
5. Further in-depth analysis is required for each patient.

www.cranfield.ac.uk

Presented (as poster presenter) in "6th Saudi Students Conference 12 -13 October 2012" at Brunel University, London, UK. "Urogenital function in morbidly obese men following bariatric surgery" and Published in Saudi Students Conference in the UK, proceedings book.

Cranfield UNIVERSITY

Cranfield Health

Urogenital function in morbidly obese men following bariatric surgery

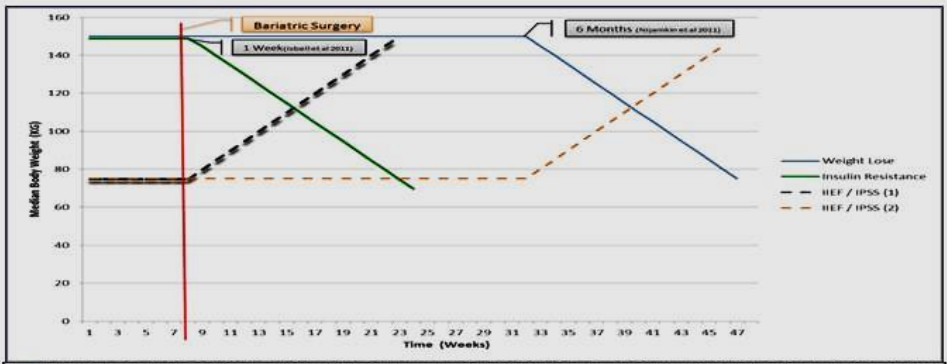
Ms. Maha Aleid[1,2], Mr. Jason George[2], Mr. Asif Muneer[2], Mr. Majid Hashemi[2] and Dr. Selim Cellek[1]
(1) Translational Medicine, Cranfield Health, Cranfield University, Bedforshire, MK43 0AL, UK.
(2) Surgical Specialties, University College Hospital, London, NW1 2PG, UK

Introduction

Bariatric surgery promotes weight loss by changing the digestive system's anatomy, limiting the amount of food that can be eaten and digested. Obesity is a complex psycho-social and endocrine disorder that may change bladder and erectile function independently. The aim of this study is to understand the effects of bariatric surgery on urogenital function.

Method

It is a prospective study of the urogenital function designed for obese men aged > 30 years with a Body Mass Index (BMI) of >35 kg/m^2 who undergo bariatric surgery with a sample size of 30 patients. The assessment of urogenital function will be performed using questionnaires: International Index of Erectile Function (IIEF) and International Prostate Symptom Score (IPSS). The two questionnaires will be requested to be completed by the patients before the surgery, four weeks, three months and six months after the surgery. The influence of bariatric surgery on urogenital function and BMI will be analysed using suitable statistical modelling.



— Blue solid line indicates the expected changes in body weight after 6 months bariatric surgery (Nijamkin et al., 2012).
— Green solid line indicates the expected changes in insulin resistance after 1 week (Pournaras et al., 2010; Wickremesekera et al., 2005; Isbell et al., 2010).
— Red solid line indicates bariatric surgery.
-- Expected recovery of urogenital function in parallel with insulin resistance.
– Expected recovery of urogenital function in parallel with weight loss.

Figure 1

Expected outcome

Successful completion of the study will examine for the first time the short-term effect of bariatric surgery on urogenital function in morbidly obese men and will investigate the relationship between urogenital function, insulin resistance and obesity.

www.cranfield.ac.uk/health