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From the Thyroid to the Heart

Knowledge, Attitudes, and Practices

Highlights

Patient Outcome in a Suburban Area

Adiposity and Cardiometabolic Diseases

Discovering Thoughts, Inventing Future



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VOLUME 23 ISSUE 1 (VER. 1.0)

OPEN ASSOCIATION OF RESEARCH SOCIETY

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GLOBAL JOURNAL OF MEDICAL RESEARCH: K
INTERDISCIPLINARY
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

From the Thyroid to the Heart

By Roy Moncayo & Helga Moncayo

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GJMR-K Classification: NLMC Code: WK 200, WG 200



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From the Thyroid to the Heart

Roy Moncayo ^α & Helga Moncayo ^σ

Abstract - The pathogenesis of human disease is commonly considered to be unique to each organ or system. This has led to specialization in medical practice leaving little space for global pathogenesis concepts. In this review we have departed from a biochemical concept of coenzyme Q₁₀ (CoQ₁₀) deficiency and its relation to the initiation of hypoxia response in a systemic way. Several conditions of secondary CoQ₁₀ deficiency are known in the literature by which the organs involved could be affected by hypoxia and switch to glycolytic metabolism. The most salient biomarkers of this situation are the low T3 syndrome and the elevation of IL-6. These parameters together with CoQ₁₀ deficiency delineate a condition of acquired mitochondrial dysfunction. Additional related biochemical deficiency conditions affect magnesium, selenium, and iron levels. Visualization of glycolysis can be clearly achieved by diagnostic imaging methods based on the use of ¹⁸F-fluoro-deoxyglucose (¹⁸F-FDG). We present several examples of diagnostic imaging with ¹⁸F-FDG to demonstrate our model of acquired mitochondrial dysfunction and disease.

I. INTRODUCTION

Through a series of observational studies on the pathogenesis of benign thyroid disease we were able to deduce in 2021 that the central pathogenetic mechanism was a condition of glycolytic

metabolism as evidenced through combined diagnostic imaging with 3D-power Doppler sonography and positron emission tomography (PET) using ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) (Figure 6 in (1)). In the ¹⁸F-FDG study both the thyroid and the heart displayed an intense tracer uptake (Figure 1), an association never commented before in the literature (2). Since the innate capability of deoxyglucose is to indicate glycolysis (3), we interpreted the image as an in-vivo depiction of this metabolic process which correlated with increased vascularity. Given that patients with benign thyroid disease frequently have low levels of coenzyme Q₁₀ (CoQ₁₀) and that experimental CoQ₁₀ deficiency is linked to hypoxia as shown by Liparulo et al., in 2021 (4), our current interpretation of the diagnostic image shown below is that it represents glycolysis and is related to conditions of hypoxia. In Liparulo's experiment with the human T67 glioma cell line, CoQ₁₀ deficiency was produced by inhibiting its biosynthesis using the competitive inhibitor 4-nitrobenzoate leading finally to low intracellular levels of oxygen, i.e., hypoxia (4).

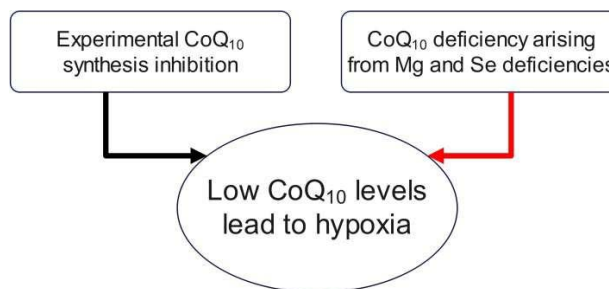
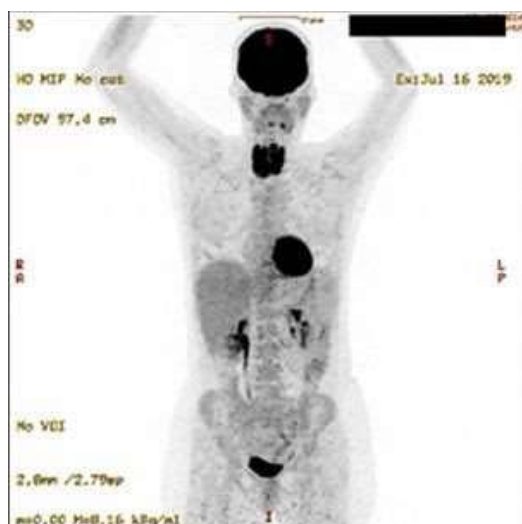


Figure 1: ¹⁸F-FDG PET Study of a Patient with Recurrent Active Thyroiditis. Intense Tracer Uptake is Seen in the Thyroid and the Heart. The Brain Shows a Physiological Uptake. The renal pelvis, the ureters, and the urinary bladder Depict the Physiological Excretion Path. Panel B Shows the Simple Pathogenetic Mechanism Leading to Hypoxia.

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Our previous experience with CoQ₁₀ deficiency had shown that this condition is reversible when CoQ₁₀ supplementation at a dose of 0.9mg/kg body weight combined with magnesium citrate 2400mg/d, and selenium 200µg/d was given. This reversibility can be demonstrated by the restitution of normal perfusion and

morphology of the thyroid (5). The clinical investigation of our patients was based on a conceptual model of coordinated interactions between magnesium, selenium, iron, and CoQ₁₀ as they relate to mitochondrial function (Figure 2). The clinical impact of these processes has been discussed elsewhere (1, 5-11).

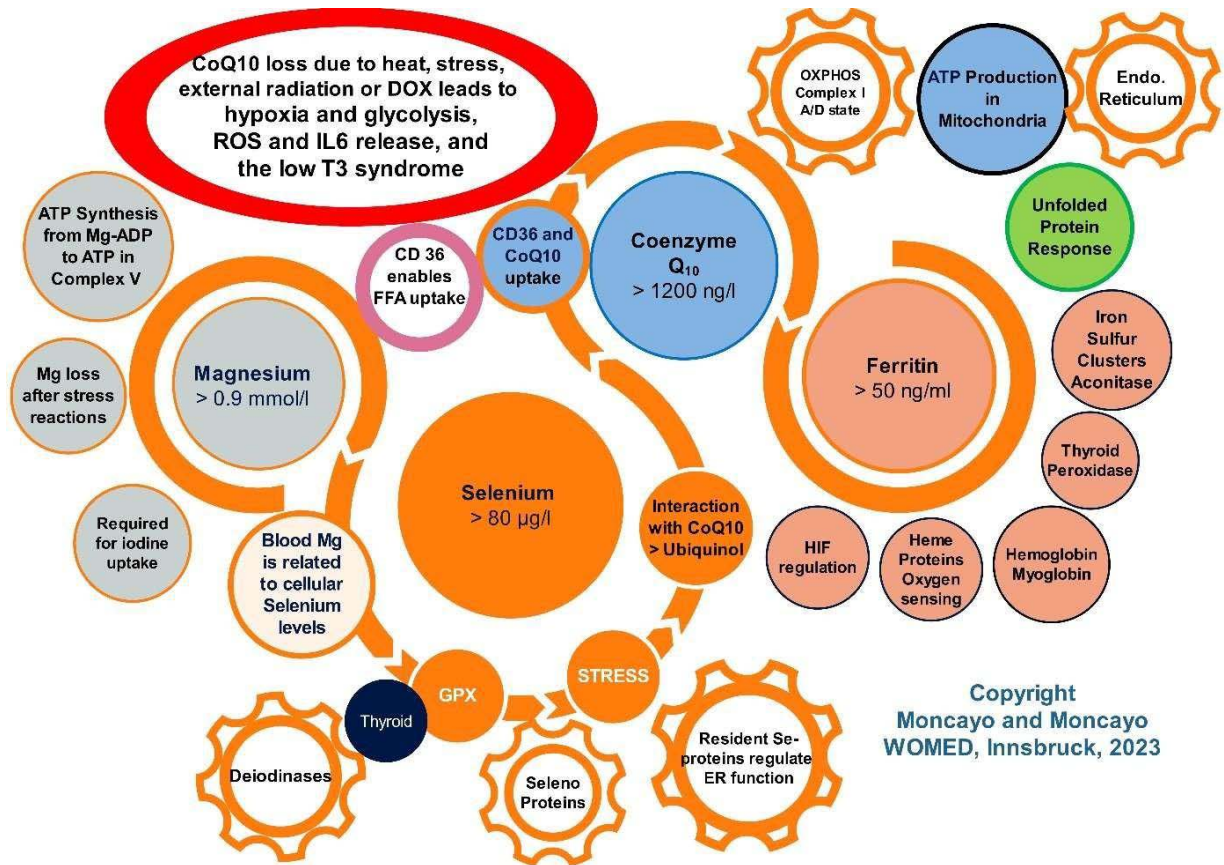


Figure 2: The WOMED model of the interactions between magnesium, selenium, CoQ₁₀, and ferritin in relation to mitochondrial function. Magnesium is required ATP synthesis, for iodine uptake, and selenium uptake. Selenium is the basic element of selenoproteins. Selenoproteins are related to the thyroid hormone deiodinases, to anti-oxidant functions, and to the endoplasmic reticulum as a resident element. Selenium is a key factor for maintaining CoQ₁₀ levels. CoQ₁₀ is the central element in Complex I of the OXPHOS chain and is maintained by CD36. Anti-oxidative actions of CoQ₁₀ arise from the conversion of CoQ₁₀ to ubiquinol, a process that requires selenium. Iron is essential for the synthesis of iron sulfur clusters which are constituents of many proteins of the OXPHOS chain. Furthermore, iron stabilizes the prolyl hydroxylases inhibiting the activation of HIF1. Desirable blood levels of the parameters are shown in the circles. The red circle signalizes the crucial situation of CoQ₁₀ in the context of hypoxia.

The main messages from Figure 2 include: 1) daily life and physical stressors can lead to magnesium deficiency (12, 13) which will affect iodine and selenium uptake and thyroid hormone formation (14-16). 2) Selenium deficiency (7) will affect the anti-oxidative protection of the body by altering selenoprotein synthesis (17, 18) and altered activation of CoQ₁₀ to ubiquinol through thioredoxin reductase (19), potentiating oxidative damage. One fact that is often overlooked is that CoQ₁₀ has a positive correlation to selenium levels (20). 3) A decrease of magnesium availability will affect primarily the production of ATP from Mg-ADP (21) as well as the uptake of selenium. 4)

The lack of ATP will alter the function of the unfolded protein response of the endoplasmic reticulum (22). Iron deficiency affects thyroid peroxidase (23), mitochondrial iron sulfur clusters (24, 25), and regulation of HIF through prolyl hydroxylases.

To demonstrate the concept of CoQ₁₀ deficiency we will first review basic concepts on the substance and add an introduction on diagnostic imaging procedures based primarily on the use of ¹⁸F-FDG.

Nuclear Medicine diagnostic imaging based on the use of ¹⁸F-FDG PET has been primarily considered as a diagnostic method for oncological work (26). This

rather restrictive notion emerged during the early years of clinical use of ^{18}F -FDG when tracer availability and imaging capacity at specialized institutions were limited (26). Disregarding these conceptual and practical limitations, in 2003 we applied the methodology for the diagnosis of arteritis (27). Visualization of fatty acid oxidation can be achieved using the specific tracer [^{123}I]- β -Methyl iodophenyl-pentadecanoic acid (BMIPP) (28,

29). The beta oxidation of free fatty acids constitutes the primary source of energy and ATP production in the heart (30). Once the oxidation of free fatty acids is diminished, glycolysis takes over in the failing heart (31). This is accompanied by increased glycolytic metabolism. Figure 3 shows summarily mechanisms of CoQ_{10} deficiency and their relation to metabolism and Nuclear Medicine diagnostic imaging.

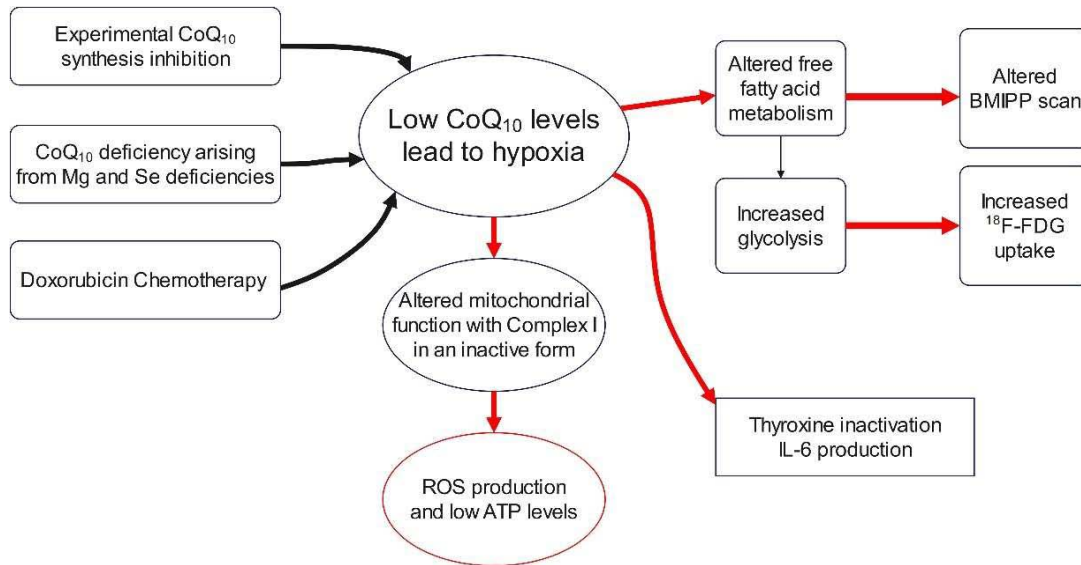


Figure 3: General changes of mitochondrial metabolism and systemic parameters under hypoxia.

a) *Basic notes on coenzyme Q_{10}*

The first description of coenzyme Q_{10} (CoQ_{10}) was done by Festenstein in 1955 who was working on the general topic of quinones (32). CoQ_{10} is a small lipophilic molecule located widely in cell membranes. Due to its distribution, it was named ubiquitous quinone. Beginning in 1957 Crane and coworkers published a series of studies on the characterization of CoQ_{10} . An early publication dealt with the isolation of a quinone from the mitochondria of beef heart. The authors described the capability of the compound to undergo oxidation and reduction in a reversible way. The denomination Q-275 for CoQ_{10} was derived from the absorption spectrum of the substance (33). Different compounds having quinone structure have been described in different species (34). In 1959 CoQ_{10} and the succinoxidase activity of the electron transport system were studied by Crane (35) as well as by Hendlin and Cook in 1960 (36). The structure of CoQ_{10} characterized as a 2,3-dimethoxy benzoquinone structure was published by Wolf et al., in 1958 (37).

The biochemical characteristics of quinones were summarized by Hoffmann-Ostenhof in 1947 (38). In 1948 Friedmann, Marrian, and Simonreuss described the antimetabolic effects of quinones in relation to their structure (39). Further information on the biochemistry of quinones was published by Barnes in 1963 (Section 3 in (40)).

Gale et al., evaluated the mean content of CoQ_{10} in different human organs in 1961 (41) showing that the brain and thyroid have the lowest concentrations (Figure 2).

Due to frequent incidence of thyroid disease in the general population, we hypothesize that organs with higher levels of CoQ_{10} can be more resistant to alteration and retain function. The thyroid would be at the end of the scale.

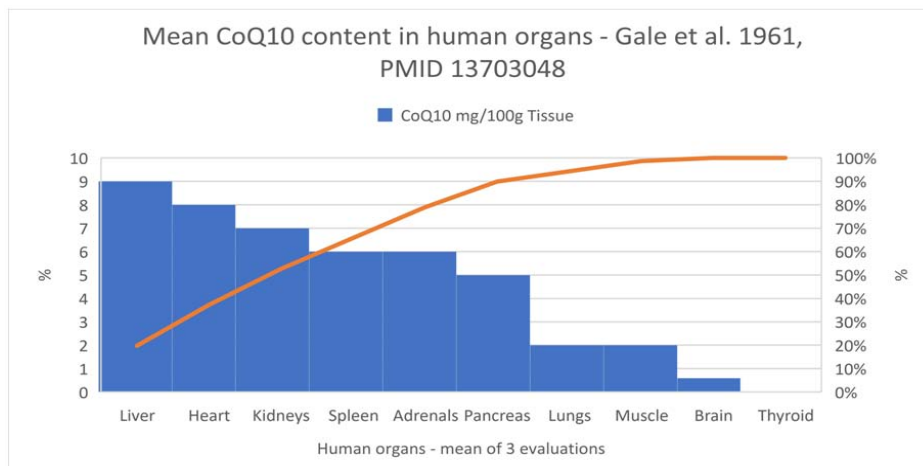


Figure 4: Mean CoQ₁₀ tissue levels in selected organs. Adapted from Gale et al. (41)

The relations between the organ content of CoQ₁₀ or ubiquinone and age have been studied by Kalén, Appelkvist, and Dallner in 1989 (42). An abridged

summary of their data is shown in Table 1. The highest levels are found in the age group 19-21 years while older subjects have lower levels.

Table 1: CoQ₁₀ levels in selected organs according to age (extracted from (42)).

	Ubiquinone Age	μg/d ww			
		0.7 - 2	19 - 21	39 - 43	77 - 81
		1-3 days	years	years	years
Heart	36.7	78.5	110.0	75.0	47.2
Kidney	17.4	53.4	98.0	71.1	64.0
Liver	12.9	45.1	61.2	58.3	50.8

In 1996 Ravaglia et al., evaluated the correlation of CoQ₁₀ levels with body composition and found that levels decreased in a parallel form as did the fat-free body mass and speculated that this diminution would affect muscle performance (43).

used a deuterium labeled molecule (44). A first peak in blood was seen at 6 hours, and the half-life was found to be 33 hours. Data on PET tracer biodistribution studies using ¹¹C-labeled CoQ₁₀ and ¹¹C-ubiquinol were reported by Watanabe et al., in 2019 (45). We have interpolated and summarized their results in Table 2.

Basic information on the pharmacokinetics of CoQ₁₀ can be found in the study by Tomono et al., who

Table 2: Biodistribution of ¹¹C-labeled CoQ₁₀ and ubiquinol (45).

CoQ ₁₀ distribution	% ID/g			
	Ubiquinol2 0min	90min	Ubiquinone2 0min	90min
Heart	0.5	0.6	1.4	0.7
Kidney	0.4	0.28	0.3	0.2
Liver	3.8	5.7	3.7	5.8
Spleen	2.0	2.2	3.5	6.0
Blood	1.9	0.8	1.4	0.6
Cerebrum	0.038		0.026	
Muscle	0.04		0.03	

Bentinger et al. published a study on the content of CoQ₁₀ in endocrine organs (46). Table 1 of this publication shows the high uptake of dietary CoQ₁₀

in steroid producing cells such as adrenal cells and ovaries while the thyroid had a much lower uptake.

b) *Oxidative processes, selenium, and CoQ₁₀*

Several investigators have evaluated the effect of external radiation and oxygen toxicity on biological systems since the 1940s. The biological extent of life has been proposed to be associated with concepts of cellular damage due to oxidative processes that produced reaction intermediates originating from unpaired electrons (47). In 1954 Gerschman et al., studied the topic of oxygen poisoning as well as x-irradiation proposing a common mechanism which was related to the oxidizing free radicals (48). In 1955 Harman published a theory of aging by describing deleterious effects arising from injuries due to free radicals (49). These investigations as well as those of Ritossa on the changes caused by heat shock (50), had in common an external component which was acting as a pathogenic factor affecting living cells ending with oxidative changes.

Early investigations on selenium addressed its role in liver disease. In 1957 Schwarz and Foltz (51) described the beneficial effect of selenium in the context of dietary necrotic liver degeneration. They identified selenium in a fraction originally called Factor 3. Modern research has described the complex array of selenoproteins with antioxidant functions including glutathione peroxidase (52-54).

We have chosen to consider selenium and CoQ₁₀ together based on observations made by Green et al., in 1961 (55) and by Hidiroglou in 1967 (56) who found a close functional relation between both substances such that selenium administration improved the tissue levels of CoQ₁₀ in experimental animals. Vadhanavikit and Ganther published similar observations in 1993 and 1994 (57, 58). The authors speculated that lowering of CoQ₁₀ levels depended on the depressed activity of GSH-Px which was the consequence of selenium deficiency (58). This finding implies that hypoxia can develop starting from selenium deficiency which then affects CoQ₁₀ levels. Unfortunately, this important physiological connection has not been considered in many studies. Putting the focus only on one of these elements in the context of supplementation have remained inconclusive (59-61). On the other hand, specific single mechanisms can be indeed characterized.

Ernster and Forsmark-Andrée described the anti-oxidant actions of ubiquinol, i.e. the reduced form of CoQ₁₀, in aerobic organisms (62). Sugiyama studied the anti-oxidative effect of CoQ₁₀ administering a dose of 2mg/k which is equivalent to ~140 mg for an adult with 70 k body weight. Both the in-vivo experiments as well as the in-vitro studies demonstrated that under CoQ₁₀ lipo-peroxides were significantly lower as compared to the controls (Table 1 in (63)). Degli Esposti et al. characterized the functional role of CoQ₁₀ in Complex I of the OXPHOS chain emphasizing its energetic function (64). In 2017 Shimizu et al. described

an association between low CoQ₁₀ levels and hospital mortality in patients with cardiac disease (65). Heart arrest patients also share this feature of having very low levels of CoQ₁₀ (66).

Under experimental conditions the administration of selenium compounds has resulted in inhibition of angiogenesis as well as of VEGF expression (67, 68). In our studies we have observed a similar action for CoQ₁₀ (5). We propose that these actions add a positive effect to counteract changes due to hypoxia.

c) *Warburg and the development of 2-desoxy-D-glucose*

The theory behind the development of 2-desoxy-D-glucose can be traced back indirectly to the work of Otto Warburg. In 1911 he carried out experiments with the sea urchin (*Arbacia pustulosa*) and with nucleated avian erythrocytes (69). The blood cells had been exposed to low temperatures between -15° and -20° C to freeze them. The frozen material was then exposed to 38° C to break the cells. This handling produced a temperature increase of approximately 60°C. The resultant experimental acellular material was a dark liquid. Oxygen consumption in the material won from younger blood cells was higher than in intact red blood cells. A closer analysis of the 1923 publication by Warburg and Minami clearly showed the influence of raised temperature (70). These experiments were unknowingly ahead of time to those on the heat shock response done in 1962 by Ritossa where heat shock was produced by setting the temperature to 30°C for thirty minutes (50). Warburg's experiments have never been interpreted in the context of the heat shock (71-74) nor of endoplasmic reticulum stress (75). Endoplasmic reticulum stress is a logical consequence since heat shock will produce protein aggregation (76). Experimental heat shock can induce glycolysis to compensate ATP balance (77) and activate the endoplasmic reticulum stress response mechanisms (78).

In 1928 Warburg published "The metabolism of tumors in the body" (79) where he described the metabolic characteristics of 2 tumor models, Flexner-Jobling's rat carcinoma (80), and Jensen's rat sarcoma (81). In their experiment they measured the glucose content in in-going and out-going tumor vessels. The average values in the experiments with the Jensen sarcoma substrate revealed a mean glucose concentration of 124 mg % in the arterial vessels, and 54 mg % in the venous vessel (Table II in (79)). On the other hand lactic acid in the tumor cavity was higher than in the aorta by 69 mg% (Table V in (79)).

In 1922 Bergmann, Schotte, and Lechinsky published their work on the development of deoxy-glucose as an antagonist of glycolysis and added experimental data aimed at elucidating the reactivity of glucosides after introducing structural changes at the

C2 position of the glucose molecule (82). Further experimental work on deoxy- glucose as an antagonist of glycolysis was published by Francis B. Cramer and Gladys Woodward in 1952 (3, 83-85). They showed a reduction of approximately 60% of glucose metabolism under anaerobic conditions working with slices of Walker 256 rat carcinoma samples when an equimolar quantity of 2-deoxy-D-glucose was added. The Walker 256 rat carcinoma originated in 1928 from a mammary gland tumor of a pregnant rat (page 261 in (86)). Confirmation of the avidity of Walker-256 tumor cells for ^{18}F -FDG was provided in 2019 by Li et al. (Figure 2 in (87)).

Woodward and Cramer (3) included only two literature references in their publication: their previous work and a 1930 translation of Warburg's previous work (88). The word "relation" was used to connect the content of both publications.

In 1957 Wick et al. described the primary metabolic block on glucose that 2-deoxyglucose produces (89). In 1961 Barban described this mechanism as follows: "... inhibits glycolysis and growth of cultured human cells" (page 1890 in (90)). These results clearly associated 2-deoxyglucose with glycolysis. With the development of ^{18}F -labelled deoxyglucose by Som in 1980, a diagnostic tool for glycolysis imaging became available (91).

d) *Narrative description of hypoxia and cardiac metabolism*

Hypoxia stands for a biochemical state where oxygen availability is limited. According to Richalet in "The Invention of Hypoxia", the term appeared in the literature about 1909 in a publication originating from Germany (92). At this time Joseph Barcroft published two studies dealing with the consequences of insufficient oxygen supply to the body. In 1908 he presented a review of the scientific evidence known up to that time (93). In 1920 he discussed the consequences of insufficient oxygen supply as follows: "The statement has been made that "anoxaemia not only stops the machine, but wrecks the machinery" (94). In modern times we can interpret this statement as suggesting multi-organ failure (95).

In 1964 Nunn and Freeman discussed that tissue hypoxia can arise from hemorrhagic shock 1964 (96). In 1969 Henderson (97) and McDowall (98) presented summaries of the biochemical concepts of hypoxia which appeared in the British Journal of Anesthesiology. In 1977 Alberti discussed the consequences of hypoxia on biochemical terms. Equation 11 of this publication identified the role of CoQ_{10} in the synthesis of ATP (99).

In 1987 Bihari discussed the relation of hypoxia to septic shock (100). Some biochemical characteristics of hypoxia were described by Webster in 1987 who

reported the relation between hypoxia and activation of glycolysis (101).

In 1988 Goldberg, Dunning, and Bunn characterized the oxygen sensing function as being associated with heme protein (102). In 1992 Loike et al. showed that when endothelial cells were exposed to hypoxia an upregulation of glucose transport could be observed (103). At a cellular level, the metabolic consequences of hypoxia include diminution of fatty acid oxidation and activation of glycolysis (Figure 1 in (104)) as well as an increased expression of interleukin 6 (105).

The transcriptional adaptation to experimental hypoxia was characterized in 1993 by Wang and Semenza defining a role for the hypoxia inducible factor 1 (HIF-1 α) using hepatoma tumor cells (Hep3B) (106). In 1999 Oudidir et al. demonstrated that the expression of the glucose transporter in alveolar epithelial cells could be upregulated by hypoxia. In their experiments this was reflected by increased uptake of deoxyglucose (Figure 2 in (107)) which is connected to increased glycolysis.

In 2010 Solaini et al. described major changes in mitochondria found in hypoxia. Figure 1 depicted a connection between hypoxia and diminished electron transport and increased ROS production. The authors conceived these changes as stabilizing factors of HIF (108). Lee, Chandel, and Simon discussed mechanisms of cellular changes following hypoxia adding the involvement of endoplasmic reticulum stress and of the unfolded protein response (Figure 2 in (109)).

Recent reviews on hypoxia research have been published by Thompson in 2016 (110) as well as by Luo et al. in 2022. Luo's publication included an informative pictorial summary of relevant landmarks (111). Kierans and Taylor idealized that increased glycolysis was the event that goes directly from hypoxia to HIF-1 α expression ending with the expression of enzymes involved in glycolysis (112). Della Rocca and coworkers summarized clinical data on diseases related to hypoxia in 2022 (113).

The beta oxidation of free fatty acids constitutes the primary source of energy and ATP production in the heart (30). Tateno and coworkers have demonstrated that myocardial infarction patients show a diminished utilization of free fatty acids which did not correlate with the findings of myocardial perfusion (114). Changes in cardiac fatty acid utilization show a dynamic course as reported by Zen et al., (115). Biswas et al., demonstrated lower BMIPP uptake following acute infarction of the myocardium (116) as well as a negative correlation between left ventricular ejection fraction and tracer wash out rate. They also described a positive correlation between washout rate of BMIPP and blood level of NT-proBNP (Figures 4 and 5, respectively in (117)).

The graphical appearance of decreased BMIPP uptake as seen in planar images was shown in Figure 6 by Biswas. Increasing levels of NT-proBNP, a biomarker of heart failure (118), correlated positively with an increased wash-out rate of BMIPP (Figure 5 in (119)) as well as a higher incidence of cardiac events when cardiac tracer uptake was low (Figure 6 in (119)).

e) *Clinical situations associated with CoQ₁₀ deficiency*

Low levels of CoQ₁₀ can be found in a series of situations. A clinical review by Boreková found that situations of poor nutrition, infection, and a variety of stressors can diminish the availability of CoQ₁₀ (120). The publication included data from a previous study by Anna Gvozdjáčková which had shown such conditions.

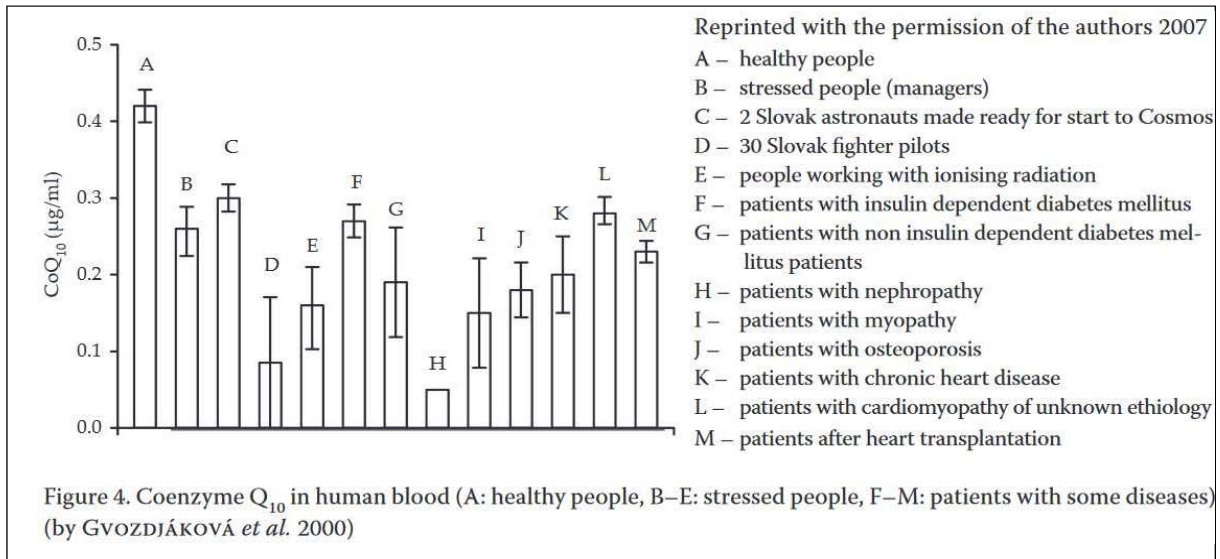


Figure 6: CoQ₁₀ levels in relation to stressors. Taken from Boreková M, Hojerová J, Koprda V, Bauerová K. Nourishing and Health Benefits of Coenzyme Q10. Czech J Food Sci (2008) 26(4): 229-41. doi: <https://doi.org/10.17221/1122-CJFS>. License CC BY NC 4.0

Low levels of CoQ₁₀ have been found in children who presented food allergies (121). The same applied to acute influenza (122). A similar situation can be found in patients after cardiac arrest as well as septic patients (66, 123) and in critical illness (124). Studies on post-operative follow-up have shown indirectly that surgery induces a decrease of CoQ₁₀ levels. This drop can be prevented by supplementation with CoQ₁₀ (125).

Experimental studies done by Fischer *et al.*, have shown alterations in CoQ₁₀ levels after dietary restriction (126). Experimental burns can lead to mitochondrial damage and dysfunction and can be corrected by CoQ₁₀ administration (127). Similar observations have been published by Xu *et al.*, relating CoQ₁₀ administration to protection against myocardial cell changes induced by heat stress (128, 129).

Experimental hypoxia in skeletal muscle of rabbits is accompanied by a reduction of the levels of ubiquinone (130). A decrease of the CoQ₁₀ levels goes along with low ATP levels in isolated rabbit ventricles under hypoxia (Table 2 in (131)).

The administration of antineoplastic antibiotics such as adriamycin can inhibit the synthesis of CoQ₁₀ (132). This interference could arise from the similar quinone structure of both CoQ₁₀ and adriamycin (133-138). A further effect of this inhibition is the decrease of

free fatty acid oxidation. In 2000 and 2003, Saito *et al.* demonstrated that cardiac BMIPP uptake was decreased after doxorubicin (139) and taxan (140) administration. On the other hand, it has been shown that doxorubicin cardiotoxicity can be prevented by administration of CoQ₁₀ (141). Bradamante *et al.* considered hypoxia to be a risk factor for doxorubicin-induced cardiotoxicity (142). Muhammed, Ramasarma, and Kurup described in 1983 that adriamycin inhibited oxidative phosphorylation in freshly prepared mitochondria (135).

In 2013 Umezawa *et al.*, demonstrated that external radiation therapy affected BMIPP uptake. The irradiated area of the heart (red arrows in Figure 4) showed no tracer uptake (143). Although the CoQ₁₀ levels were not evaluated, the image pattern is highly suggestive of induced CoQ₁₀ deficiency. In a subsequent publication the authors described a relation between the radiation dose applied and the degree of BMIPP alteration (144).

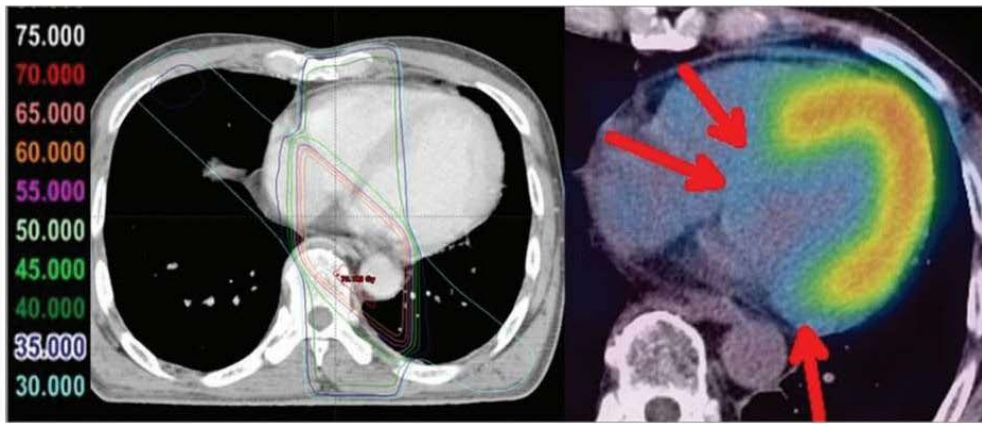


Fig. 3. Images of a remarkable case (62-year-old male) at 29 months after radiotherapy for esophageal cancer. Reduced uptake corresponding to radiation fields was distinct in this case.

Figure 4: Taken from Umezawa (143). The Figure is used on the basis of Creative Common CC-BY-NC. Umezawa R, Takase K, Jingu K, Takanami K, Ota H, Kaneta T, et al. Evaluation of Radiation-Induced Myocardial Damage Using Iodine-123 B-Methyl-Iodophenyl Pentadecanoic Acid Scintigraphy. *J Radiat Res* (2013) 54(5): 880-9. Epub 2013/02/16. doi: <https://doi.org/10.1093/jrr/rrt011>

Following the concept of metabolic switch from free fatty oxidation to glycolysis, Yan et al., have demonstrated that radiation-induced changes in myocardial metabolism are accompanied by a high uptake of ^{18}F -FDG (Figures 2 and 3 in (145)), thus reflecting glycolysis.

A series of studies have demonstrated that altered free fatty acid oxidation can be restituted by administrating the ACE-inhibitor enalapril (146-150) (Figure 5).

Fig. 2. Scintigraphic findings. Significantly more cardiac uptake of ^{123}I -BMIPP (H/M) was observed 3 months after treatment (right) than before treatment (left).

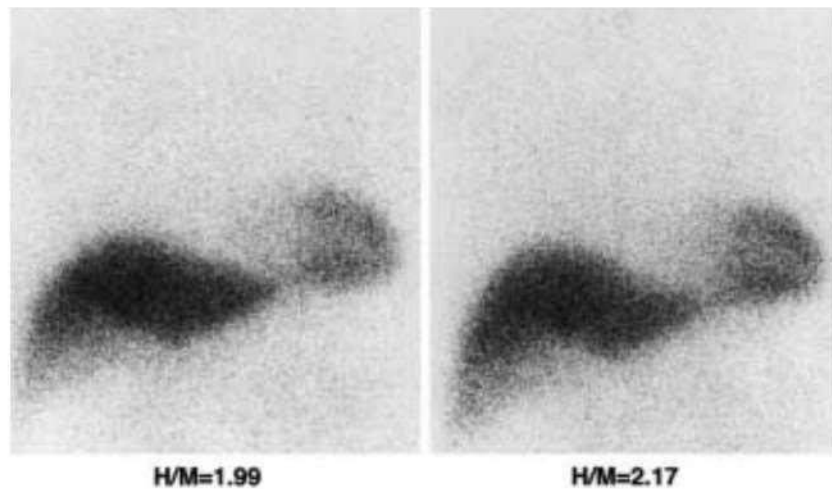


Figure 5: Taken from Watanabe et al. (148). Copyright granted for this reproduction. Watanabe K, Sekiya M, Tsuruoka T, Funada JI, Miyagawa M. Usefulness of ^{123}I -Bmipp with Myocardial Imaging for Evaluation of the Efficacy of Drug Therapy in Patients with Chronic Heart Failure. *J Card Fail* (2001) 7(3): 257-64. doi: <https://doi.org/10.1054/jcaf.2001.26313>

f) *Clinical situations associated with diminished BMIPP uptake*

The uptake mechanism of free fatty acids requires a transport system that involves the CD36 molecule. When there is a deficiency of this structure, ^{18}F -FDG uptake has been shown to be increased. This alteration can be corrected by administrating carvedilol (151) (Figure 6).

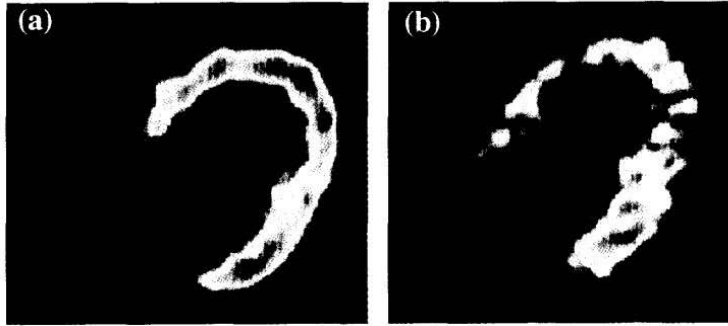


Fig 3. FDG-PET in the fasting state before and after 3 months of carvedilol therapy. (a) FDG uptake was enhanced throughout the left ventricle and (b) alleviated by carvedilol therapy.

Figure 6: Taken from Hirooka et al. (151). Hirooka K, Yasumura Y, Ishida Y, Komamura K, Hanatani A, Nakatani S, et al. Improvement in Cardiac Function and Free Fatty Acid Metabolism in a Case of Dilated Cardiomyopathy with Cd36 Deficiency. Jpn Circ J (2000) 64(9): 731-5. doi: <https://doi.org/10.1253/jcj.64.731>. License granted

The complementary situation, i.e., diminished free fatty oxidation, can be found in patients with CD36 deficiency. Nishimura demonstrated that subjects with CD36 deficiency and cardiomyopathy had low BMIPP

uptake. This defect could be corrected by the administration of CoQ₁₀ using a dose of 30mg/d for 35 days (152) (Figure 7).

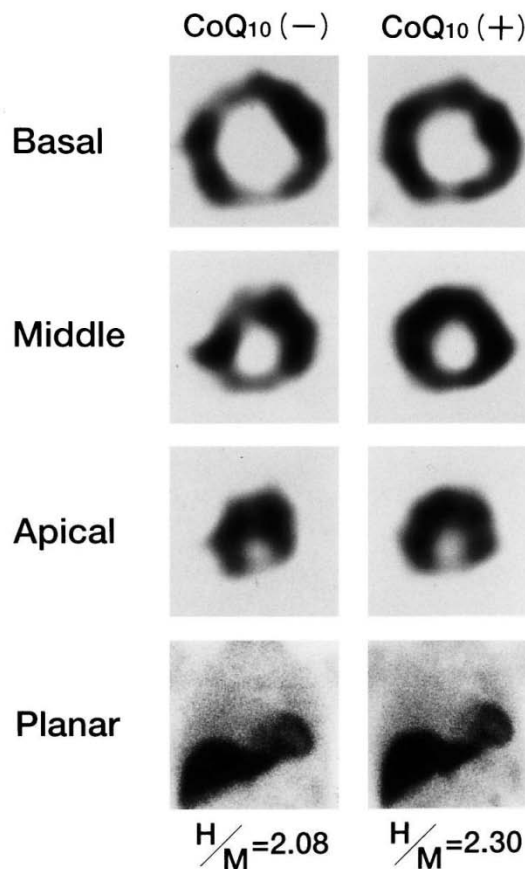


Fig. 2. ¹²³I-BMIPP myocardial SPET images before and after Q10 treatment in a representative patient (case 3) with idiopathic dilated cardiomyopathy

Figure 7: Taken from Kim et al.(152). Therapeutic Effect of Co-Enzyme Q10 on Idiopathic Dilated Cardiomyopathy: Assessment by Iodine-123 Labelled 15-(P-Iodophenyl)-3(R,S)- Methylpentadecanoic Acid Myocardial Single-Photon Emission Tomography. European journal of nuclear medicine (1997) 24(6): 629-34. Epub 1997/06/01. License CCBY. <https://doi.org/10.1007/bf00841400>.

The images presented above demonstrate the ability of Nuclear Medicine to reveal the metabolic situation of the heart. Besides the therapeutic use of CoQ₁₀, enalapril administration has also led to normalization of BMIPP defects. This supports the clinical value of enalapril in the treatment of patients with heart failure with reduced cardiac function (153). The data suggest that there is a restitution of normal oxidative phosphorylation (154-156).

Alba Timón-Gómez, and Antoni Barrientos have summarized data on changes of the functional status of mitochondrial Complex I from active to dormant under hypoxia (157). In addition to this the microRNA molecule miR-210 has been found to be involved in these changes.

Inhibition of NDUFS, NDUFA4, and NDUFA4L2 affect also Complex I and Complex IV (Figure 1 in (157)). NDUFS is the mitochondrial NADH-ubiquinone oxidoreductase 75 kDa subunit and NDUFA corresponds to NADH:ubiquinone oxidoreductase subunit A. Alterations of these molecules affect the function of Complex I.

The scientific literature contains scarce information about CoQ₁₀ and hypoxia in human disease. Hypoxemia is a recognized problem associated with congenital heart disease (158), and with viral infections (Figure 2 in (159), Figure 2 in (160)). The role of hypoxia in chronic kidney disease has been discussed by Wang et al., (161). Chen et al., depicted the progression of kidney disease linking hypoxia and fibrosis (Figure 4 in (162)). Hypoxia in the context of COVID-19 has been recently summarized by Østergaard in 2022 setting a focus on capillary changes (163).

The condition of chronic hypoxemia is associated with diminished cardiac function and low levels of ATP (164). Morita et al. described the beneficial effect of CoQ₁₀ in an experimental model of hypoxemia-reoxygenation injury done with heart tissue homogenates (164).

Recent studies on the rare disease Moyamoya have revealed some single possible similarities to the changes we have found in patients with thyroid disease. These findings include excessive collateral vessels and elevated VEGF levels (165), expression of HIF-1 and TGF-beta in the endothelium (166) as well as specific vascular changes (167). In 2022 Ma et al., described that the blood levels of CoQ₁₀ in this rare disease were significantly lower as compared to controls (168).

The selective evolution of mitochondrial diversity has been described as a central element for cell type-specific expression (Figure 1 in (169)). A recent statistical meta-analysis has added information on the polymorphisms of the hypoxia-inducible factor 1-alpha gene finding specific associations with different entities such as cardiovascular disease, skin disease, COPD, and complications of diabetes (170). Following

stabilization of HIF there is a downstream signaling activation in several organs (171). This finding tells us that hypoxia has different phenotypes.

g) *Clinical conditions and biochemical features associated with hypoxia*

Figure 8 shows our theoretical abstraction of biochemical processes arising from hypoxia where we place CoQ₁₀ deficiency as a key central element. In the following sections we will describe the biochemical changes associated with hypoxia such as the the low T3 syndrome and elevation of interleukin-6 (IL-6) levels.

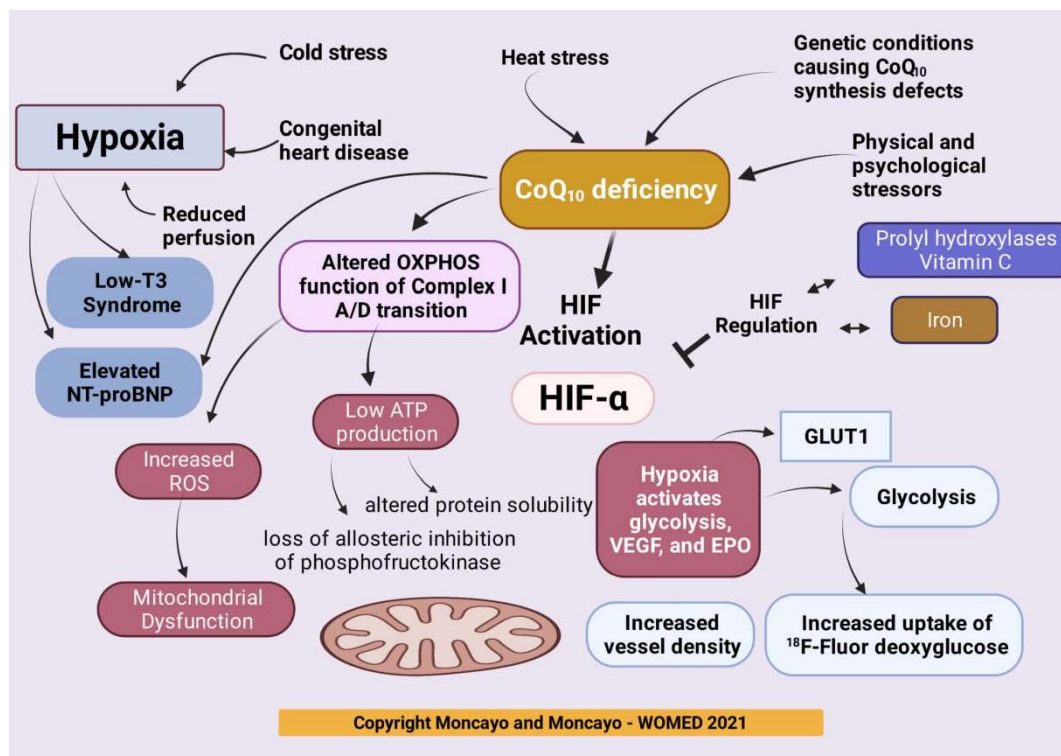


Figure 8: Biochemical pathways involved in hypoxia. Key elements include the initiation of glycolysis arising from diminished levels of CoQ_{10} together increased ROS production, low-T3 syndrome, and diminished ATP production. Glycolysis can be detected by Nuclear Medicine diagnostic imaging using ^{18}F -Fluor deoxyglucose. An equivalent image of glycolysis in the thyroid can be achieved by 3D power Doppler sonography. This method shows a condition of increased vascularity.

h) Hypoxia and the low T3 syndrome – a causal path?

The low T3 syndrome or euthyroid sick syndrome has been described by several authors as being associated with many different conditions. In 1974 decreased levels of total triiodothyronine were observed in patients with chronic liver disease, chronic obstructive lung disease, chronic renal failure, and intensive care situations. The authors attributed these changes to lower production of TRH following stress or undernutrition (172). A review on the euthyroid sick syndrome by Wartofsky and Burman published 1982 mentioned possible endocrine mechanisms behind this condition. In Table 2 they listed fasting, anorexia nervosa, and protein-calorie malnutrition as conditions that presented the low T3 situation. Many other factors related to the low T3 syndrome can be found in this review. One interesting postulate was that this condition is related to energy conservation by reducing catabolism (173).

In 1983 Vitek, Shatney, Lang, and Cowley studied the time relation between induction of hemorrhagic shock in dogs and changes in the level of thyroid hormones. They described lower levels of T3 and T4 after 20 minutes of shock. A similar situation was described in 3 patients with trauma or shock. The authors interpreted the changes as belonging to the euthyroid sick syndrome (174). In the late 1990s, several

investigators had observed changes of thyroid function parameters in relation to severe illness (172), systemic illness (173), and aging (175). This last study by Schroffner considered the low T3 syndrome to be quite frequent in different clinical conditions (175). The mechanisms leading to this condition were described as reduced activation of T4 (176), and as increased degradation of thyroid hormone in septic shock patients (177). In 1980, Moshang et al. reported that hypoxia affected thyroid function parameters (178). Also in 1980, Becker et al., described low levels of triiodothyronine in patients who had suffered thermal injuries (179). In 1990 Sawhney, and Malhotra had demonstrated that hypoxia was related to low levels of thyroid hormones (Figure 1 in (180)).

In 2001 Ross and Petros reviewed the euthyroid sick syndrome in pediatric cardiac patients including those treated at the intensive care unit (181). The authors discussed three potential settings in this situation: adaptive reduction of the metabolic rate, contributor to the disease, of simply due to the severity of illness (181). Table 2 included potential triggers, however hypoxia was not included.

In 2003 Iervasi et al. found that the low T3 syndrome had a prognostic relevance predicting fatal outcome in cardiac patients. The authors evaluated the data from 1058 patients seen at a National Council

Research Institute of Clinical Physiology in Pisa in 1999 (182). The authors expressed doubt as to whether changed thyroid metabolism had contributed to impairment of heart function.

In 2007 Adler and Wartofsky reviewed the euthyroid sick syndrome and considered it to represent an adaptation to several clinical conditions (183).

An important mechanistic finding relating thyroid hormone metabolism to hypoxia was described in 2008 by Simonides et al.. In their study HIF interacted with thyroid hormone deiodinases leading to the low T3 syndrome (184). Their study was based on a previous observation that transforming growth factor beta, a target for HIF, could promote thyroid hormone inactivation (185). This process resulted in lower levels of T3, which are the key feature of the low-T3 syndrome. Considering that deiodinases are selenoproteins (186, 187) and that our model of acquired mitochondrial dysfunction includes selenium deficiency (10, 11), we must add that selenium deficiency must be quite severe to affect the deiodinase system (188). The study by Fraczek-Jucha et al., demonstrated that selenium deficiency does not correlate with the low T3 condition. Their study found a significant association between low T3 and elevated NT-proBNP levels (Table 2 in (189)). Elevated levels of NT-proBNP correlate with diminished dysfunction of the left ventricle in cardiac disease patients (190).

The low T3 syndrome has been found to show an inverse correlation with coronary artery disease (191) as well as with elevated blood levels of NT-proBNP (192, 193).

Bolen et al., described an association of low T3 syndrome with elevated levels of IL-6 (194). In a clinical study with patients that had presented an acute coronary syndrome, Brozaitiene et al., found an association between mortality and low T3 levels as well as with elevated values of NT-proBNP (195). Minai analyzed the data from 625 heart failure patients in 2021 and found that low T3 and NT-proBNP showed an inverse correlation (196).

Many publications hypothesize that changes leading to the low T3 syndrome arise from the thyroid (Figure 1 in (197)) or from the heart in patients with heart disease (Figure 5 in (198)). The incidence of the low T3 syndrome in patients with congestive heart failure has been called "unexpectedly high" (199).

Bieglmeyer et al., reported that low T3 levels are prevalent among non-critically ill patients and that they are predictive of 30-day hospital mortality (200). Cerillo added an observation as to the relation between low T3 and decreased cardiac output in patients scheduled for coronary bypass surgery (201). Abdu et al. reported a higher incidence of cardiac events in patients with MINOCA (Figure 1 in) (202).

A review published by Langouche, Jacobs, and Van den Berghe in 2019 described the appearance of

the nonthyroidal illness syndrome across all ages. The authors added a comment as to the still unknown causality of the disease (203).

i) *Sepsis and critical illness*

Several investigations on the metabolism of sepsis by L'Her, and Sebert have described an environment of altered mitochondrial function where oxygen utilization and Complex I function are affected (204, 205) stating: "Energy- metabolism disturbances during sepsis are characterized by enhanced glycolytic fluxes and reduced mitochondrial respiration. However, it is not known whether these abnormalities are the result of a specific mitochondrial alteration, decreased pyruvate dehydrogenase (PDH) complex activity, depletion of ubiquinone (CoQ₁₀; electron donor for the mitochondrial complex III), or all 3".

Low levels of CoQ₁₀ have been described in patients with sepsis (123). He et al., conducted a study on pediatric sepsis evaluating levels of CoQ₁₀ as well as the activity of Complex I and III. They found that low levels of these parameters were associated with mortality in children affected by sepsis (206).

Vassiliou et al., reported that septic patients in a critical condition had low levels of CoQ₁₀ (207). Coppadoro et al., described that low levels of CoQ₁₀ are found in a broad range of critically ill patients (124).

Abitagaoglu et al., reported carried out an experimental study on the effect of CoQ₁₀ administration in sepsis. They found that multi-organ involvement of the heart, kidney, and spleen, was decreased under this treatment (208). Soltani et al., carried out a clinical study on the effect of CoQ₁₀ in sepsis and found a positive effect on clinical parameters and mitochondrial function (209). In 2001 Fink advanced the notion of cytopathic hypoxia as a mechanism of disease (210). In 2002 Brealey et al., discussed the association between outcome of septic shock and mitochondrial dysfunction (211). Cornu et al., evaluated the prognostic value of low T3 syndrome in patients with septic shock and found an association with high mortality (212).

j) *Energetics and physical exercise: nutritional theories vs. ¹⁸F-FDG imaging*

Several publications dealing with nutritional theories and energetics have a common element, i.e., the so-called reference man. The original publication on the reference man from 1974 (ICRP 23) corresponds to a description of the chemical composition of the body, the mass of the organs, as well as to data on physiology (213). This publication originated from the need to respond to concerns about the medical effects of ionizing radiation. The International Commission on Radiological Protection was founded in 1928 at the second International Congress of Radiology (ICRP). It is obvious, that energy intake analysis was not the primary worry of the ICRP. Section B of the publication deals with Energy Expenditure stating that food and oxygen

are used according to energy requirements. Oxygen was described together with the process of combustion. Section B7 described energy requirement arising during pregnancy and lactation showing that these conditions require a higher level of energy. The ICRP 23 publication was followed by ICRP 89 in 2002 which was again dedicated to workers dealing with radiation protection (214).

The concept of energetics in the field of ecology does not include biochemical parameters in relation to function (Figure 1 in (215)). In the field of life history research, the economics model discussed by Pontzer and McGrosky mentions metabolic energy as being involved, however the publication contains no evidence as to how energy can be generated in the mitochondria (216). One important aspect included in Life History Theory is that of trade-off between survival and reproduction (217) as well as resource allocation (218). An example of this philosophy can be taken from Jasieńska, who described suppressed ovarian function in relation to physical work (219). This concept is closer to general physiology since it considers at least 2 bodily functions while conventional medical physiology picks out single players, e.g., the heart, the thyroid, or human reproduction. It should be noted that classical research on resilience also lacks the inclusion of basic biochemical processes (220, 221).

Energetics changes occurring during lactation have been described since decades. Bauman and Currie discussed a process of nutrient partitioning in 1980 (222). Mowry et al. described metabolic changes aimed at increasing mitochondrial efficiency in relation

to reproduction (223). Energetics and fatigue in sports have been described as being related to brain and body functions (224). The theory launched by St. Clair Gibson, Swart, and Tucker has little connection to biochemistry. Their model idealizes a competitive homeostasis system that involves psychological and physiological elements without mentioning mitochondrial function.

Lavin et al., discussed the spectrum of adaptations to exercise at a molecular level putting the item physiological resilience on top (Figure 3 in (225)). Their definition of resilience states “resilience (i.e., ability to tolerate and recover from stressors)” (Page 11 in (225)).

In a previous publication we launched a concept of shared resources as being the central event related to health and disease. When the level of resources is sufficient, survival is assured resulting in resilience. Unbalanced levels of resources are connected to disease (Figure 12 in (1)). Elements of organ function as well as the so-called psychosomatic components of life can be traced down to specific biochemical parameters where magnesium deficiency plays a central role (9).

Mitochondrial function and the generation of ATP via oxidative phosphorylation constitute a central biochemical element in physiology. This function was summarily described by Brand, Orr, Perevoshchikova, and Quinlan in 2013 (226) stating that ATP generation results from the energy release after nutrients have been oxidated (Box 1).

The classic role of mitochondria is oxidative phosphorylation, which generates ATP by utilizing the energy released during the oxidation of the food we eat. ATP is used in turn as the primary energy source for most biochemical and physiological processes, such as growth, movement and homeostasis.

Box 1: Role of oxidative phosphorylation in relation to food. Adapted from (226)

The topic of mitochondrial adaptation to nutrient availability was addressed by Liesa and Shirihai in 2013 (227). In 2022 Kyriazis et al., described processes of mitochondrial adaptation to changes in diet (Figure 5 in (228)). The simplistic idea that dietary evaluations and simple calory counting reflect the level of energetics in the body contradict this physiological principle. Anorexia nervosa represents a condition of severe nutritional alteration. It has been included in the list of diseases associated with low-T3 syndrome (173). Niklowitz et al., described signs of CoQ₁₀ depletion in patients with anorexia nervosa (229).

A similar situation can be found in the setting of physical exercise. Loucks and Callister published a study that combined energy cost and exercise intensity in 1993 (230). They showed that the low T3 condition occurred in amenorrhoeic women under energy limitation. They concluded that exercise could have

compromised energy availability. Low energy availability is a term used frequently in relation with physical exercise. Slater, Brown, McLay-Cooke, and Black evaluated this aspect in exercising subjects (231). Loucks discussed the role of energy availability in relation to reproductive disruption in 2003 (232).

In the field of sports physiology, the term “Relative Energy Deficiency in Sport (RED- S)” is being used currently. A recent review on this topic published by Cabre et al. in 2022 insisted on the concept of energy availability in terms of kcal/kg (Figure 1 in (233)). The publication does not include any biochemical data as to how the body can use this apparent energy supply (Table 2 in (233)). This simplified model contrasts sharply with the biochemical adaptation of mitochondrial respiration responding to energetic needs and nutrient availability as described by Bennett, Latorre-Muro, and Puigserver (Figure 2 in (234)). We have taken the

following statement from Box 3 to reinforce our hypothesis:

Mitochondrial respiratory chain activity is required for normal function in tissues with high energy demand such as brain, heart and skeletal muscle. Diseases caused by underlying mitochondrial dysfunction often affect these organ systems.

Following our line of thought on hypoxia we would like to add data related to exercise. Exercising subjects can develop hypoxemia (235, 236) and physical activity can lead to HIF activation in skeletal muscle (237). Experimental hypoxia in skeletal muscle of rabbits is accompanied by a reduction of the levels of ubiquinone (130). A decrease of the CoQ₁₀ levels is

seen together with diminished ATP levels in isolated rabbit ventricles under hypoxia (Table 2 in (131)). Metabolic changes related to exercise can be seen with diagnostic ¹⁸F-FDG imaging. Nakase et al., demonstrated focal uptake in football players (238) (Figure 9).

Whole Body Muscle Activity during the FIFA 11+

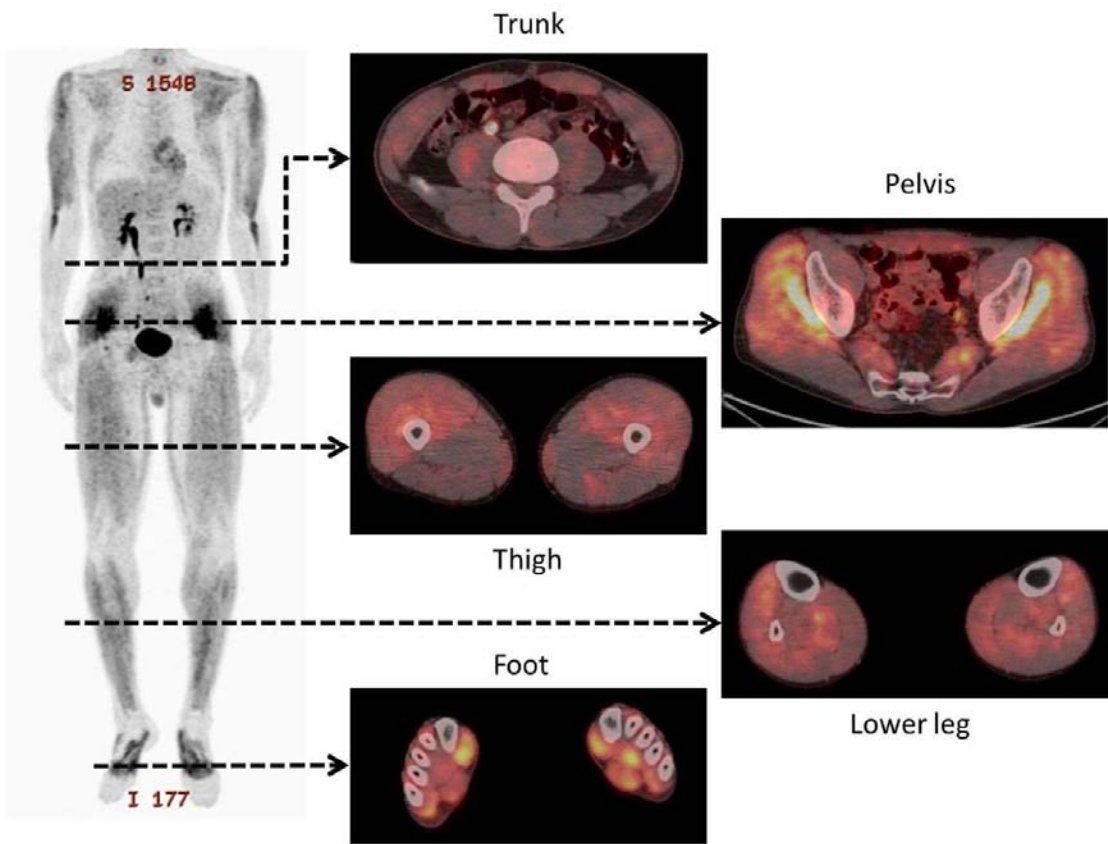


Figure 2. Representative whole-body positron emission tomography images after performance of the 11+ by patients in the exercise group.
doi:10.1371/journal.pone.0073898.g002

Figure 9: Taken from Nakase J, Inaki A, Mochizuki T, Toratani T, Kosaka M, Ohashi Y, et al. Whole Body Muscle Activity During the Fifa 11+ Program Evaluated by Positron Emission Tomography. *PLoS One* (2013) 8(9):e73898. Epub 2013/09/26. doi: <https://doi.org/10.1371/journal.pone.0073898>. License: Creative Commons Attribution License

Tracer uptake can be more intense according to the intensity of exercise such as weightlifting as shown by Yoshimizu et al., in 2022 (239). Not only the muscle involved in weightlifting but also the heart showed intense tracer uptake (figure 10) revealing the systemic dimension of exercise.

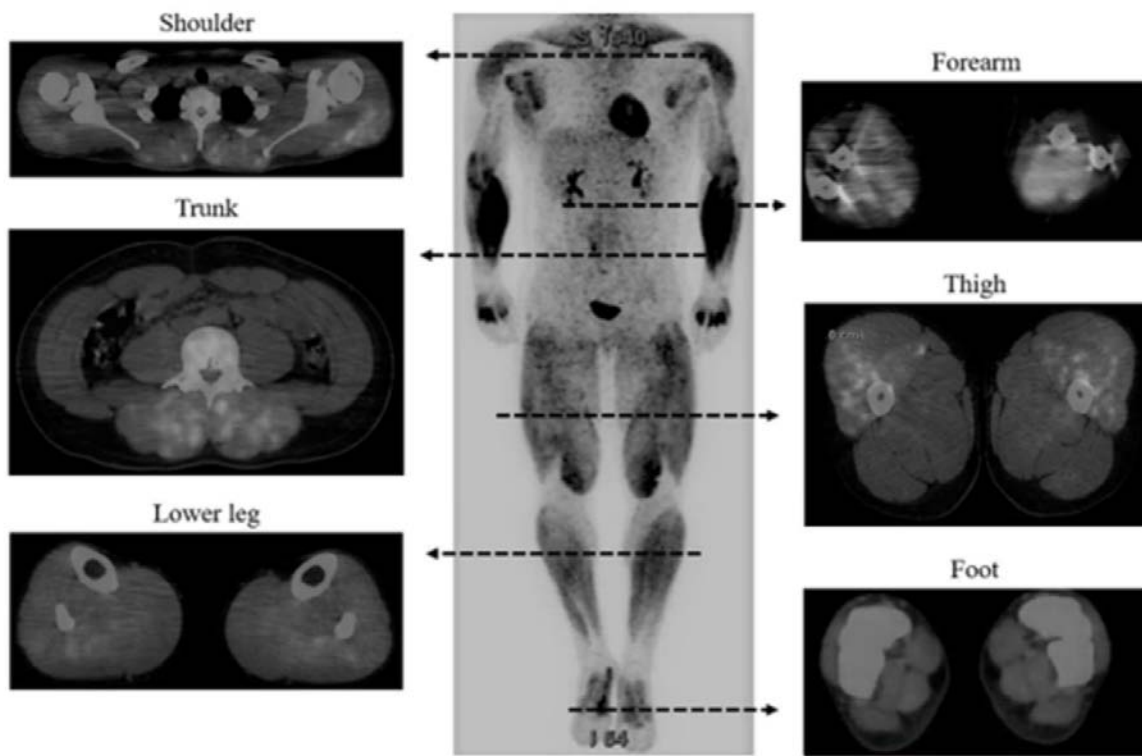


Figure 2

Representative whole-body PET images after performance of HPC

Representative whole-body PET images of the HPC group are shown. SUVs were significantly increased in 29 of 71 skeletal muscles in the whole body. PET; positron emission tomography, HPC; hang power clean

Figure 10: Taken from Yoshimizu R. Whole Body Muscle Activity During Weightlifting Exercise Evaluated by Positron Emission Tomography (2022). Available from: <https://www.researchsquare.com/article/rs-612816/v2>. License: CC BY 4.0

k) COVID-19: the low T3 syndrome, IL-6, and ¹⁸F-FDG imaging

Zou et al., evaluated the data from 149 COVID-19 patients in 2020 looking for the characteristics of the low T3 syndrome, which was indeed found in forty-one cases. Disease severity and parameters of inflammation were significantly associated with the changes of thyroid parameters (240). The low T3 syndrome is an indicator of poor prognosis and mortality in COVID-19 patients (241). The low T3 syndrome together with elevated levels of NT-proBNP are indicators of poor outcome (242).

Leyfman et al. discussed an interaction of IL-6 and hypoxia in COVID-19 patients. They postulated an interaction between viruses and different organs which led to IL-6 elevation (Figure 1 in (243)). In this depiction, hypoxia appears as an isolated element. This idea of disease can be found in many publications, e.g., (the graphical abstract in (112)), (Figure 1 in (244)).

COVID infection is related to glycolysis (245), therefore diagnostic imaging with ¹⁸F-FDG should demonstrate organs affected by hypoxia. The characterization of persisting symptoms of long-COVID has been recently demonstrated by Kiatkittikul et al., (246). The image panel shows a variety of ¹⁸F-FDG uptake patterns (Figure 10) including skeletal muscles, heart, vessels, and the lung. We interpret these changes as being related to hypoxia and consequently highly suggestive of CoQ₁₀ deficiency and altered mitochondrial function.

Fig. 1 Maximal intensity projection F-18 FDG PET images of patients with post-acute COVID-19. (a) Case 1: diffuse hypermetabolism of the skeletal muscle throughout the body (arrow). (b) Case 7: multiple hypermetabolism at respiratory muscle (arrow) and quadratus lumborum muscle (dot arrow) with hypermetabolic node at right hilar region (arrow head). (c) Case 2: diffuse hypermetabolism along the vascular wall throughout the body. (d) Case 4 with bacterial pneumonia: focal hypermetabolism along the vascular walls of bilateral popliteal vessels (arrow) with focal hypermetabolism in the right lung (arrowhead) and diffuse bone marrow and splenic uptake. (e) Case 13 with psoriasis exacerbation: multiple hypermetabolic skin lesions (arrow). Abbreviation: FDG fluorodeoxyglucose, PET positron emission tomography, COVID-19 coronavirus disease 2019

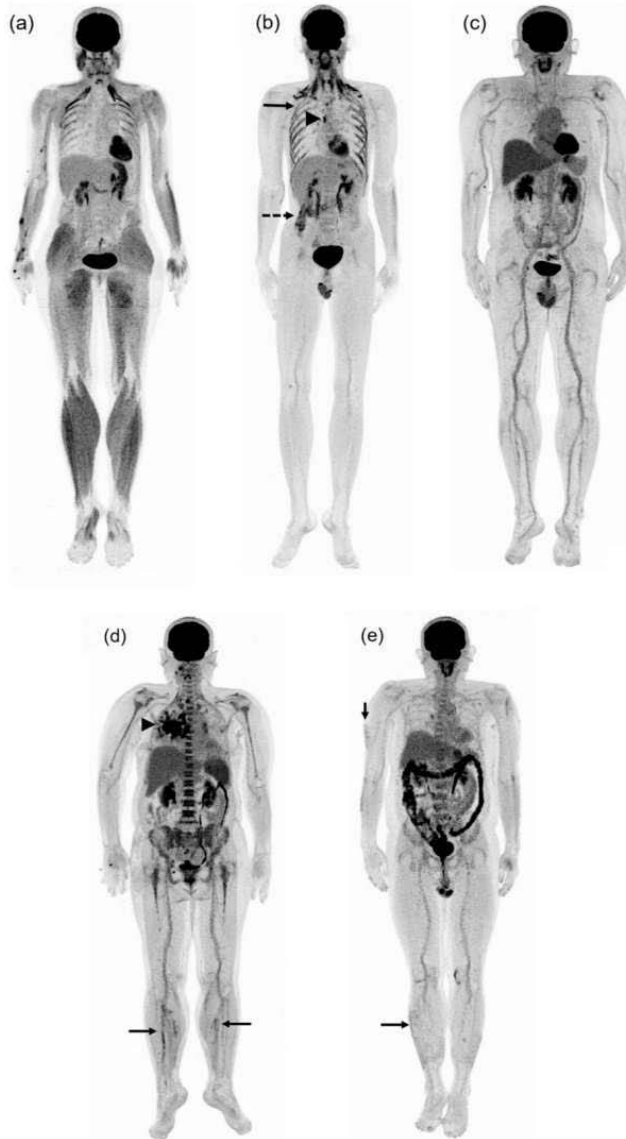


Figure 10: Taken from Kiatkittikul P, Promteangtrong C, Kunawudhi A, Siripongsatian D, Siripongboonsitti T, Ruckpanich P, et al. Abnormality Pattern of F-18 Fdg Pet Whole Body with Functional Mri Brain in Post-Acute Covid-19. *Nucl Med Mol Imaging* (2022) 56(1): 29-41. Epub 20220115. doi: <https://doi.org/10.1007/s13139-021-00730-6>. License granted.

A recent case report on hypoxia in COVID-19 infection was delivered by Serbanescu-Kele et al., in 2022 (247). The publication presented the decreasing course of oxygen saturation during hospital treatment. Quite unfortunately the authors utilized the term “happy hypoxaemia” ignoring the fatal outcome for the patient. Figure 1B of this publication showed the macroscopic appearance of a dark arterial blood sample which to our clinical understanding did not look happy at all (247).

The term happy hypoxia in relation to COVID-19 disease was used by Jennifer Couzin-Frankel in 2020 referring to the clinical experiences of Reuben Jesse Strayer, an emergency physician working at the Maimonides Medical Center, New York (248). It is quite

important to know that the Jennifer Couzin-Frankel has a major in history of science, but no medical education and works as a staff writer for Science. Her article was not peer-reviewed and contained no scientific references. The original publication by Strayer on hypoxia and COVID-19 patients (249) was not cited. The original authors acknowledged that by 2020 little was known about the pathophysiology of COVID-19 disease. It is our personal feeling that this misleading and erroneous term should be banned from the literature.

A recent study of the UK Biobank, published 19 January 2023, found that cardiovascular disease and mortality were associated with long term COVID-19 disease. The authors could not identify conclusively any

mechanism involved and simply provided a rather general and disappointing recommendation for ongoing clinical monitoring (250). Affected patients need indeed monitoring, however treatment implementation should be added since it has a higher ethical priority.

In 2022 Hansen et al., published an industry-backed study (Pharma Nord) that evaluated a high dose therapy with CoQ₁₀ in patients presenting a post COVID condition. A sound and scientific rationale for choosing the dose of 500mg CoQ₁₀ was not given (251). Initial and final CoQ₁₀ levels in the patients were not evaluated. The duration of CoQ₁₀ administration was quite short (6 weeks). In our experience, the combined supplementation with magnesium, selenium, and CoQ₁₀ starts to show recovery results after 9-12 months. Full recovery of the thyroid requires two to three years. Our recommended dose for CoQ₁₀ supplementation is 0.9mg/kg, i.e., app. 60mg/d.

l) Heat stress and cardiac disease – a pathogenesis proposal

Recently two publications have looked at the relationship between cardiac disease and heat stress. Ranek et al., described changes of heat shock proteins in heart failure, pointing towards the increased expression of hsp70, hsp90 and BAG-3 (252). In 2012 Iguchi et al., looked at cardiovascular and hormonal changes following heat stress produced by sitting in a heat stress chamber for 30 minutes at 73°C (253). They demonstrated that this stimulus had an elevation of hsp72 and prolactin. The increase in prolactin levels seemed related to the endurance capacity in response to exercise under heat conditions (254). Heat exposure and muscular activity can also affect blood magnesium levels inducing a severe decrease to sub-optimal levels (255).

Given these concepts, we can state that Ritossa observed the effects of an external heat source which led to the heat shock and the unfolded protein reactions. A modern view of heat shock response includes more toxic elements besides heat exposure. Trautinger provided the following description: “All organisms respond to sudden environmental changes with the increased transcription of genes belonging to the family of heat shock proteins (hsps). Hsp-inducing stress factors include elevated temperatures, alcohol, heavy metals, oxidants, and agents leading to protein denaturation. The induction of heat shock proteins is followed by a transient state of increased resistance to further stress, and the heat shock response is generally thought to represent an evolutionary conserved adaptive mechanism to cope with hostile environmental conditions” (256). Current knowledge of the complex processes involved in the hsp response describes essential interactions with ATP in the case of ATP-dependent hsp chaperones (257, 258). Alteration in

protein structure will also involve the repair mechanisms of the unfolded protein response (259).

Heat stress has been investigated under clinical conditions. Bouchama, from Saudia Arabia, has published a series of studies dealing with heatstroke in humans. In 1995 a historical review on heatstroke included a discussion on the potential role of endotoxins in the disease (260). Recently the effects of acute, supra-physiological temperature stress have been examined at the transcriptome level. The test subjects were exposed to a mean temperature of 75°C in a sauna. The analysis of blood mononuclear gene expression revealed several patterns of change (Figure 2 in (261)). One key finding referred to altered mitochondrial function involving several complexes of the OXPHOS chain, including Complex I. Both electron transfer, as well as ATP production, were repressed. Bouchama et al., also identified an alteration of cytochrome C oxidase, corresponding to Complex IV (262). Both Complex I and Complex IV depend on iron-sulfur clusters for their function. Situations of physical exertion in hot environments with temperatures up to 41.5°C can be found in sports activities (263). Elevated temperature as a source of stress is not only limited to sports. It can also affect everyday activities (264). Furthermore, these changes are like those seen in heart failure, where the function of the OXPHOS chain is altered due to changes in Complex I and V (265). As a whole, ATP production can be disturbed (266). It must be kept in mind that the heat stress response requires sufficient ATP since some hsp are ATP-dependent (258). Experimental repeated exposure to heat stress can negatively affect the heat shock response of the heart (267). The increase of hsp70 levels after heat stress appears to decline with time, thus increasing the susceptibility of the heart to damage (268). This propensity to a myocardial injury can be corrected by CoQ₁₀, resulting in higher hsp70 levels (128). In a similar study, the use of the selenium analog ebselen, resulted in improved expression of hsp70, which was associated with reduced myocardial infarct size (269).

Experimental work by Liedtke and Hughes in 1976 showed the detrimental effect of hyperthermia on cardiac specimens producing functional impairment together with increased glycolysis and lower ATP levels. The authors described the results as an additional energy drain to the heart (270). In 1989 Huang and Liedtke described the metabolic situation in re-perfused myocardium as being unable to synthesize ATP due to an inefficient electron transport and OXPHOS (271).

In a recent epidemiological analysis, Wang et al. described an association between previous heat stress situations and heart and kidney disease (272). Mechanisms leading to these changes were not discussed; however, these observations imply that heat exposure had left an altered biochemical system behind. Nzvere et al., have reached similar conclusions in

evaluating the long-term consequences of heatstroke on cardiac disease (273).

Heat stress is also a serious condition in human medicine (274). Heat stress per-se stimulates the production of mitochondrial superoxide (275). The administration of dietary CoQ₁₀ can attenuate oxidative changes produced by heat shock in chickens (276). A similar protection can be observed through administration of 300mg CoQ₁₀ prior to heat exposure in elite swimmers (277). The production of mitochondrial small heat-shock protein (1mw Hsp) protects electron transport from CI to CIV (278). The authors declared that ubiquinone is the most thermo-labile protein in Complex I.

We have included this description keeping in mind the condition of postpartum cardiomyopathy (279) as studied by Cénac 30 years ago where the central deficiency was low selenium (280). Due to birth customs in Nigeria these women are exposed to extreme heat stress in the postpartum period. Experimental data on heat stress effects on the chicken heart has shown that these deleterious effects can be modulated by CoQ₁₀ (281). An indirect hint on prolonged cardiac dysfunction following heatstroke was published by Zahger, Moses and Weiss in 1989 (282). A description of the characteristics of heat stroke and cardiac dysfunction published by Marchand and Gin were centered on thermoregulation and heat dissipation (Figure 1 in (283)). Other authors have found a relation between biomarkers and mortality after exertional heat stress where fatal cases had higher levels of NT-proBNP (284). A current view on heatstroke which does not consider the role of CoQ₁₀ was published by Bouchama (285).

II. DISCUSSION AND OUTLOOK

Our clinically oriented literature review has disclosed that benign thyroid disease and several other entities including notable heart disease and COVID-19 share common features such as the symptom fatigue, and the events of hypoxia and glycolysis, elevated IL-6 levels, and the low T3 syndrome. We propose that CoQ₁₀ deficiency plays a fundamental role in these diseases affecting the functionality of Complex I of the mitochondrial respiratory chain. The following Table contains an approximation to this process.

1. Initiation of glycolysis resulting from stabilization of HIF-1 α (4). Interactions with CoQ₁₀ and iron.
2. Increased production of reactive oxygen species follows functional alteration of respiratory Complex I (286)
3. Altered OXPHOS lead to reduced ATP production (287)
4. In situations of lack of oxygen – hypoxia - Complex I can be modified to a deactive state (288)
5. Experimental function loss of Complex I goes along glycolysis and with ¹⁸F-FDG uptake (289)

We have briefly reviewed the role of diagnostic imaging keeping our eyes on glycolysis as demonstrated by ¹⁸F-FDG scans, and on fatty acid uptake based on the use of iodine-labeled methyl iodophenyl-pentadecanoic acid (BMIPP) (28). The clinical rationale for imaging these metabolic paths has been summarized by Yoshinaga et al. in 2007 (290). Contrasting with this structured description we must refer to a study by Dilsizian et al. where ideas about the interpretation of BMIPP scans were given. The conclusions offered by the authors had no profound biochemical foundation (291). What is useful in this publication is Figure 2 where a comparison between a heart perfusion and heart BMIPP study is shown. This image clearly shows that perfusion does not reveal metabolic changes (Figure 11).

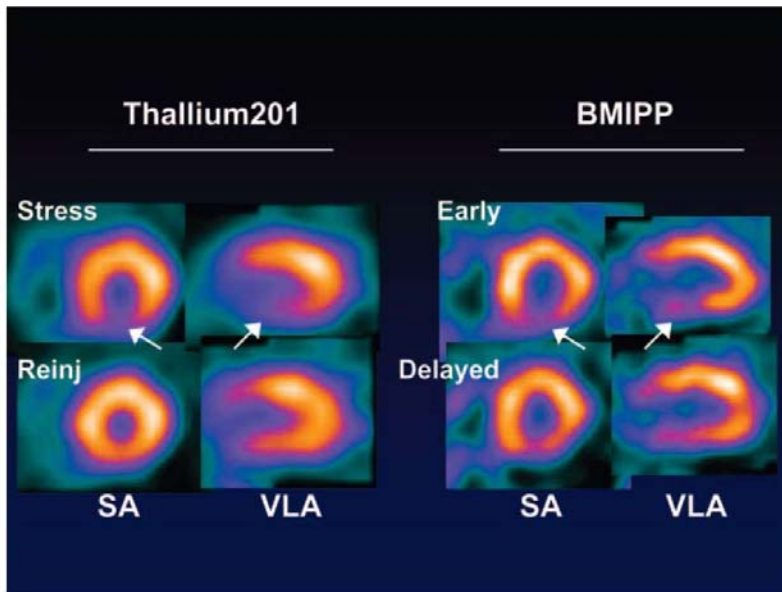


Figure 2. Left, Thallium-201 stress and reinjection (Reinj) images after treadmill exercise in the short-axis (SA) and vertical long-axis (VLA) SPECT tomograms (left). Thallium images demonstrate a severe reversible inferior defect (arrows), consistent with exercise stress-induced ischemia. Right, A similar defect is seen on the early BMIPP images in the same tomographic cuts (arrows), with BMIPP injected 22 hours after the stress-induced ischemia. The defect on the delayed BMIPP image is less prominent than on the early image. These image data suggest that BMIPP detects prolonged postischemic suppression of fatty acid metabolism for up to 22 hours after stress-induced ischemia.

Figure 11: Taken from Dilsizian V, Bateman TM, Bergmann SR, Des Prez R, Magram MY, Goodbody AE, et al. Metabolic Imaging with B-Methyl-P-[(123)I]-Iodophenyl-Pentadecanoic Acid Identifies Ischemic Memory after Demand Ischemia. *Circulation* (2005) 112(14): 2169-74. Epub 2005/09/28. doi: <https://doi.org/10.1161/circulationaha.104.530428>. License granted.

An interesting observation on altered mitochondrial function can be taken from studies dealing with cardiac disease and the influence of cardiac surgery in restoring fatty acid metabolism. Morishima et al. found persistent alteration of fatty acid metabolism in patients with atherosclerotic changes even though the surgical intervention had resolved the

ischemic condition (292). Our interpretation of persistent glucose utilization is that such patients present persistent, unrecognized, CoQ₁₀ deficiency.

In 2014 Yoshinaga referring to the mystical-magical term of ischemic “memory brought” stated the following (293):

Metabolic imaging has been used to detect the footprint left by previous ischaemic episodes evident due to delayed recovery of myocardial metabolism (persistent dominant glucose utilization with suppression of fatty acid oxidation).

The following graphical allegory describes the medical setting relating hypoxia and cardiac disease. Superficial research has not considered biochemical changes sufficiently. Adding the biochemical background one can see that there are many more components to be explored. It is evident that keeping an eye only on the flow or on the uptake of ¹⁸F-FDG will not open a perception for fatty acid uptake. The following graphical allegory about the swimmer and the diver illustrates this situation (Figure 12).



A

Superficial view of the situation as seen by a skin diver, i.e., looking only at myocardial perfusion studies.



B

Deep view of the situation as seen by a scuba diver. A profound look will find hypoxia activation after CoQ₁₀ deficiency and hypoxia-related changes such as elevated IL-6, low T3 syndrome.

Figure 12: A. Graphical allegory - Myocardial perfusion studies correspond to the left image of the superficial snorkeling diver who sees nothing but flow. B. The lower panel shows the option to go deeper into the process by using additional gear signaled by the self-contained underwater breathing apparatus (SCUBA). This second image represents biochemical elements as described throughout the text. The images were taken from WikiCommons.

Additional data on the information delivered by BMIPP as compared to FDG can be found in publications authored by Yoshinaga (294). Yamagishi et al., summarized the impact of BMIPP and FDG diagnostic imaging going well beyond perfusion (Table 29 in (295)).

Looking beyond organ-related disease, the transmission of intergenerational trauma is a process that is also related to hypoxia and mitochondrial dysfunction (296).

Figure 13 illustrates our proposal on the essential biochemistry of resilience that maintains health.

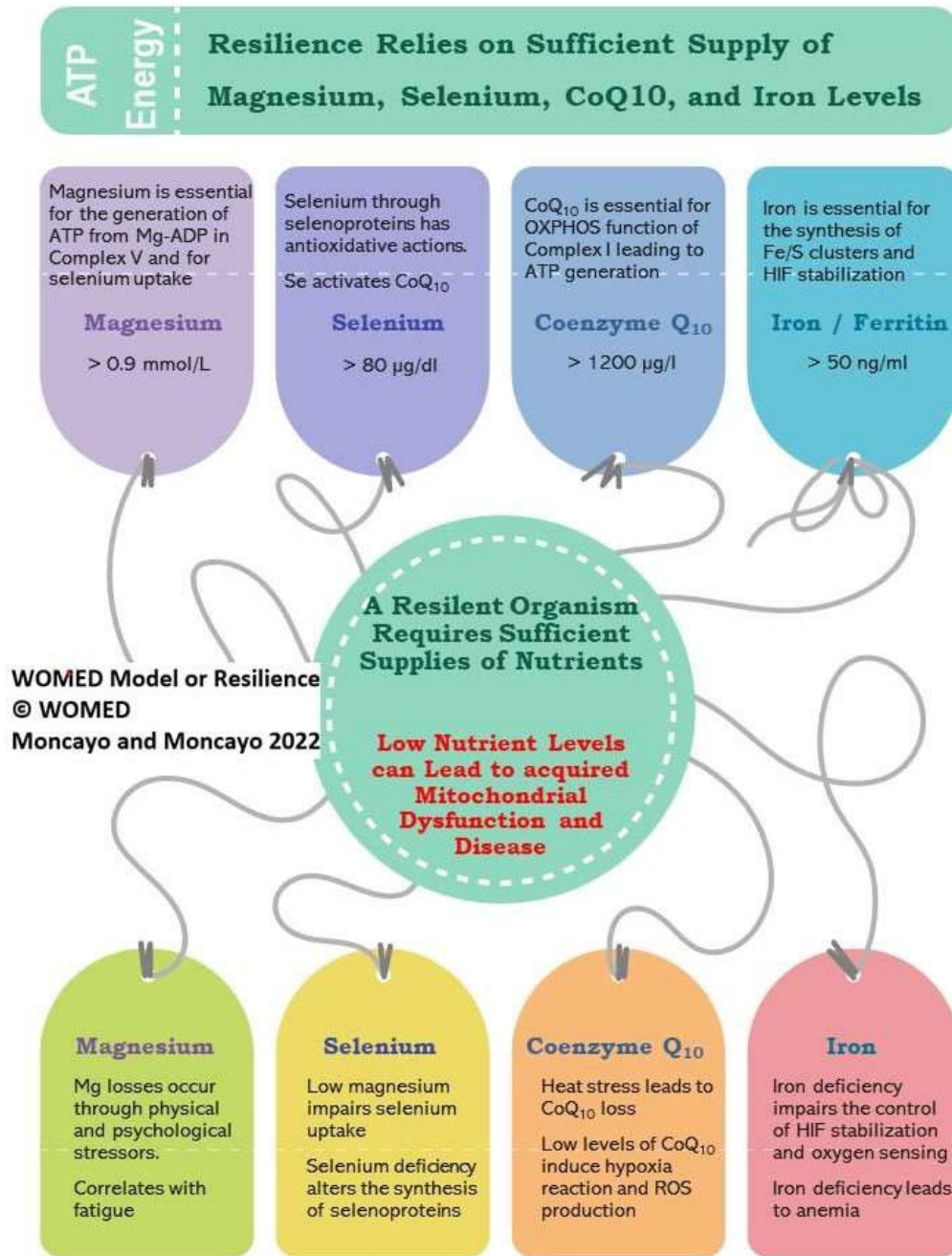


Figure 13: The 2022 WOMED concept of resilience and health based on essential biochemical parameters.

Figure 14 illustrates our model of cardiac disease based on the information reviewed here. The model can be applied to other clinical conditions related to hypoxia.

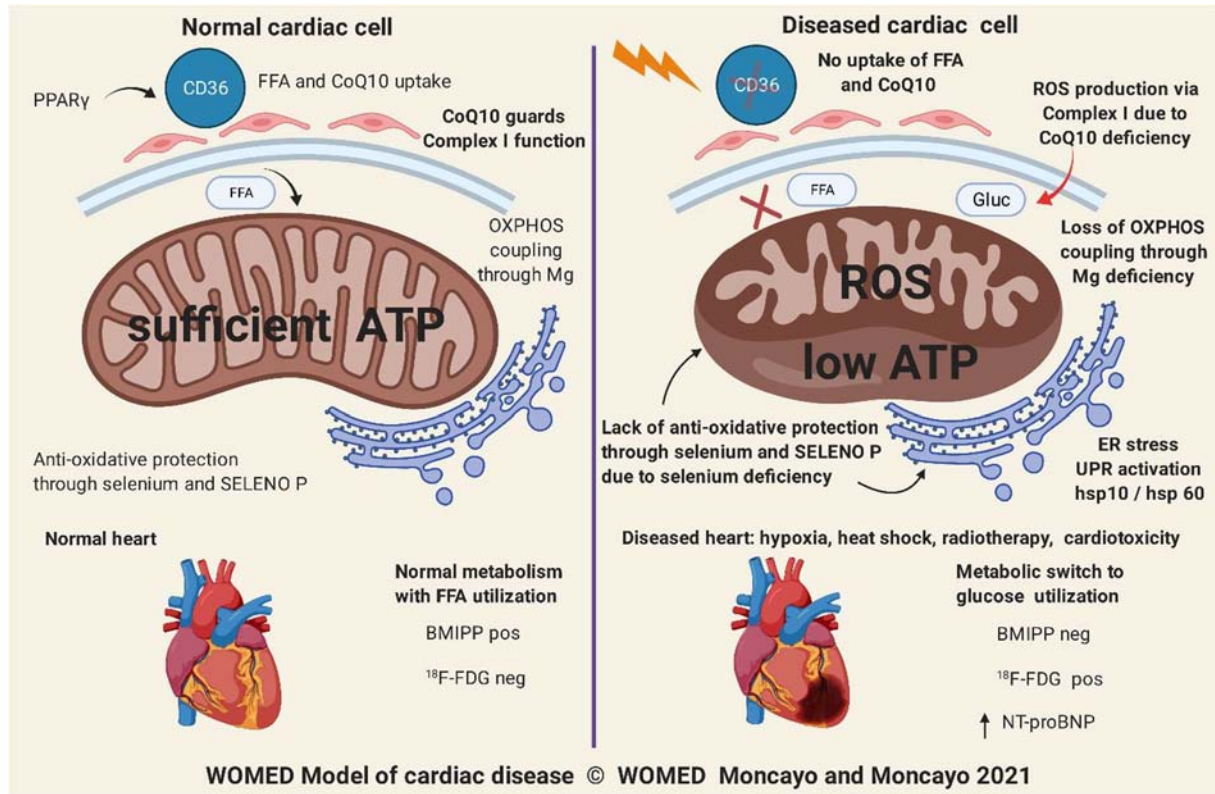


Figure 14: The 2021 WOMED model of cardiac disease

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Supplemental information

A simplified clinical description of the symptoms of hypoxia has been published by the Cleveland Clinic.

Hypoxia: Causes, Symptoms, Tests, Diagnosis & Treatment (clevelandclinic.org)

An overview of causes and diseases related to hypoxia authored by Rhiannon Brett can be found in the Calgary Guide to Understanding Disease.

Hypoxemia: Pathogenesis and clinical findings | Calgary Guide (ucalgary.ca)



GLOBAL JOURNAL OF MEDICAL RESEARCH: K
INTERDISCIPLINARY
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Anthropometric Indicators as Predictors of Adiposity and Cardiometabolic Diseases

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Abstract- Objective: To evaluate the ability of anthropometric indicators to identify adiposity and metabolic syndrome (MS) in patients with arterial hypertension (AH).

Materials and Methods: Cross-sectional study with patients of both sexes, age ≥ 20 years, with AH and overweight, and in outpatient care. Lifestyle, clinical, and anthropometric data were collected, and the following indicators were calculated: body mass index, waist-to-height ratio (WHtR), and conicity index (CI).

Results: A total of 181 patients (53.3 ± 12.6 years) participated. There was a predominance of women (69.6%), adults (69.1%), patients with obesity (81.2%) and sedentary lifestyle (79.0%).

Keywords: obesity. overweight. abdominal adiposity. Anthropometric indicators. waist circumference. waist-to-height ratio. conicity index. cardiometabolic diseases. metabolic syndrome. arterial hypertension.

GJMR-K Classification: DDC Code: 574.192 LCC Code: QP514.2



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Anthropometric Indicators as Predictors of Adiposity and Cardiometabolic Diseases

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Abstract- Objective: To evaluate the ability of anthropometric indicators to identify adiposity and metabolic syndrome (MS) in patients with arterial hypertension (AH).

Materials and Methods: Cross-sectional study with patients of both sexes, age ≥ 20 years, with AH and overweight, and in outpatient care. Lifestyle, clinical, and anthropometric data were collected, and the following indicators were calculated: body mass index, waist-to-height ratio (WHtR), and conicity index (CI).

Results: A total of 181 patients (53.3 ± 12.6 years) participated. There was a predominance of women (69.6%), adults (69.1%), patients with obesity (81.2%) and sedentary lifestyle (79.0%). Waist circumference (WC) was a good discriminator of adiposity in women (AUC 0.91; 95%CI 0.85-0.95; $p < 0.001$) and men (AUC 0.92; 95%CI 0.82-0.98; $p < 0.001$), and the best discriminator in the elderly. The CI was the best indicator and more specific in determining MS in women, differing from men, observing better results with WC.

Conclusion: Adiposity was best discriminated by WC and WHtR in patients with AH and overweight, and the indicators suggested in predicting MS were WC and CI.

Keywords: obesity. overweight. abdominal adiposity. Anthropometric indicators. waist circumference. waist-to-height ratio. conicity index. cardiometabolic diseases. metabolic syndrome. arterial hypertension.

1. INTRODUCTION

In recent decades there has been an increase in chronic non-communicable diseases (CNCDs), such as cardiovascular diseases (CVD), cancer, diabetes, and chronic respiratory diseases, being the leading causes of death today, responsible for just over 70% of deaths worldwide. Among the main risk factors, these share behaviors that can be modifiable, such as tobacco use, physical inactivity, poor diet, and harmful alcohol consumption, which in turn contribute to overweight, increased blood pressure, altered plasma

lipids, and, finally, diseases (1). Moreover, CVD is the leading cause of death in Brazil and worldwide, accounting for about one-third of these deaths (2).

The association between blood pressure and weight gain has been reported, with a higher prevalence of arterial hypertension (AH) in obesity, representing a public health problem. Another consideration involving overweight is the arrangement of fat cells that, when concentrated in the abdominal region, has a vast association with cardiovascular events, and abdominal adiposity measurements can be used as a complementary approach to determine the risk of premature death (3).

It is also noteworthy that the presence of abdominal adiposity implies the development of metabolic alterations, among them, glucose intolerance and hypertriglyceridemia, considered important factors in the emergence of metabolic syndrome (MS). These increase morbidity and mortality due to atherosclerotic disease and its consequences, such as coronary artery disease (4).

The evaluation of adiposity is necessary for cardiometabolic risk assessment and prevention of obesity comorbidities. Although the diagnostic imaging technique is the most efficient method to evaluate adiposity, it becomes limited due to its high cost and methodological difficulties, which justifies the use of alternative, low-cost methods with greater clinical applicability. In this context, anthropometry stands out, in which adiposity is evaluated by means of isolated measurements, such as waist circumference (WC), or associated, from the construction of other anthropometric indicators such as body mass index (BMI), waist-to-height ratio (WHtR) and conicity index (CI) (5).

The anthropometric indicators of adiposity can establish important relationships with cardiometabolic diseases, namely, the AH and MS (6). Both anthropometric indicators of total obesity (BMI) and central obesity (WHtR and CI) are predictors of AH (7), but in metabolic abnormalities, the indicators of abdominal obesity stand out, such as a classic measure, WC (8). The correlation between the anthropometric indicators is also observed, such as between WC and BMI, these being the indicators that were most associated with the other anthropometric variables and also with alterations in plasma lipids (9).

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Studies aiming to understand and diagnose more easily and reliably the possible relations of adiposity indicators with health problems are of utmost importance. Moreover, CVD and metabolic diseases are of great concern in developing countries. Considering the importance of adiposity in cardiometabolic risk and the verification of the accuracy of anthropometric indicators in this context, the objective of this study was to evaluate the capacity of anthropometric indicators in the identification of adiposity and MS in patients with AH.

II. MATERIALS AND METHODS

a) Study design

This is a cross-sectional study, with non-probability sampling design and convenience sampling, with patients seen at the nutrition, cardiology, endocrinology, and metabolism outpatient clinics of the University Hospital of the Federal University of Grande Dourados, in the state of Mato Grosso do Sul, Midwest region of Brazil.

Patients who attended the outpatient units in that period and met the selection criteria for the study were invited to participate, and were included upon agreement and signing of an informed consent form. The individuals who were not participating in the study had ample and unrestricted access to care. The present study was approved by the Research Ethics Committee for human beings of Anhanguera-Uniderp, opinion number 838.813 (CAAE 35187214.8.0000.5161), according to Resolution No. 466/2012 of the Health Council - Ministry of Health.

b) Sample

Inclusion criteria were age ≥ 20 years, overweight, BMI ≥ 25 kg/m² in adults (10) and ≥ 28 kg/m² in the elderly (age ≥ 60 years) (11), diagnosis of AH under drug treatment. Pregnant and puerperal women, indigenous patients, those whose anthropometric measurements were not possible, patients unable to communicate verbally, and those who did not present complete medical records with the data necessary for the study were excluded.

Initially 313 patients were selected in the research period, and after checking the eligibility criteria, 208 patients were invited to participate, with refusal of 27 patients. In total, 181 patients aged between 20 and 80 years were evaluated.

c) Data collection

Data was collected through personal interview and from electronic medical records of outpatient care. Socio-demographic (age, gender, marital status, education, race/color), economic (monthly income), lifestyle (physical activity, tobacco and alcohol use), clinical (diagnosis of chronic diseases and medication use) and anthropometric (weight, height and waist

circumference) data were collected. The practice of physical activity was assessed according to personal reports: "no physical activity" (no/sedentary), "physical activity" (yes), when individuals exercised, according to recommendations of the Institute of Medicine/Food and Nutrition Board (12).

To collect anthropometric measurements we used the methodology recommended by the Food and Nutrition Surveillance System - SISVAN (13), which is an information system that aims to monitor the nutrition and feeding conditions of the Brazilian population. For the measurement of height (m), the patient was positioned barefoot and with head free of adornments, in the center of the equipment (stadiometer). He stood upright, with arms extended along his body, head up, looking at a fixed point at eye height. The individual placed his heels, calves, buttocks, scapulae, and the back of his head (occipital region) against the Altorexata® precision multifunctional portable stadiometer, whose maximum height is 200 cm, with a 0.5 cm interval.

To measure the weight (kg), the individual was standing in the center of the base of the scale, barefoot and with minimal clothing. Balmak Actilife® digital scales were used, with a capacity of up to 200 kg. The WC (cm) was measured with the individual standing, with the tape positioned at the midpoint between the last rib and the iliac crest. For this measurement the Sanny "Starret"® tape measure was used, inelastic and flexible, with an accuracy of 0.1 cm.

d) Anthropometric indicators of adiposity and metabolic syndrome classification

The anthropometric indicators analyzed were BMI, WC, WHtR, and CI. BMI, obtained by dividing weight by squared height (kg/m²), was classified for the adult population (20-59 years) into pre-obesity (BMI between 25 and 29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²) (10). For the elderly (60-80 years) different BMI cut-off points were used, and in this population the values proposed by the Pan American Organization were considered (11): pre-obesity (BMI ≥ 28 and < 30 kg/m²) and obesity (BMI ≥ 30 kg/m²). WC was classified as high when greater than 80 cm for women and greater than 90 cm for men (14).

To calculate the WHtR, we used the WC divided by height - both in centimeters - with a result ranging from values close to zero (0) to one (1). The cut point considered was 0.5, a single cut point for both sexes, used in the evaluation of excess abdominal fat and risk of obesity comorbidities (15).

The CI was determined by means of weight, height and WC measurements, expressed in meters, using the following mathematical equation: CI= waist circumference

$$0.109 \frac{\sqrt{\text{weight}}}{\text{Height}}$$

The cut-off point considered was 1.25 for men and 1.18 for women, which configures a high risk for CVD and metabolic diseases (16).

The presence of two or more of the following components was considered for the diagnosis of MS: WC (>90 cm for men and >80 cm for women); triglycerides \geq 150mg/dL and/or men HDL-c < 40mg/dL and women HDL-c < 50 mg/dL or use of hypolipemiant; blood pressure \geq 130/ 85 mmHg or use of anti-hypertensives; serum glucose > 100 mg/dL (including type 2 diabetes mellitus (DM), as suggested by the International Diabetes Federation (IDF) (14).

e) Statistical Analysis

The IBM SPSS (Statistical Package for the Social Science) Statistics®, version 22 and MedCalc Statistical®, version 17.4, software was used for statistical analysis. To test the best fit for normal distribution the Kolmogorov-Smirnov test was applied. Categorical data in percentages were analyzed by the chi-square test or Fisher's exact test. Continuous data were described as mean and standard deviation and analyzed by the t-student or Mann-Whitney test. The capacity of anthropometric indicators in the identification of adiposity, as well as their sensitivity and specificity, was evaluated by the ROC curve (Receiver Operating Characteristic), using BMI as the test index. Furthermore, the ROC curve was applied to analyze the capacity of anthropometric indicators in predicting MS, applied to the groups of patients with and without MS. The predictive power of anthropometric indicators regarding adiposity and MS was tested in subgroups consisting of gender (men/women), age (adults/elderly) and race/color (white and non-white individuals). Significant differences were considered to be values of $p \leq 0.05$.

III. RESULTS

A total of 181 patients were evaluated, most of them female (69.6%), with a mean age of 53.3 ± 12.6 years. As for socio-demographic characteristics, patients were predominantly adults (69.1%), non-white (58.6%), had attended elementary school or were not literate (67.9%), had a monthly income of 1 to 3 minimum wages (80.1%), and had a partner (65.2%). Regarding lifestyle habits, most were nonsmokers (61.3%), did not consume alcoholic beverages (75.7%), and did not practice physical exercise (79.0%) (Table 1). When assessing the presence of diseases, 47% had DM, 44.2% had dyslipidemia, and 71.8% had MS. MS was associated with increasing age ($p=0.003$) and male gender ($p=0.002$) (Table 1).

The mean BMI was $36 \pm 6.4 \text{ kg/m}^2$, 81.2% were classified as obese, and all patients had increased WC and WHtR. The mean values of WC ($p=0.014$), WHtR ($p=0.047$) and CI ($p<0.001$) were higher in the group of patients with MS, while the BMI value ($p=0.721$) did not

differ between these groups. High cardiometabolic risk, according to the CI, was observed in 93.9% of patients, being present in 97.7% of those with MS ($p=0.001$) (Table 2).

The AUC values, cutoff points, sensitivity, specificity, and positive and negative predictive values of the anthropometric indicators (WC, WHtR, CI) evaluated in the identification of adiposity in patients with AH are shown in Table 3. Among the indicators, WC was a good discriminator both in men (AUC 0.92; 95%CI 0.82-0.98; $p<0.001$) and in women (AUC 0.91; 95%CI 0.85-0.95; $p<0.001$), with cutoff points of 111 cm for men and 98 cm for women. It was possible to observe that WC showed 100% specificity in men, while in women CC showed higher sensitivity (87.4%). The positive predictive values were 80.0% and 81.8% for men and women, respectively. The WHtR showed AUC of 0.84 (men) and 0.90 (women), therefore a good discriminator, especially in women.

Considering only the adults, the WHtR (AUC 0.93; 95%CI 0.87-0.97; $p<0.001$) followed by WC (AUC 0.92; 95%CI 0.86-0.96; $p<0.001$) were good discriminators. In the elderly, WC (AUC 0.82; 95%CI 0.82-0.98; $p<0.001$) was the best discriminator, with 100% specificity and 63.3% sensitivity, and a positive predictive value of 87.5%. As for race/color, in whites, WC and WHtR were the best predictors of adiposity, with similar results for sensitivity and specificity, but in non-whites, the sensitivity of WC was higher. Figure 1 shows the ROC curve in relation to the ability to identify adiposity in the subgroups evaluated.

The areas under the ROC curve to evaluate the capacity of anthropometric indicators (BMI, WC, WHtR, CI) to identify MS, as well as cutoff points, sensitivity, specificity of the indicators and positive and negative predictive values are shown in table 4. In men, BMI and WHtR showed higher values for sensitivity, 64.6% and 60.4%, respectively, with a positive predictive value of 87.3%, and WC had the highest AUC and specificity. In women, CI had an AUC of 0.71 (95% CI; 0.63-0.79; $p<0.001$), and was also the most specific indicator (81.8%), while BMI was more sensitive (97.6%). In both adults and the elderly, WC was more sensitive (84.3% and 93.6%, respectively), but in adults, CI had an AUC of 0.70 (95%CI; 0.61-0.78; $p<0.001$), being the best discriminator of MS in this subgroup. When analyzing race/color, both groups showed CI with better AUC. Figure 2 shows the ROC curve of the anthropometric indicators able to identify MS in the subgroups studied.

IV. DISCUSSION

The findings of this study show that WC showed the best discriminatory power of adiposity in patients with AH of both sexes, which reinforces the role of WC in the identification of obesity in this population. WC is a traditional anthropometric measurement, with a simple

measurement technique and low cost, which provides clinical practicality in its use, besides the solid association with cardiometabolic abnormalities, as observed in the study by Domínguez-Reyes et al. (8), who also elected WC as the best discriminator of adiposity for both sexes in a Latin American population.

Anthropometric indicators are presented in a clear, objective and easy-to-apply way, however they suffer some influences such as gender, age and race (17), being extremely relevant the evaluation of the indicators behavior in the identification of adiposity in different subgroups of patients, as presented in this work.

Another point that draws attention in the current investigation is that only patients diagnosed with AH participated, but the majority presented MS, an undiagnosed and consequently untreated disorder in this population. MS configures the presence of combined cardiometabolic risk factors that are responsible for worsening the health of patients with AH (4). It is also noteworthy that, differently from women, who presented as the best indicator to discriminate MS the CI, in men the WC had the highest AUC. This may be explained by the larger number of female participants or by the distribution of abdominal fat in this population.

The study by Camhi et al. (18) makes it evident that fat distribution between men and women is different. Study only with women, the clinically useful indicators to discriminate coronary risk were WC, WHtR and CI (19). Another study brought that the CI has contributed to the stratification of cardiovascular risk in women (20), data that are similar to the current study, since the CI was the best predictor of MS in this group.

With the aim of having some anthropometric indicator capable of easily and quickly notifying MS in clinical/outpatient care, in order to promote treatment to this subclinical portion of patients, the most sensitive indicators in the identification of MS in this study were obtained as BMI (according to sex) and WC (age, race/color), but the best discriminators of MS were WC (men) and HF (other subgroups), and in other studies, BMI, WC and WHtR, besides attributing the strong relationship of these indicators with visceral fat deposition (21, 22).

Studies report that, among the indicators, WC is a good parameter of visceral fat and can be used as an alternative marker. The WHtR is an index to measure obesity and predict metabolic risks, being more sensitive than BMI, especially in the older population. Another good predictor of metabolic disorders is the CI (23-25), which in the current study was the anthropometric indicator that best identified MS, except in men, whose best discriminator was WC. That said, and in view of the vast literature on alternative methods and indicators to predict or diagnose metabolic disorders, this study has as a weak point the failure to explore a method that has been much commented on in

the current literature, the neck circumference and abdominal volume index, which has proven to be very accurate in relation to BMI (26, 27).

Results obtained from a systematic review indicate that WHtR is the best anthropometric index when used alone, while WHtR and WC showed better discriminatory power in predicting cardiovascular risk factors compared to the other indices (28).

The WHtR has shown to be efficient in the discrimination of adiposity in most subgroups (women, adults, whites and non-whites), and it has been placed as a practical advantage the use of a single cut point, and even though there is still no consensus about the best cut point, the most commonly used is the value of 0.5 (15). In the present study, the cutoff point for WHtR was 0.62 in men and 0.64 in women, agreeing with the findings of Rezende et al. (7), regarding a cutoff point higher than 0.5 and different between genders, and Oguoma et al. (2021) (21), who identified in the presence of cardiometabolic diseases a higher cutoff point for WHtR.

The possible relationship between abdominal adiposity and MS was evident, because all anthropometric parameters of fat tissue deposition were increased in patients with MS. Moreover, it is clear the importance of comparing the anthropometric methods, especially because in the present study there was no difference in BMI between patients with and without MS, corroborating the statements that BMI may not be a good indicator to determine cardiometabolic risk by not considering the distribution of body fat (29).

In this study it was observed that among the anthropometric indicators, WC and WHtR were the best discriminators of adiposity in the presence of AH. These results converge with other studies, such as Milagres et al. (30), who conclude that the increase in body fat, diastolic blood pressure, triglycerides, glycemia, and the reduction in HDL-cholesterol are associated with an increase in the cutoff points of these anthropometric indices, with a greater association of WHtR with cardiometabolic risk factors.

Moreover, studies with the Brazilian population also suggest that anthropometric indicators of total (BMI) and central (WC and WHtR) obesity are predictors of hypertension, as well as the CI (31, 7). And for other populations, both WHtR and WC were the best predictors of MS (32-34). It is worth emphasizing the need for population-specific cut-off points, given the existence of differences in an individual's body composition due to sex, age, race, and the occurrence of height loss in the elderly (35).

A limiting factor of the study was the larger number of women (69.6%) and adults (69.1%) in the sample, besides the significant number of patients with MS (71.8%), which may have impaired the identification of anthropometric indicators that predict MS in the subgroups, especially in men and the elderly.

In conclusion, this research allowed us to warn about the need to evaluate anthropometric indicators in overweight patients in the presence of comorbidities, such as hypertension, the most prevalent condition associated with obesity today. Adiposity in the studied population was better discriminated by WC and WHtR, considering the different subgroups, culminating in the identification of greater abdominal accumulation of body fat, which in itself already predicts risk in the development of cardiometabolic diseases. The high prevalence of MS in this population portrays an undiagnosed condition, which in the light of anthropometric indicators of adiposity can be identified in a practical and fast way by the CI, especially in adult, female patients of different races (white and non-white).

Sponsorship

This study was sponsored by Federal University of Grande Dourados.

ACKNOWLEDGMENTS

The authors thank the support of the Federal University of Grande Dourados and the permission of all participants.

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Table 1: Characterization of patients with hypertension and overweight (n=181), with and without metabolic syndrome, and in ambulatory care, Dourados/MS, Brazil.

Variables	Total n= 181	WITH MS n=130	WITHOUT MS n=51	p
Age (in years; mean±SD)	53.3±12.6	55.1±11.5	48.9±14.3	0.003*
Sex	n (%)	n (%)	n (%)	
Male	55 (30.4)	48 (36.9)	07 (13.7)	0.002†
Female	126 (69.6)	82 (63.1)	44 (86.3)	
Race	n (%)	n (%)	n (%)	
White	75 (41.4)	55 (42.3)	20 (39.2)	0.704†
Non -White	106 (58.6)	75 (57.7)	31 (60.8)	

Age classification	n (%)	n (%)	n (%)	
Adult	125 (69.1)	83 (63.8)	42 (82.3)	0.015†
Elderly	56 (30.9)	47 (36.2)	09 (17.7)	
Education	n (%)	n (%)	n (%)	
Illiterate	16 (8.8)	15 (11.5)	01 (2.0)	0.085†
Elementaryschool	107 (59.1)	78 (60.0)	29 (56.9)	
Highschool	43 (23.8)	26 (20.0)	17 (33.3)	
HigherEducation/ Post-graduation	15 (8.3)	11 (8.5)	04 (7.8)	
Income (minimumwage)	n (%)	n (%)	n (%)	
Upto 1	40 (22.1)	29 (22.3)	11 (21.6)	0.820†
From 1 to 2	40 (22.1)	28 (21.5)	12 (23.5)	
From 2 to 3	65 (35.9)	45 (34.7)	20 (39.2)	
More than 3	36 (19.9)	28 (21.5)	08 (15.7)	
Marital status	n (%)	n (%)	n (%)	
Withpartner	118 (65.2)	85 (65.4)	33 (64.7)	0.931†
Withoutpartner	63 (34.8)	45 (34.6)	18 (35.3)	
Tobacco Use	n (%)	n (%)	n (%)	
Ex-smoker	61 (33.7)	45 (34.6)	16 (31.4)	0.817†
Smoker	09 (5.0)	07 (5.4)	02 (3.9)	
Non-smoker	111 (61.3)	78 (60.0)	33 (64.7)	
Consumptionofalcoholicbeverages	n (%)	n (%)	n (%)	
Yes	44 (24.3)	31 (23.8)	13 (25.5)	0.816*
No	137 (75.7)	99 (76.2)	38 (74.5)	
Physicalactivitypractice	n (%)	n (%)	n (%)	
Yes	38 (21.0)	24 (18.5)	14 (27.4)	0.181*
No	143 (79.0)	106 (81.5)	37 (72.6)	

SD - standard deviation; MS -metabolic syndrome; (*) Student t-test; (†) Chi-square or Fischer's exact test. Significant difference: p≤0.05.

Table 2: Anthropometric variables of patients with arterial hypertension and overweight (n=181), with and without metabolic syndrome, and in ambulatory care, Dourados/MS, Brazil.

Variables	Total n= 181	WITH MS n=130	WITHOUT MS n=51	P
BMI (kg/m ² ; mean±SD)	36.0±6.4	35.9±6.2	36.3±6.8	0.721*
WC (cm; mean±SD)	110.0±13.7	111.6±12.8	106.0±15.3	0.014*
WHtR (mean±SD)	0.69±0.09	0.70±0.08	0.67±0.09	0.047*
CI (median, min-max)	1.34 (1.07-1.96)	1.35 (1.11-1.60)	1.29 (1.07-1.96)	<0.001*
BMI				
Pre-obesity	34 (18.8)	25 (19.2)	9 (17.6)	0.806†
Obesity	147 (81.2)	105 (80.8)	42 (82.4)	
CI				
Hih CR	170 (93.9)	127 (97.7)	43 (84.3)	0.001†
Low CR	11 (6.1)	3 (2.3)	8 (15.7)	

SD - standard deviation; MS - metabolic syndrome; (*) Student's t-test; (†) Chi-square or Fischer's exact test; BMI: body mass index; WC: waist circumference; WHtR: waist-to-height ratio. CI: conicity index; CR: cardiometabolic risk. Significant difference: p≤0.05.

Table 3: Comparison of cutoff points and areas under ROC curves of anthropometric indicators of adiposity discriminated from standard BMI, in hypertensive and overweight patients, according to sex, age and race.

	AUC	95%CI	P	Cut-off point	Sensibility %	Specificity %	PV + %	PV - %
Homens								
WC (cm)	0.92	0.82-0.98	<0.001*	111	72.7	100.0		
CI	0.65	0.50-0.77	0.12	1.36	59.1	72.7	80.0	20.0
WHtR	0.84	0.72-0.92	<0.001*	0.62	81.8	72.7		
Women								
WC (cm)	0.91	0.85-0.95	<0.001*	98	87.4	82.6		
CI	0.65	0.56-0.73	0.02*	1.27	69.9	60.9	81.8	18.2
WHtR	0.90	0.83-0.94	<0.001*	0.64	83.5	82.6		
Adults								
WC (cm)	0.92	0.86-0.96	<0.001*	98	89.8	85.2		
CI	0.66	0.57-0.74	0.005*	1.27	74.5	55.6	78.4	21.6
WHtR	0.93	0.87-0.97	<0.001*	0.64	78.6	92.6		
Elderly								
WC (cm)	0.82	0.70-0.91	<0.001*	111	63.3	100.0		
CI	0.56	0.42-0.69	0.582	1.47	89.8	28.6	87.5	12.5
WHtR	0.70	0.56-0.81	0.041*	0.67	69.4	71.4		
White								
WC (cm)	0.98	0.92-0.99	<0.001*	95	94.1	100		
CI	0.87	0.78-0.94	<0.001*	1.29	67.6	100	90.7	9.3
WHtR	0.99	0.93-1.00	<0.001*	0.60	94.1	100		
Non-white								
WC (cm)	0.86	0.78-0.92	<0.001*	98	91.1	66.7		
CI	0.55	0.45-0.65	0.417	1.27	75.9	37.0	74.5	25.5
WHtR	0.85	0.77-0.91	<0.001*	0.64	79.7	77.7		

AUC: Area under the ROC curve; 95%CI: Confidence Interval; PV: predictive value; *statistically significant; WC: Waist circumference; CI: conicity index; BMI: Body mass index; WHtR: Waist-to-height ratio. p value in relation to body mass index.

Table 4: Comparison of cutoff points and areas under ROC curves of anthropometric indicators of adiposity in patients with and without metabolic syndrome, according to sex, age and race.

	AUC	95%CI	P	Cut-off point	Sensibility %	Specificity %	PV + %	PV - %
Homens								
BMI	0.51	0.38-0.65	0.861	30.9	64.6	14.3		
WC (cm)	0.53	0.39-0.67	0.782	113.8	58.3	57.1	87.3	12.7
CI	0.51	0.37-0.65	0.910	1.34	31.2	42.9		
WHtR	0.50	0.36-0.63	0.990	0.69	60.4	14.3		
Women								
BMI	0.51	0.42-0.60	0.822	27.6	97.6	13.6		
WC (cm)	0.63	0.54-0.71	0.015*	101	74.4	50.0	65.0	34.9
CI	0.71	0.63-0.79	<0.001*	1.33	54.9	81.8		
WHtR	0.63	0.54-0.72	0.008*	0.7	54.9	68.2		
Adults								
BMI	0.51	0.42-0.60	0.799	37.7	62.7	47.6		
WC (cm)	0.62	0.53-0.71	0.016*	97	84.3	38.1	66.4	33.6
CI	0.70	0.61-0.78	<0.001*	1.33	51.8	81.0		
WHtR	0.57	0.48-0.66	0.159	0.7	43.4	73.8		
Elderly								
BMI	0.55	0.42-0.69	0.635	33.2	68.1	66.7		
WC (cm)	0.50	0.37-0.64	0.952	99	93.6	33.3	83.9	16.0
CI	0.65	0.51-0.77	0.209	1.34	70.2	66.7		
WHtR	0.56	0.42-0.69	0.621	0.62	87.2	33.3		
White								
BMI	0.50	0.38-0.62	0.977	36.9	45.5	45.0		
WC (cm)	0.61	0.49-0.72	0.136	107.5	76.4	45.0	73.3	26.7
CI	0.70	0.58-0.80	0.005*	1.33	61.8	75.0		
WHtR	0.59	0.47-0.70	0.198	0.7	54.5	65.0		

Non-white							
BMI	0.53	0.43-0.62	0.645	36.1	69.3	45.2	
WC (cm)	0.63	0.54-0.72	0.03*	101	74.7	54.8	
CI	0.71	0.62-0.79	<0.001*	1.32	61.3	77.4	70.7
WHR	0.58	0.48-0.68	0.171	0.57	94.7	22.6	29.3

AUC: Area under the ROC curve; 95%CI: Confidence Interval; PV: predictive value; *Statistically significant; WC: Waist circumference; CI: conicity index; BMI: Body mass index; WHtR: Waist-to-height ratio. *p* value in relation to body mass index.

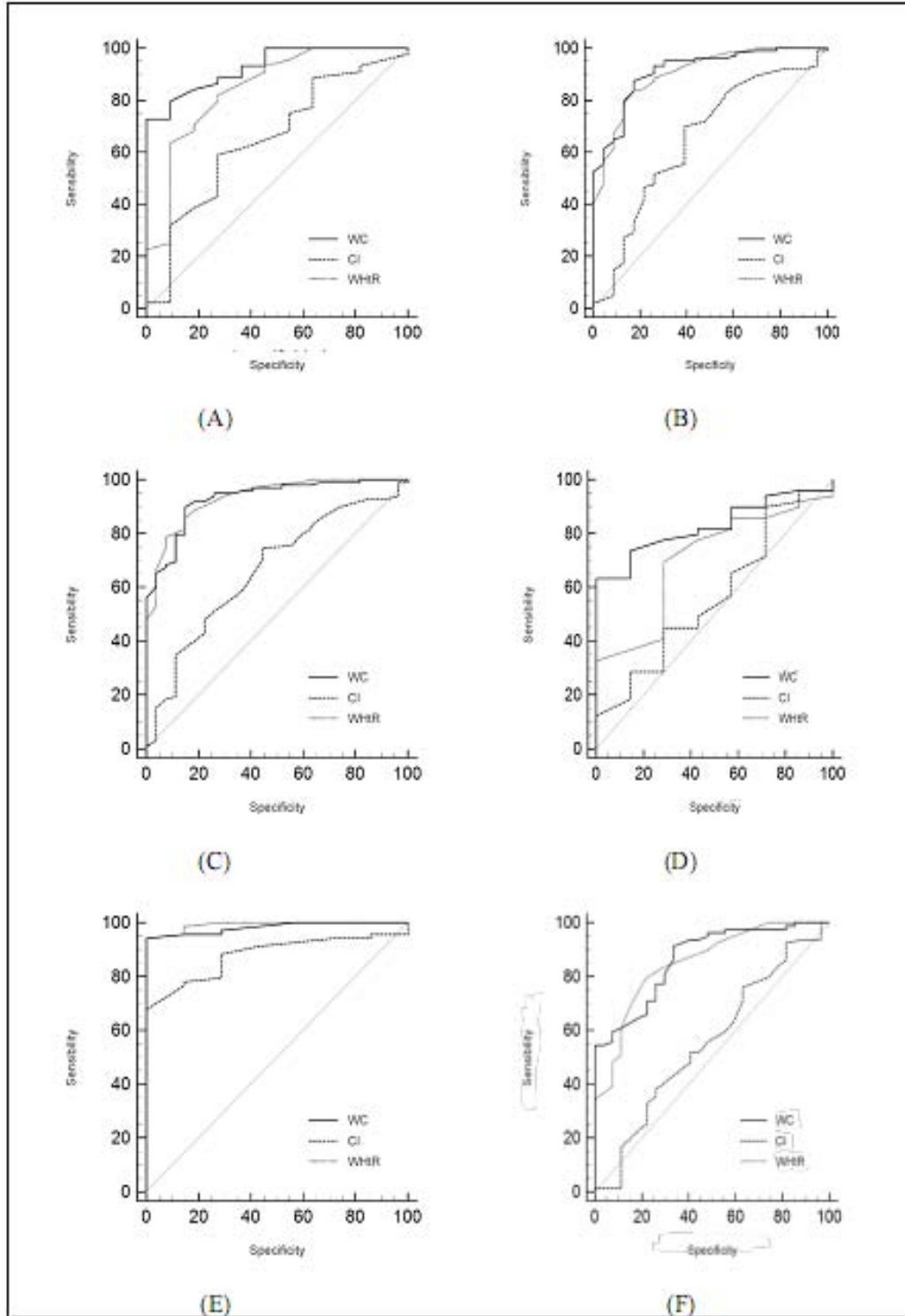


Figure 1: ROC curve of anthropometric indicators in relation to the ability to identify adiposity in men (A) and women (B); adults (C) and elderly (D); whites (E) and non-whites (F).

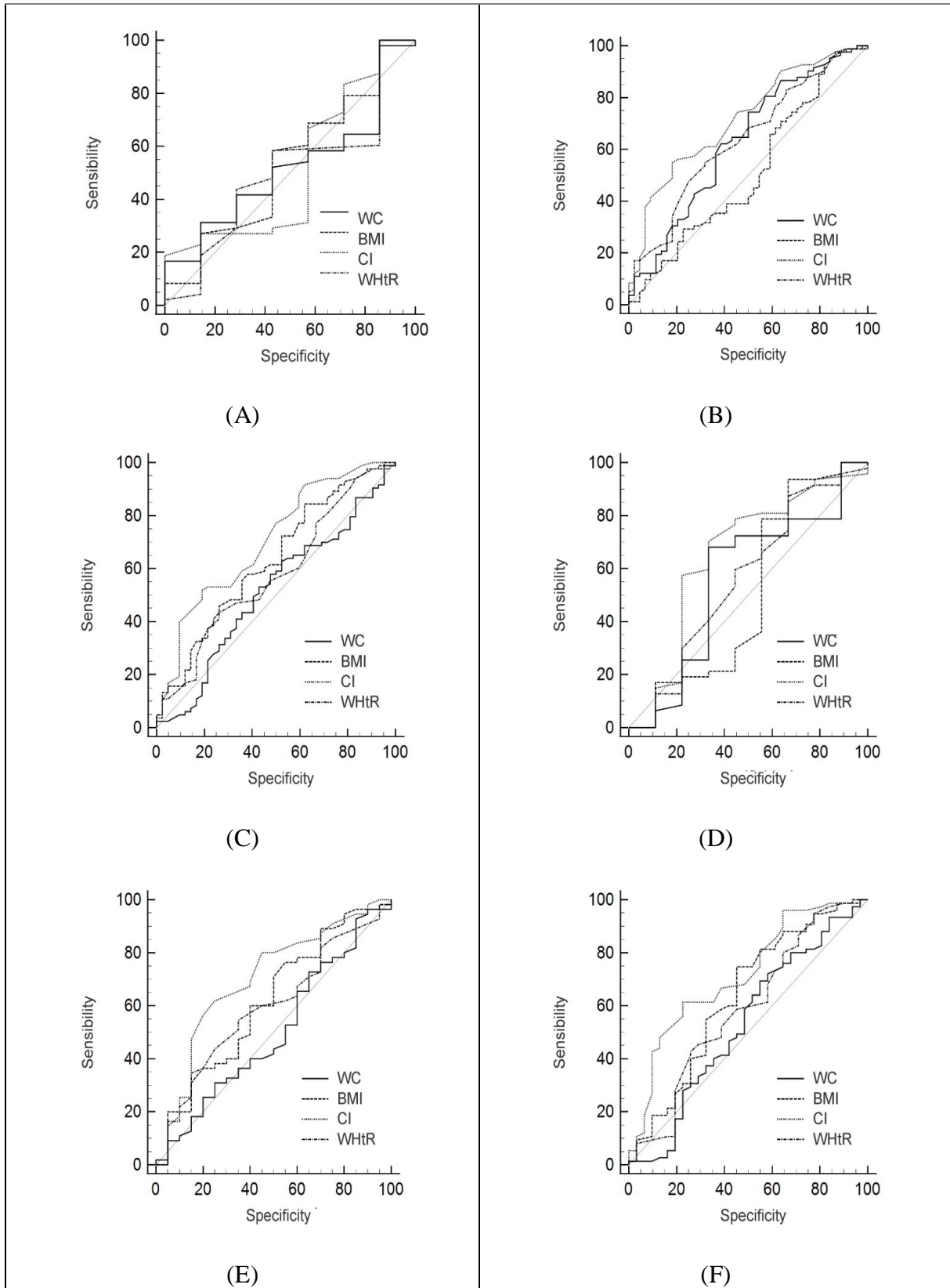


Figure 2: ROC curve of anthropometric indicators in relation to the ability to identify MS in men (A) and women (B); adults (C) and elderly (D); whites (E) and non-whites (F).



GLOBAL JOURNAL OF MEDICAL RESEARCH: K
INTERDISCIPLINARY
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Intracranial Hypertension and the use of External Ventricular Drain - EVD: Correct Management Avoids Complications

By Marli Christiane Nogueira de Amorim & Polliana Nogueira de Amorim Oliveira

Abstract- Introduction: Intracranial hypertension (ICH) is a neurological disorder caused by several factors. The positioning of the external ventricular shunt (EVD) is considered the gold standard in the care of severe neurological patients, being a surgical procedure with the purpose of draining the cerebrospinal fluid (CSF) to the outside. It is a closed drainage system, introduced into the skull to one of the cerebral ventricles in an operating room environment. Correct handling prevents complications during the patient's recovery.

Objective: To know the correct management with the external ventricular drain - EVD to avoid complications.

Methods: This is a study with a qualitative, bibliographic and descriptive approach. The information was acquired through the LILACS, BVS, MEDLINE, SCIELO database, in Portuguese between the years 2003 and 2018. There are 09 articles and one book useful for research, carefully read in the light of the objectives, grouped and arranged in tables for better understanding of the results.

GJMR-K Classification: DDC Code: 616.132 LCC Code: RC685.H8



INTRACRANIAL HYPERTENSION AND THE USE OF EXTERNAL VENTRICULAR DRAIN EVD CORRECT MANAGEMENT AVOIDS COMPLICATIONS

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Intracranial Hypertension and the use of External Ventricular Drain - EVD: Correct Management Avoids Complications

Hipertensão Intracraniana E O Uso Do Dreno Ventricular Externo - DVE: Manejo Correto evita Complicações

Marli Christiane Nogueira de Amorim ^α & Polliana Nogueira de Amorim Oliveira ^ο

Resumo- Introdução: A hipertensão intracraniana (HIC) é um transtorno neurológico ocasionado por fatores diversos. O posicionamento da derivação ventricular externa (DVE), é considerada padrão - ouro na assistência a pacientes neurológicos graves, sendo um procedimento cirúrgico com a finalidade de drenar para o exterior o líquido cefalorraquidiano (LCR). Trata-se de um sistema fechado de drenagem, introduzido no crânio até um dos ventrículos cerebrais em ambiente de bloco operatório, o manejo correto evita complicações durante a recuperação do paciente.

Objetivo: Conhecer o manejo correto com o dreno ventricular externo - DVE para evitar complicações.

Métodos: Trata-se de estudo com abordagem qualitativa, bibliográfico e descritivo. As informações foram adquiridas através do banco de dados da LILACS, BVS, MEDLINE, SCIELO, na língua portuguesa entre os anos de 2003 e 2018. Formam úteis para pesquisa 09 artigos e um livro, lidos criteriosamente à luz dos objetivos, agrupados e dispostos em quadros para melhor compreensão dos resultados. Resultados: O estudo destaca riscos e ou complicações decorrentes do manejo inadequado do DVE e muitos por motivo de desconhecimento do profissional de enfermagem ou falta de atenção.

Conclusão: Entende-se que o atendimento imediato e a estabilização do paciente é essencial para uma recuperação exitosa, todavia, a busca por atualização do profissional de enfermagem com relação as boas práticas e com desenvolvimento para o senso de responsabilidade ao que se propôs a prestar merece atenção, a fim de evitar maiores danos ao paciente e comprometimento profissional e ético.

Abstract- Introduction: Intracranial hypertension (ICH) is a neurological disorder caused by several factors. The positioning of the external ventricular shunt (EVD) is considered the gold standard in the care of severe neurological patients, being a surgical procedure with the purpose of draining the cerebrospinal fluid (CSF) to the outside. It is a closed drainage system, introduced into the skull to one of the cerebral ventricles in an operating room environment. Correct handling prevents complications during the patient's recovery.

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Results: The study highlights risks and/or complications arising from inadequate handling of EVD, many of which are due to lack of knowledge on the part of the nursing professional or lack of attention.

Conclusion: It is understood that the immediate care and stabilization of the patient is essential for a successful recovery, however, the search for updating of the nursing professional in relation to good practices and with the development of a sense of responsibility for what they set out to provide deserves attention, in order to avoid further harm to the patient and professional and ethical commitment.

I. INTRODUÇÃO

A lesão cerebral resulta do impacto direto no tecido cerebral ou através de evento hipóxico-isquêmico o que contribui para o surgimento de edema e aumento da pressão intracraniana – PIC, ocasionada por diversos fatores, sendo responsável por um número considerado de ocupação em leitos de UTI e, sobretudo, pela necessidade de intervenção cirúrgica para reparar o dano através do posicionamento de derivação ventricular externa (DVE), considerada padrão-ouro na assistência a pacientes neurológicos graves². A derivação ventricular externa (DVE), é um procedimento destinado a drenar para o exterior o líquido cefalorraquidiano (LCR) em situações de hipertensão intracraniana, através de sistema fechado de drenagem introduzido no crânio, posicionado em um dos ventrículos cerebrais e realizado em ambiente de bloco cirúrgico^{1,6}.

A drenagem é um procedimento simples e muito rápida, entretanto, qualquer descuido permite o completo esvaziamento do sistema ventricular repentino causando desequilíbrio hidrodinâmico e que pode levar ao rompimento de vasos corticais e a conseqüentemente formação de hematoma subdural

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agudo com suas complicações nefastas para o paciente e às herniações¹⁹

O manejo correto e a assistência de enfermagem no período pós operatório da implantação do dreno ventricular externo é de suma importância, deve-se atentar aos sinais e sintomas que identifiquem possibilidades de complicações e, assim, intervir com brevidade. O esvaziamento do sistema ventricular, observar a rafia na inserção do dreno, inspecionar e medir o conteúdo drenado e o aspecto, verificar aparecimento de sinais flogísticos ou ausência do funcionamento do dreno é de responsabilidade da enfermagem⁶⁹

Não diferente, a aferição dos Sinais Vitais em especial, a temperatura que deve ser rigorosamente aferida e manter o paciente normotérmico, uma vez que a hipertermia acarretará aumento no metabolismo cerebral e a hipotermia diminuição dos leucócitos aumentando o risco de infecção e distúrbios no fator de coagulação⁹

A possível obstrução do dreno deve ser avaliada para evitar o aumentada pressão intracraniana, confirmados através da presença de sinais como cefaléia, hipertensão, dor, rebaixamento do nível de consciência⁴. O transdutor externo deve ser mantido num ponto de referência fixo, em relação à cabeça do paciente, chamado Forame de Monroe para não ocorrer erros de medida, principalmente se for feita por diversos dias, há ainda a presença de náuseas, risco de bronco aspiração e aumento da PIC⁶.

Ao completar 10 dias de uso do dreno ventricular seja lembrado à equipe médica de neurocirurgia para tomada de decisão pois há grande risco de infecção, devido ao meio líquido, conteúdo drenado, que favorece crescimento bacteriano, complementa ainda que no máximo a permanência do dreno é de 14 dias, para minimizar o risco de infecção utiliza-se a antibioticoterapia profilática⁴.

Evidentemente que para uma contribuição da equipe de profissionais da enfermagem atualizada e segura é necessário que recebam especial atenção durante o desenvolvimento de intervenções educativas³. Acredita-se que intervenções pautadas em metodologias ativas de ensino e usando estratégias de ensino participativas possa contribuir para a sensibilização desses profissionais para a adoção das boas práticas no serviço^{4 7}. Da mesma forma que a adoção das boas práticas tendo em vista o adequado funcionamento da DVE, o que inclui cuidados com o posicionamento da DVE e da bolsa coletora – ajustes na altura, nivelamento do sistema quando ocorrer a mudança de decúbito; - com o sítio de inserção do cateter – troca de curativo de forma asséptica; – com o sistema de drenagem – inspeção de todo o sistema de DVE, inclusive do sítio de inserção do cateter, para localização de vazamentos; – e com o monitoramento do líquido drenado – observação da quantidade, cor e aspecto do líquido⁸.

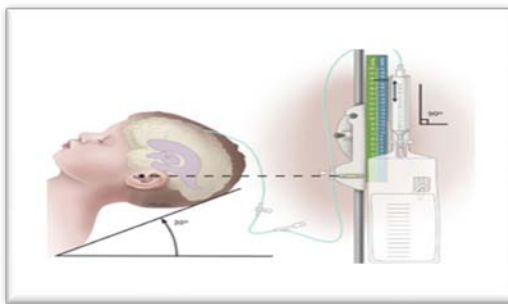
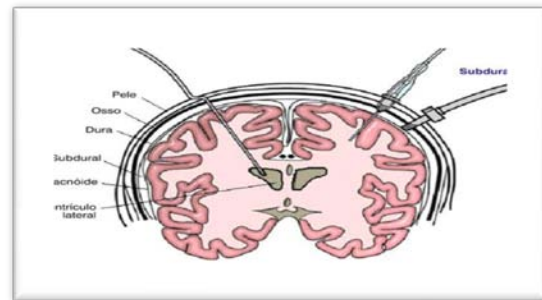


Imagem 1: Ângulo de 30 - 45°



Fonte: Multisaúde

Imagem 2: Implantação do DVE

II. OBJETIVO

Conhecer o manejo correto com o dreno ventricular externo - DVE para evitar complicações.

III. METODOLOGIA

Trata-se de pesquisa bibliográfica, do tipo descritiva, com abordagem qualitativa, de periódicos de enfermagem indexados na LILACS (Literatura Latino Americana do Caribe em Saúde) e MEDLINE (Literatura internacional em Ciências da Saúde), acerca da temática no período de 2002 – 2018. O estudo descritivo trouxe informações que possibilitam verificar condições e ações do objeto em estudo para melhor

planejar e proporcionar as práticas de saúde.⁵ A busca do material ocorreu em bibliotecas virtuais BVS (Biblioteca Virtual de Saúde), Internet Google Acadêmico e um livro, bem como através da BIREME (Centro Especializado da Organização Pan-americana de Saúde). Foram consideradas publicações que abordassem a temática dreno ventricular externo - DVE, utilizando-se descritores: enfermagem, UTI, manejo com DVE. Foram selecionados 22 artigos e um livro, todos na língua portuguesa e destes 09 artigos participaram do estudo, lidos criteriosamente à luz dos objetivos da análise, foram agrupados e dispostos em quadros para melhor compreensão dos resultados.

IV. RESULTADO E DISCUSSÃO

Quadro 1: Manejo correto do DVE e as possíveis complicações

Autor	Ano	Manejo Correto	Complicações
SAKAMOTO	2018	<ul style="list-style-type: none"> Manter a cabeceira do leito elevada ao ângulo de 30 - 45° para otimizar o retorno venoso Permanecer com o sistema de drenagem ao nível do Forame de Monroe, ponto referência anatômico O circuito do dreno deve ser trocado apenas por enfermeiro habilitado ou equipe de neurocirurgia 	<ul style="list-style-type: none"> Aumento da PIC Tontura, náuseas Risco para bronco aspiração Crise convulsiva Risco de ventriculite e meningite Sepse A descompressão rápida pode causar hematoma subdural Herniações
CEZIMBRA	2016	<ul style="list-style-type: none"> Nunca tentar desobstruir o dreno 	<ul style="list-style-type: none"> Risco de desencadear hemorragia
MASET	2005	<ul style="list-style-type: none"> Ao secar o conteúdo do saco coletor do dreno deve-se fechar o Clamp e após a coleta não esquecer de abrir novamente 	<ul style="list-style-type: none"> Aumento da PIC Cefaleia intensa Aumento da PA
FERREIRA	2016	<ul style="list-style-type: none"> Realizar curativo diário no sítio de inserção do dreno com clorexidina alcoólica sob técnicas assépticas Observar quantidade e aspecto do líquido drenado e registrar em prontuário Desprezar conteúdo da bolsa coletora quando chegar ao nível de 2/3 	<ul style="list-style-type: none"> Risco para Infecção Risco para desprendimento do dreno
COSTA FAM	2018	<ul style="list-style-type: none"> Atenção ao administrar medicamentos, verificar horário, dose, medicamento, via de administração em especial anticonvulsivantes 	<ul style="list-style-type: none"> A convulsão acarretará hipoxemia Aumento da PIC Laceração da cirurgia
GIUGNO	2003	<ul style="list-style-type: none"> O tempo ideal de permanência do cateter deve ser entre 10 e 14 dias no máximo 	<ul style="list-style-type: none"> Risco para infecção devido ao meio líquido drenado
COSTA RRO	2015	<ul style="list-style-type: none"> Manter paciente hemodinamicamente estável com destaque para PA e T° 	<ul style="list-style-type: none"> Hipertensão aumente PIC Hipertermia – acarreta aumento no metabolismo cerebral Hipotermia – diminui leucócitos aumentando o risco de infecção Distúrbios no fator de coagulação
MANZO	2018	<ul style="list-style-type: none"> Pacientes com tubo oro traqueal devem ser aspirados sob analgesia 	<ul style="list-style-type: none"> Risco do aumento da PIC

Fonte: autora, 2023

A maioria dos autores convergem em suas descrições e posicionamentos com relação a importância do profissional da enfermagem buscar aprimorar seus conhecimentos teórico e prático, para que assim, saiba o que fazer com o saber de maneira segura e ética, de modo a evitar erros com danos irreversíveis.

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GLOBAL JOURNAL OF MEDICAL RESEARCH: K
INTERDISCIPLINARY

Volume 23 Issue 1 Version 1.0 Year 2023

Type: Double Blind Peer Reviewed International Research Journal

Publisher: Global Journals

Online ISSN: 2249-4618 & Print ISSN: 0975-5888

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Abstract- Background: Limb amputation significantly impacts the patient's physical, emotional, and social life. Multiple etiological factors may lead to limb amputation. Unfortunately, there is limited data about amputation in Saudi Arabia. Since Sultan Bin Abdulaziz Humanitarian City (SBAHC) is a tertiary center receiving such patients, we collected data from ten years to look at the etiology, characteristics, and clinical impact of amputations in the Kingdom.

Objective: This study aimed at identifying the etiology, characteristics, and risk factors for amputation cases in Saudi Arabia.

Methods: Differences in amputee patients' data at SBAHC collected over ten years were analyzed using appropriate statistical tests. In addition, we collected Functional independent measurement (FIM) scores for 618 SBAHC rehabilitation program participants.

GJMR-K Classification: DDC Code: 616.8106 LCC Code: RC388.5



ETIOLOGY AND CHARACTERISTICS OF AMPUTATIONS IN SAUDI ARABIA: A RETROSPECTIVE STUDY FROM A TERTIARY REHABILITATION CENTER

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Abstract- Background: Limb amputation significantly impacts the patient's physical, emotional, and social life. Multiple etiological factors may lead to limb amputation. Unfortunately, there is limited data about amputation in Saudi Arabia. Since Sultan Bin Abdulaziz Humanitarian City (SBAHC) is a tertiary center receiving such patients, we collected data from ten years to look at the etiology, characteristics, and clinical impact of amputations in the Kingdom.

Objective: This study aimed at identifying the etiology, characteristics, and risk factors for amputation cases in Saudi Arabia.

Methods: Differences in amputee patients' data at SBAHC collected over ten years were analyzed using appropriate statistical tests. In addition, we collected Functional independent measurement (FIM) scores for 618 SBAHC rehabilitation program participants.

Results: 1409 amputees participated in the study, with men making up the vast majority (75.7%). Males averaged 45 years old, whereas females averaged 36 years ($P < 0.001$). The most common causes of amputation in this cohort were vascular disorders ($n=597$; 42.3%), followed by trauma ($n=519$; 36.8%). Diabetes mellitus was the most frequent comorbidity ($n=570$, 40.5%), followed by hypertension ($n=370$, 26.2%). Trans-tibial amputations were the most typical (135/597, 22.6%), followed by trans-femoral amputations (84/597, 14.1%) in vascular-related amputations. Traumatic trans-femoral amputation was more prevalent among young adults than traumatic trans-tibial amputation. Trauma related amputation cases were highest in the age group of 21-30 years (359/519, 69.2%), while vascular-related amputations were highest in the age group of 70 and above years (534/597, 89.5%). FIM scores, following rehabilitation at SBAHC, improved mostly in locomotion (10.8/14 from 6.4/14, +33.6%) followed by transfer (17.3/21 from 11/21, +30.6%) and self-care (36.6/42 from 29.6/42, +16.4%) at six-month post-discharge compared to admission (all P -values $< .01$).

Conclusions: Vascular pathology that develops as a result of chronic diseases, followed by trauma, is the most common cause of amputation in Saudi Arabia, which justifies the need for primary and secondary preventive measures.

I. INTRODUCTION

Amputation has a profound and long-lasting impact on an individual's economic, psychological, and social status [1, 2]. Complications arising from various peripheral vascular diseases and, or diabetes form the most important causes of amputations [3, 4]. However, traumatic experiences at the extremities and, to a lesser extent, cancer, as well as other causes, also have a role [5]. Studies have shown that age and gender play a significant role in the pattern of limb loss [6, 7]. Older adults with several chronic conditions are disproportionately affected by limb loss due to peripheral vascular disease, while young men are disproportionately affected by limb loss due to trauma [8, 9]. Most patients requiring prosthetic restoration and rehabilitation services are older adults with lower limb amputations due to vascular disease [10]. The lifetime risk of amputation in the elderly is 10–15%, 10–30 times higher than in the general population [11]. Additionally, reports indicate that amputations caused by trauma and cancer may be decreasing, whereas congenital amputations remain stable [12]. Diabetes is responsible for at least 50 % of non-traumatic lower-limb amputations worldwide, according to studies [13]. The prevalence of amputations performed has been rising worldwide [14]. In the United States, lower limb loss was estimated to affect 1.6 million people in 2005, with that figure expected to more than double to 3.6 million by 2050 [15]. The studies regarding amputation among countries in Asia have many similarities, as trauma and disease incidence occur in similar patterns [16, 17]. In contrast, the patterns are not the same as those in the United States, Denmark, Finland, or Australia [18], where peripheral vascular disorders, notably arteriosclerosis, are the most common cause of amputations. In these countries, the patterns differ. There has been a paucity of research published about the prevalence of amputees in Saudi Arabia. A 14-year retrospective study published in 1993 for the amputee population in Saudi Arabia was a comprehensive study

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listing all cases of amputations in a particular rehabilitation center in Riyadh, Saudi Arabia, from 1977 to 1990 [19]. In 2012, Alzahrani, in his study, concluded that around half a million amputations of the lower extremities would likely occur in Saudi Arabia and other Middle East and North African countries, and this number includes only amputations arising out of diabetic complications [20]. Whether so many diabetes-related amputations have occurred in the last decade is difficult to assess, the primary reason being the lack of a national registry of amputations in Saudi Arabia and limited such published reports, which still represents a significant challenge for healthcare policymakers [19, 21]. This study was thus designed to fill up some of these gaps in the literature.

In Saudi Arabia, the number of people with peripheral vascular diseases, diabetes, and people who die in car accidents is also going up [22, 23]. So, it may have also led to a rise in the number of amputations in this country. More data needs to be published to assess better the etiology, characteristics, and risk factors for amputation in this country. This may assist healthcare providers in planning and establishing effective and timely interventions and may also help improve rehabilitation services so that amputee patients can be functionally independent and productive members of their communities. This fact has increased the interest in studying the impact of etiology, characteristics, and clinical status on amputees. Besides, identifying the etiology, the study aimed to identify the characteristics and risk factors for amputation cases in Saudi Arabia.

II. METHODS

This investigation is a retrospective hospital-based study with 1409 amputee patients' data collected between June 2010 to June 2020. Sultan bin Abdul Aziz Humanitarian City (SBAHC), a tertiary care rehabilitation center, adopted proper evaluation management and quality of life assessment for its clients where we conducted this study. All amputees' medical records were evaluated by medical coders at the Research facility at SBAHC using a pre-designed case report form to determine the pattern of amputations and etiological factors. Inclusion criteria included all patients with amputations who visited outpatient limb loss clinics. The exclusion criteria included the patients whose medical records were incomplete during the study period regardless of the level, site, or type of amputation. Collected data included demographic variables, etiology, site, level, and type of amputations. In addition, the cohort distribution from different provinces, namely Central, Northern, Southern, Eastern, and Western, was collected in addition to patient nationality. This study was approved by the Institutional Review Board of SBAHC.

Out of the selected cohort, 618 patients were required to be admitted because of pre- and post-prosthetic rehabilitation. The functional outcomes of the cohort were evaluated based on the functional independent measurement score (FIM Score) at admission and six months after discharge. Clinical evaluation in weight, height, BMI, and systolic/diastolic blood pressure was also collected from the patient's medical files. Progress with rehabilitation, if any, was recorded during the follow-up. The FIM instrument contains 18 items classified into six major scales: self-care, sphincter control, transfer, locomotion, communication, and social cognition [24, 25]. These interviews at admission and discharge were conducted by a team of medical doctors, physical therapists, and nurses on the guidelines laid down by the Center. On each item, the patients rated their level of independence using a 1–7 scale, on which one (1) means assistance was needed, and seven (7) means a person was entirely independent.

Statistical analysis of the data collected from the study was analyzed using SPSS ver. 22 (IBM, Armonk, NY, USA). For continuous normal variables, the data were provided as the mean and standard deviation, whereas for continuous non-normal variables, the data were shown as the median (Q1-Q3). The frequency of each subject was determined based on their distribution according to etiology, age, and level of amputation, and the results were reported as a percentage. A P -value of <0.05 was considered significant. For rehabilitation data, 618 subjects were interviewed before admission and at discharge using a self-reported version of the FIM instrument. Summing up responses to each item gave us a scale score ranging from several items to seven times the number of items, i.e., the total FIM score ranges from 18 to 126. FIM improvement (%) was calculated by subtracting FIM at admission from FIM at discharge, and this score served as an outcome measure in the study.

III. RESULTS

a) Demographic characteristics of the Study Subjects

The demographic characteristics of the study subjects are presented in table 1. A total of 1409 patients were recruited, of which 75.6% were male and 24.4% were female. The patients' ages ranged from 1 to 96 years, with the average male age being 45 years and the average female age being 36 years. Out of the total population studied, Saudi nationals constituted 86.9% ($n=1224$), and the rest were non-Saudis ($n=185$, 13.1%). Most of the studied population ($n=849$, 60.3%) was from the Central region of Saudi Arabia, followed by the Western ($n=235$, 16.7%), Southern ($n=160$, 11.4%), and other regions. Most amputees were affected by vascular and traumatic amputations ($n=597$, 42.4% and $n=519$, 36.9%, respectively), followed by congenital

(n=204, 14.4%) and infection/others. The study cohort consists of patients with a duration of amputation of 5 years or less (n=566, 40.4%), followed by 6–10 years

(n=417, 29.7%). Among comorbidities, the most prevalent was diabetes (n=570, 40.5%), followed by hypertension (n=370, 26.3%).

Table 1: Demographic Characteristics of study subjects

Total		All (1409)	Males (1066)	Females (343)	P-value
Age Mean (SD)		43 (21)	45 (20.8)	36 (20.0)	< .001
Nationality N (%)	Saudi	1224 (86.8)	920 (75.1)	304 (24.9)	< .001
	Non-Saudi	185 (13.1)	146 (78.9)	39 (21.1)	< .001
Province N (%)	Central	849 (60.2)	650 (76.5)	199 (23.5)	< .001
	Northern	59 (4.1)	37 (62.7)	22 (37.3)	.006
	Southern	160 (11.3)	126 (78.7)	34 (21.3)	< .001
	Western	235 (16.6)	181 (77.1)	54 (22.9)	< .001
	Eastern	106 (7.5)	72 (67.9)	34 (32.1)	< .001
Etiology N (%)	Trauma	519 (36.8)	425 (81.8)	94 (18.2)	< .001
	Vascular	597 (42.3)	479 (80.2)	118 (19.8)	< .001
	Congenital	204 (14.4)	109 (53.4)	95 (46.6)	.16
	Infection	89 (6.3)	53 (59.5)	36 (40.5)	.01
Duration of amputation N (%)	≤5	566 (40.3)	447 (78.9)	119 (21.1)	< .001
	6 - 10	417 (29.6)	329 (78.8)	88 (21.2)	< .001
	11-15	186 (13.2)	137 (73.6)	49 (26.4)	< .001
	16 - 20	84 (5.9)	55 (65.4)	29 (34.6)	< .001
	>20	152 (10.7)	95 (62.5)	57 (37.5)	< .001
Comorbidity N (%)	Diabetes	570 (40.4)	468 (82.1)	102 (17.9)	< .001
	Hypertension	370 (26.2)	301 (81.5)	69 (18.5)	< .001
	Hyperlipidemia	74 (5.2)	63 (85.1)	11 (14.9)	< .001
	Cardiac	118 (8.3)	102 (86.4)	16 (13.6)	< .001
	Others	277 (19.6)	193 (69.6)	84 (30.4)	< .001
Weight Mean (SD)		72.5 (32.4)	72.4 (32.4)	62.8 (31.7)	< .001
Height Mean (SD)		158.5 (54.6)	158.50 (54.6)	146.5 (48.3)	< .001
BMI Mean (SD)		30.2 (12.5)	30.58 (12.5)	26.9 (12.3)	.03
Systolic Blood Pressure Mean (SD)		125.9 (42.5)	128.9 (42.5)	120.6 (49.1)	< .001
Diastolic Blood Pressure Mean (SD)		76.3 (24.8)	76.3 (24.8)	74.5 (22.7)	0.47

Note: Data is presented as prevalence (%). The difference between the groups is tested by the Chi-square test. P<.05 is considered significant.

When comparing the level of amputation with etiology, trans-tibial amputations were found to be the highest (135/597, 22.6%), followed by trans-femoral amputations (84/597, 14.1%) in the case of patients with vascular diseases. Among trauma patients, trans-femoral amputation was the highest (53/519, 10.9%), followed by transtibial (50/519, 9.6%). The amputation level among congenital cases was highest in the case of trans-radial (2.4%), followed by partial hand (1.8%) and trans-femoral (1.6%) (Figure 1).

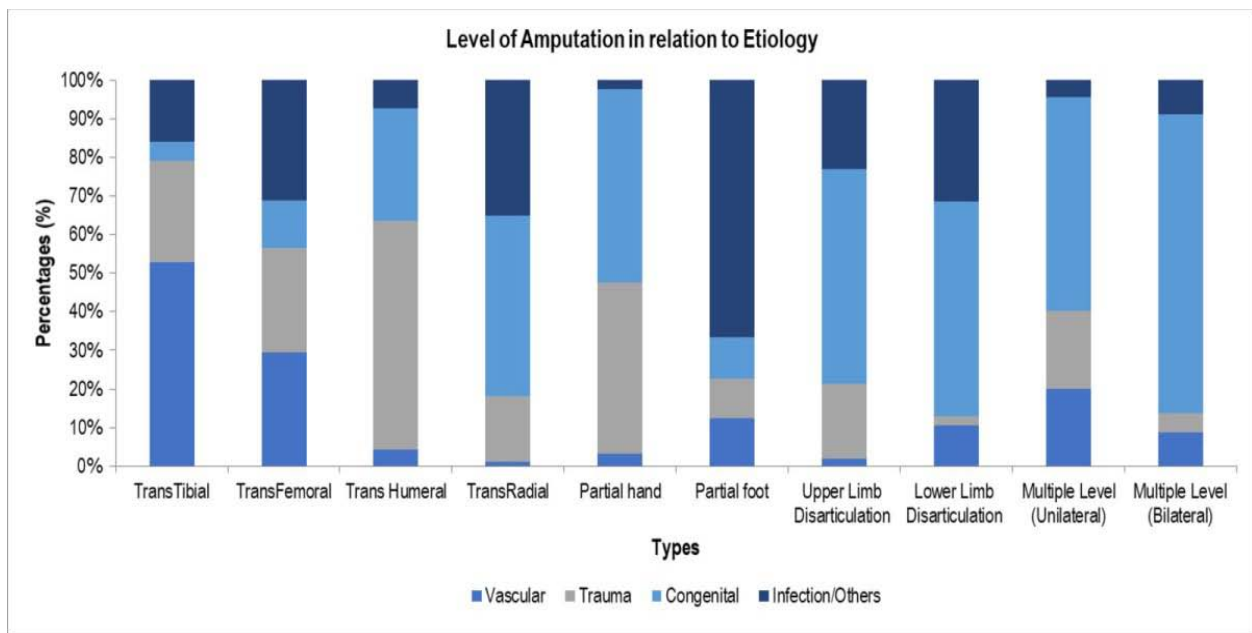


Figure 1: Level of amputation according to etiology.

b) Etiology

When comparing the etiology of amputation with life span (Figure 2), we found that trauma-related amputation cases were highest in the age group between 21 to 30 years (359/519, 69.2%) and lowest in people over 70 years of age (36/519, 7%).

Amputations due to vascular disease were most common in those aged 70 and older (534/597, 89.5%) and least common in children aged 0–10 (23/597, 3.9%). Congenital amputation was, as expected, most frequent in the age group 0–10 years (162/204, 79.4%) and was least in the age group 51–60 years (1/204, 0.5%).

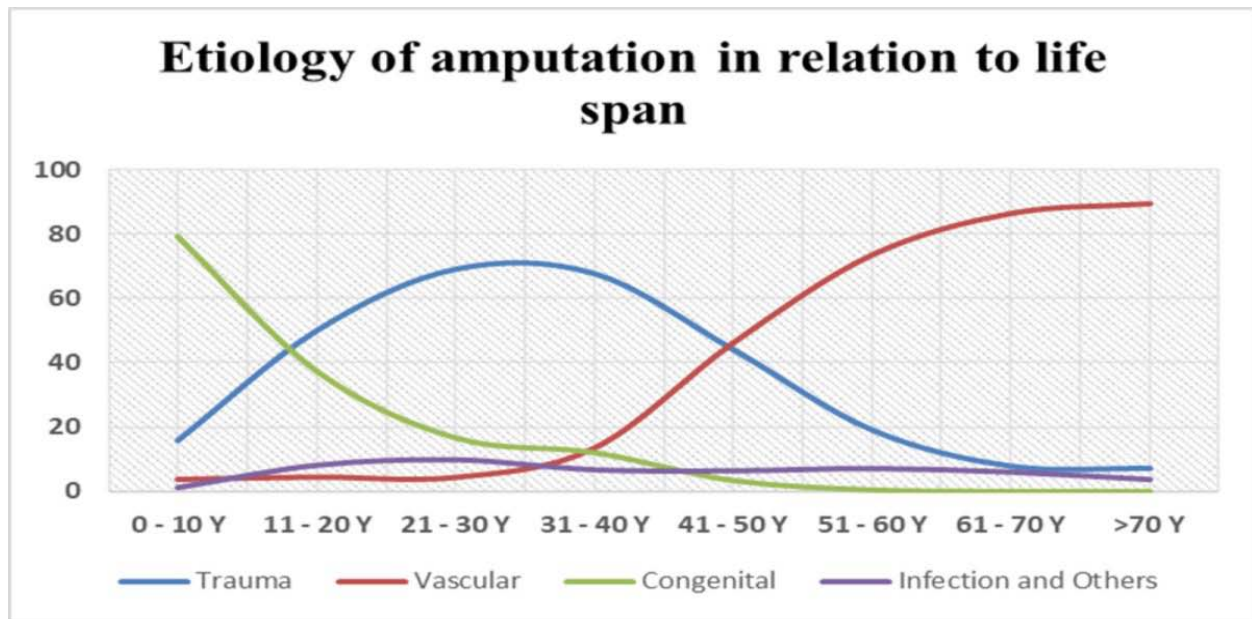


Figure 2: Etiology of amputation according to life span.

c) Improvement in FIM scores

Admission and discharge FIM score data were presented in Table 2. There is a significant difference ($P=.005$) between admission and discharge scores in self-care, transfer, and locomotion (all P -values $<.001$). Also, the overall FIM score improved 6months post-discharge as compared to the admission ($P<.001$). FIM

showed a maximum improvement in the case of locomotion (score of 6.4 at admission to 10.8 at discharge out of a total of 14, an increase of 33.6%, $P<.001$), followed by transfer and self-care. An improvement of 15.1% was also found in the total FIM score, which increased from 89.8 to 107.5 out of the maximum score of 126.

Table 2: Patient's functional status according to Functional Independence Measurement (FIM) Score value from admission to discharge

FIM Scale Mean (SD)	Admission	Discharge	P-value	Max Score	Admission (% score)	Discharge (% score)	Improvement (%)
Self-care	29.6 (0.5)	36.6 (0.3)	< .001	42	71.4	87.8	16.4
Sphincter-Control	12.5(0.2)	12.5 (0.2)	.34	14	88.0	91.8	3.8
Transfer	11.0 (0.4)	17.3 (0.2)	< .001	21	52.6	83.2	30.6
Locomotion	6.4 (0.3)	10.8 (0.2)	< .001	14	45.9	79.5	33.6
Communication	13.6 (0.1)	13.7 (0.1)	.19	14	97.6	98.8	1.2
Social-Cognition	20.3 (0.1)	20.4 (0.1)	.29	21	97.0	97.9	0.9
Total FIM	89.8 (1.2)	107.5 (1.1)	< .001	126	74.4	89.5	15.1

Note: Data is presented as prevalence (%). The difference between the groups is tested by Chi-square test. $P < 0.05$ is considered significant.

IV. DISCUSSION

This study aimed to present our experiences with major limb amputations in Saudi Arabia and compare the results to those of similar studies conducted in other regions of the world. The purpose of this comparison was to highlight the differences in the pattern and indications for amputations and suggest relevant preventive interventions. In addition, this study aimed to present our experiences with major limb amputations in Saudi Arabia.. As expected, most of amputees in this study were males with vascular diseases, followed by trauma being the leading cause of amputation. In causes related to vascular diseases, diabetes was the major culprit, while trans-tibial and trans-femoral amputations being the leading amputations related to trauma. Younger adults in the age-group of 21-30 years formed the most prevalent group when it comes to trauma-related amputations, while vascular-related amputations were highest in older adults of age 70 and above. This study also reported the improvement in FIM scores following a rehabilitation period in the SBAHC facility.

Numerous factors, including levels of technology, access to medical and surgical care, and living conditions, may account for differences in the prevalence of amputees not only between countries but also within them. This research reveals a picture of the geographic and pathological distribution of amputations across Saudi Arabia's five most populous provinces. SBAHC rehabilitation center, located in Riyadh, the capital of Saudi Arabia, is easily accessible to receive patients from all major provinces of the Kingdom This study was carried out in order to provide a clearer picture of the physical and pathological distribution of amputations.

This study's male predominance among amputees is consistent with the findings of other researchers [26, 27] who, irrespective of race and geographical dispersion, have reached similar conclusions. This could be linked to male having more severe peripheral artery disease, higher smoking rates,

and a greater propensity for road traffic accidents. On the other hand, estrogen and its influence on reducing vascular pathology may account for the lower frequency of amputations due to vascular disease [14]. The fact that diabetic patients have a 15-fold increased risk of lower limb amputation, along with the rising incidence of diabetes and vascular disease-related increases in lower limb amputation, underscores the significance of early detection, medical education, patient compliance, and reasonable glycemic control in this population. Diabetic neuropathy, which can cause loss of feeling, aberrant gait, and deformity, raises the risk of foot pathology, which raises the risk of lower limb amputation when combined with vascular abnormalities [28]. In addition, the presence of chronic foot ulcers invites infection, especially deep wound, and osteomyelitis infections that may end in amputation[29, 30]. In a study from South Africa and India, infection and ulcers were the most common causes of amputation in diabetic individuals. At the same time, ischemia was the most common cause in nondiabetic people, which was not the case in our studied cohort. This could be related to the better care provided to this cohort since medical care is free and provided by secondary and tertiary care centers [31, 32].

In the studied cohort, trauma is the second observed cause of amputation, which is similar to what has been found in developed countries, contrary to what has been found in developing countries, where trauma is the first cause of amputation [33]. These variations in amputation patterns reflect differences in comorbidities. This is the finding of the current study, which could provide a scientific reason for the increased incidence when compared with Traumatrauma. Previous research has shown that the risk of amputation increases with the number of comorbidities that a patient has. SBAHC, being a tertiary care center, receives most of its patients within five years of amputation, reflecting the efficiency of this hospital in providing services for such patients. Although trauma was ranked second in this study, it was the most common reason for amputation in young adults in their productive and active age group.

In this study, the relationship between etiology and amputation level demonstrates the significant variations between amputation and surgical decisions by medical staff. Most of our amputations were in the lower limbs, with transtibial amputation the most common, regardless of the etiology[34]. This data supports previous findings that lower limbs are wounded more frequently than upper extremities, and diabetic gangrene is more common in the lower extremities than in any other part of the body. Transfemoral amputation is more prevalent than transtibial amputation, according to the findings of other studies. This could be a reflection of the severity of the infection in the lower limb that necessitates transfemoral amputation, or it could be a surgical attitude.[35, 36]. When comparing Trauma to the degree of amputation, the transfemoral and transtibial amputation rates were nearly the same, at 9.6% and 10.9%, respectively. That could be the effect of a wide age range in this cohort. According to research published in 1993, Trauma was the leading cause of lower limb amputation in Saudi Arabia (52.9%). The most common location of amputation was the trans-tibia, followed by the transfemoral, trans-radial, partial hand, and trans-humeral[37, 38]. Since that time, there have been no reports of amputations in this country that have been found in the PubMed database. This could be explained by the rising prevalence of comorbidities, particularly diabetes, as well as the increased enforcement of laws requiring people to wear safety belts [39]. In the population that we researched, we found that the etiology varied throughout the various age groups. According to the findings of our research, the most common age range for trauma-related amputations was between the ages of 20 and 40 years. This is consistent with a WHO report indicating that road traffic accidents are among the top causes of death in those aged 15 to 29 years old [40]. The first few months after receiving a license are extremely hazardous, and the report indicates that road traffic accidents are among the top causes of death in this age group. When taking into account the effect that age has on amputations and how it relates to the etiology of the condition, vascular disease is the most common cause of amputations. This was seen in people in their 30s and 40s, and it was the same as what other developed and developing countries found.[41].

Consequently, vascular disease-related amputation was most common in older people aged over 60 years. Furthermore, older people are more likely to have more than one ailment that may result in amputation due to vascular etiology [42]. Congenital limb deficiency, on the other hand, accounted for 79.4% of lower limb deficiency in children under the age of 10 years in this study, compared to 67% in the Krebs and Fishman study [43], 32% in the Yigiter et al. study [44], and 73.3% in the Boonstra et al. study[45]. This could be at the expense of trauma-related limb loss based on

strengthening children's car safety rules. In addition to data from tertiary centers receiving patients from all over the Kingdom, these demographic parameters of children with limb deficits showed a high degree of consistency throughout the literature.

There was a significant difference between FIM scores at admission and discharge and a total FIM gain during hospitalization. On follow-up visits, we saw a considerable improvement in the total FIM score and its motor and transfer subscales. The average total FIM scores for admission and discharge were 89.811.2 and 107.51.1, respectively. A FIM score of greater than 108 indicates home independence [46]. On six-month follow-up visits, individuals in this study achieved this independence degree. This improvement was most noticeable in the self-care, transfer, and locomotion categories. The results showed an improvement in self-care, transfer, and locomotion in the FIM scores between admission and discharge, comparable with the findings of the Hall et al. study [47] and others [48, 49]. According to the findings of the study, improvements in the motor domain were significantly higher than those in the cognitive domain; however, the cognitive score was not the focus of this particular investigation. This study's strength comes from being conducted in the largest tertiary rehabilitation center in the country, which was able to represent amputees nationwide and covers all age spectrums. The second strength is that amputees in this institution are subject to a multidisciplinary approach that would give a better clinical, physical and, mental assessment, as shown in this study. Finally, although this study was limited to be a retrospective study and receiving patients after five years, that would not provide data related to immediate amputation outcomes.

In conclusion, vascular pathology caused by chronic illnesses is the key risk factor for amputation in Saudi Arabia, necessitating primary and secondary preventive efforts. A multidisciplinary approach, an in-depth understanding of the functional impacts of amputation, and a comprehensive and detailed examination of the patients and their surroundings should serve as the cornerstone for post-amputation rehabilitation programs.

ACKNOWLEDGMENTS

The authors are grateful to the Research and Scientific Center at SBAHC for the assistance in conducting this study.

Conflicts of interest

None declared.

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GLOBAL JOURNAL OF MEDICAL RESEARCH: K
INTERDISCIPLINARY
Volume 23 Issue 1 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Lessons Learnt during the Second Wave of COVID-19: A Prospective Observational Study of the Effect of Single-Dose COVID-19 Vaccination on the Clinical Profile and Patient Outcome in a Suburban Area of Pune, India

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Abstract- Background: The COVID-19 pandemic, in the first wave in India, had a high case fatality rate. Vaccination and other preventive measures were implemented soon after. Our study was conducted with an aim to assess the effect of a single dose of COVID-19 vaccine on patient outcome and clinical profile of patients admitted with the disease in the second wave.

Methods: A prospective observational study was carried out at three community hospitals in a suburban area of Pune, during the second wave, after prior informed consent of patients through a digital questionnaire to record clinical, demographic and laboratory data.

Keywords: vaccination, severity, outcome, COVID-19, oxygen, survived.

GJMR-K Classification: DDC Code: 791.4372 LCC Code: PN1997.2



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Lessons Learnt during the Second Wave of COVID-19: A Prospective Observational Study of the Effect of Single-Dose COVID-19 Vaccination on the Clinical Profile and Patient Outcome in a Suburban Area of Pune, India

Effect of COVID-19 Vaccination on Patient Outcome

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Abstract- Background: The COVID-19 pandemic, in the first wave in India, had a high case fatality rate. Vaccination and other preventive measures were implemented soon after. Our study was conducted with an aim to assess the effect of a single dose of COVID-19 vaccine on patient outcome and clinical profile of patients admitted with the disease in the second wave.

Methods: A prospective observational study was carried out at three community hospitals in a suburban area of Pune, during the second wave, after prior informed consent of patients through a digital questionnaire to record clinical, demographic and laboratory data.

Results: Out 643 patients were admitted to these hospitals during the aforementioned duration and were enrolled for the study. Out of these, 12.753% patients were vaccinated with a single dose while 87.247% were unvaccinated. Vaccinated patients required lower oxygen therapy ($p = 0.007$), heparin ($p = 0.002$), steroids ($p=0.017$). 100% of vaccinated patients survived while 95.365% survived and 4.635% of died among non-vaccinated persons ($p = 0.047$).

Conclusion: We established through this study that vaccination to have reduced disease severity and improved outcomes among patients affected with COVID-19.

Keywords: vaccination, severity, outcome, COVID-19, oxygen, survived.

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I. INTRODUCTION

The Centers for Disease Control and Prevention (CDC) refers to a pandemic as “an epidemic that has spread over several countries or continents, usually affecting a large number of people.” [1]

The first wave of COVID-19 in India began in March 2020, with the peak affliction occurring in the month of September 2020 [2]. Patients affected with the SARS COV-2 virus during the first wave in India had an increased infliction of the respiratory system, with a heightened disease severity especially among an elderly and co-morbid demographic [3]. Common symptoms encountered in the first wave included fever, chills, cough, breathlessness, nasal congestion, loss of taste or smell, nausea or vomiting, diarrhoea, joint or muscle pain, and headache [4].

Important lessons learnt from the first wave of COVID-19 were manifold. Training of staff for the effective management of COVID-19 patients, adopting protective measures like masks and social distancing and testing symptomatic patients early to reduce disease transmission, testing costs, therapeutic expenditure and overburdening of healthcare facilities. Adequate and timely enforcement of legislative measures to contain the disease along with vaccine development and administration.

Development of effective vaccines to prevent the infection and to reduce the severity of the disease was probably the most important lesson learnt during the first wave. The first vaccine to receive emergency validation from the WHO on 31st December 2020 was Pfizer/BioNTech's sBNT162b2 mRNA Covid-19 Vaccine [5,6] Subsequently, India also developed its own vaccine – Bharat Biotech's BBV152, and also started vaccinating people with the ChAdOx1 nCoV-19 vaccine [7]

The second surge of COVID-19 started in April 2021 and peaked in May 2021. However, healthcare

professionals as well as healthcare systems were better equipped during the second wave due to an increased number of hospital beds, trained staff, better pharmacotherapeutic guidelines, and an increase in the vaccinated population. The vaccination drive implemented in India proved to be highly effective in reducing disease severity during the second wave of COVID-19 [8]. Thus, along with healthcare vigilance, even a single dose of vaccination seemed to prove effective to reduce healthcare burden in terms of hospital inpatient admissions and oxygen and ventilator requirements.

Our study aims to help clearly delineate the effect that a single dose of COVID-19 vaccines has had in reducing clinical symptoms and signs, and its effect on laboratory parameters and treatment strategies during the second wave of COVID-19 in Pune, India.

II. MATERIALS & METHODS

This was a prospective observational study conducted in coherence with the STROBE guidelines, in three general community hospitals in a suburban area of Pune, India with the assistance of a local non-government organisation SPHERE (Society for Prevention Healthcare Education and Research). Data was obtained from a period of 1st March, 2021 to 30th June, 2021 (duration of the second wave in India). Digital informed consent on a pre-designed informed consent sheet in native as well as national languages was obtained from the patient/legally accepted representative of the patient (in cases of seriously ill patients). All patients admitted for COVID-19 infection in these hospitals and if patients or relatives (if patient was critically ill) willing to consent to sharing their data were included.

The study was conducted using a clinical assessment questionnaire designed using the available literature was incorporated in a software designed by Mobicloud Technologies and installed in all the participating centres. Demographic data, vital parameters, details about their clinical symptoms,

clinical signs, laboratory parameters, and treatment given were entered into the questionnaire along with vaccination details which was then subjected to further statistical analysis.

The data on categorical variables was represented by n (% of cases) and the data on continuous variables was presented by Mean and Standard Deviation (SD) or Median and Interquartile Range (IQR). The inter-group statistical comparison of continuous variables is done using the independent samples t-test. The underlying normality assumption and homogeneity of variances were tested before subjecting the study variables to the independent samples t-test. The inter-group statistical comparison of categorical variables was done using the Chi-Squared test. Logistic regression was used to evaluate the association between variables. In the entire study, p-values less than 0.05 were considered to be statistically significant. All the hypotheses were formulated using two tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data is statistically analysed using JASP 0.16.3 for MS Windows.

III. RESULTS

A total of 643 patients were admitted to these hospitals during the aforementioned duration and were enrolled for the study. Out of these, 82 (12.753%) patients were vaccinated with a single dose of either ChAdOx1 nCoV-19 (AZD1222) vaccine (COVISHIELD™) or BBV152 (COVAXIN®) while 561 (87.247%) patients were unvaccinated. Only 2 (2.439%) vaccinated patients were given BBV152 (COVAXIN®), while the remaining received ChAdOx1 nCoV-19 (AZD1222) vaccine (COVISHIELD™). The male to female ratio in vaccinated patients was 2.037:1 while the male to female ratio in unvaccinated patients was 1.318. Symptoms were comparable among the 2 groups. The vital parameters were better among vaccinated patients as compared to non-vaccinated patients (Table 1).

Table 1: Comparison between clinical signs between vaccinated and unvaccinated patients

Symptom	Vaccinated (n=82), mean±SD	Unvaccinated (n=561), mean±SD	p-value
Pulse rate (bpm)	93.293±13.331	98.831±15.493	<0.001***
Respiratory rate (cpm)	18.671±1.988	19.444±2.950	<0.001***
Body temperature (F)	98.123±1.442	99.062±3.682	<0.001***
Oxygen saturation (%)	96.598±1.246	95.528±3.140	0.002**

Evaluated using the Mann-Whitney test.

*p <.05, **p <.01, ***p <.001

Significantly lower CT severity score, higher haemoglobin levels, lower D-dimer levels, and lower lymphocyte levels were seen in the vaccinated group (Table 2).

Table 2: Comparison between laboratory parameters between vaccinated and unvaccinated patients

Laboratory parameter	Vaccinated (n=82), mean±SD	Unvaccinated (n=561), mean±SD	p-value
CT severity score (0 to 25)	6.429±3.275	10.955±5.280	0.002**
Hemoglobin (gm %)	13.235±1.998	12.392±2.012	<0.001***
CRP (mcg/mL)	36.056±17.342	39.745±32.032	0.782
LDH (U/L)	794.720±77.955	756.013±277.499	0.132
Ferritin (mcg/L)	272.952±80.430	291.944±139.477	0.411
D-dimer (ng/mL)	56.308±160.789	59.965±170.048	0.046*
Blood urea (mg/dL)	53.524±56.947	46.778±41.876	0.324
WBC (/mm ³)	8592.22±1792.506	8246.219±3782.777	0.137
Neutrophils (%)	65.829±12.119	68.110±10.564	0.156
Lymphocytes (%)	25.476±10.548	39.299±299.213	0.030*
Eosinophils (%)	2.683±1.699	2.881±4.551	0.735
Monocytes (%)	3.866±1.891	3.679±2.731	0.209
Basophils (%)	1.585±1.663	1.268±0.900	0.108
Platelets (/mm ³)	236426.829±79397.582	239502.317±91703.532	0.802

Evaluated using the Mann-Whitney test.

*p <.05, **p <.01, ***p <.001

A significantly lower proportion of vaccinated patients required oxygen therapy (p = 0.007), heparin (p = 0.002), steroids (p = .017) (Table 3).

Table 3: Comparison between requirement of various treatments in vaccinated and unvaccinated patients

Management	Vaccinated (n=82), n (%)	Unvaccinated (n=561), n (%)	p-value
Oxygen therapy	2 (2.439%)	70 (12.478%)	0.007**
Heparin	4 (4.878%)	106 (18.895%)	0.002**
Steroids	9 (10.976%)	126 (22.460%)	0.017*
Steroid duration (mean±SD in days)	4.111±2.028 days	6.405±3.091 days	0.014* (Mann-Whitney test)
NIV	10 (12.195%)	111 (19.786%)	0.100
Ventilator	0 (0%)	7 (1.248%)	0.309
Antiviral therapy	79 (96.341%)	509 (90.731%)	0.090
Tocilizumab	8 (9.756%)	74 (13.191%)	0.384
Oral antipyretics	32 (39.024%)	266 (47.415%)	0.155

Evaluated using the chi-squared test of independence (unless stated otherwise)

*p <.05, **p <.01, ***p <.001

Age, history and duration of hypertension, a high mean arterial pressure, non-vaccinated status, a low oxygen saturation, high CRP level and ventilatory requirement were significant predictors of poor outcomes (Table 4).

Table 4: Univariate & forward stepwise multivariate logistic regression for various variables predicting the outcome in patients

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (years)	0.965	0.941-0.990	.007**	-	-	-
Hypertension	0.216	0.090-0.519	<.001***	0.306	0.077-1.208	.091
Duration of HTN (years)	0.881	0.810-0.959	.003**	-	-	-
Vaccination (1 dose)	1.897	1.479-2.252	.007**	1.974	1.765-2.378	<.001***
Mean arterial pressure	0.909	0.858-0.964	.001**	0.937	0.859-1.02	.143
SpO2	1.091	1.006-1.183	.036*	-	-	-
CRP	0.988	0.980-0.995	.001**	0.986	0.978-0.994	<.001***
Need for oxygen therapy	0.260	0.109-0.623	.002**	-	-	-
Need for ventilator	0.027	0.006-0.127	<.001***	0.016	0.003-0.086	<.001***

Out of 643 total patients, 518 (80.56%) patients were vaccinated against tuberculosis with the BCG vaccine. Patients who were vaccinated with BCG were less likely to develop generalized weakness ($p < 0.001$), and nausea ($p < 0.001$). Furthermore, patients who were vaccinated with BCG had a lower pulse rate (mean = 96.527 beats per minute, $p < 0.001$), had a lower respiratory rate (mean = 19.236 cycles per minute, $p = 0.025$), and had lower body temperature (mean = 98.746 F, $p < 0.001$) possibly indicating a less intense cytokine induced response.

Out of 82 patients who were vaccinated, 82 (100%) were discharged (survived). Out of 561 patients who weren't vaccinated, 535 (95.365%) were discharged (survived) while 26 (4.635%) died ($p = 0.047$).

IV. DISCUSSION

SARS-CoV-2 is a single-stranded RNA virus [9] with the established capacity to transmit from human to human [10] by virtue of an envelope-anchored spike protein which mediates viral entry into the host and fusion of viral and host cell membranes[11].

Various components of the virus including the spike protein, plasmid DNA and or mRNA were utilised to make different vaccines. At present the vaccines available in India are , plasmid DNA vaccine- ZyCoV-D, Gam-COVID-Vac combined vector vaccine, Biological E's novel Covid-19 vaccine containing Receptor Binding Domain of SARS-CoV-2, Intranasal Adenoviral vector COVID-19 vaccine (BBV154), mRNA based vaccine (HGCO19) and are certified safe to use for above the age of 18years; Covishield (SII-ChAdOx1 nCoV-19), Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152)- COVAXIN™ permitted for use among adults and children above 12 years of age, CORBEVAX-a protein subunit COVID-19 permitted for use among everyone including children above 5 years of age and COVOVAX (SARS-CoV-2 recombinant spike protein nanoparticle vaccine with Matrix-M1™ adjuvant) for everyone including children above 2 years of age[12].

In this study we found a better clinical and biochemical profile and improved survival statistics ($p < 0.05$) among vaccinated patients with merely one dose. Prior vaccination is postulated to have improved humoral and cell mediated immune response to the virus and viral proteins. There have been many trials on vaccines for safety and efficacy since the very advent of the pandemic. Certain trials assessing efficacy of administering a different vaccine booster to a cohort previously administered a different vaccine against COVID-19 found a more robust immune response owing to greater reactogenicity of the mixed vaccine with minimal to no serious adverse effects.[13]. In the CombiVacS study [14], which was a phase two randomised controlled trial conducted to assess immunogenicity of heterologous vaccination of

BNT162b2 booster in ChAdOx1-S-primed participants, showed a significantly high immune response in the test arm as opposed to the control arm (95% CI 7371-53-8161-96 at day 14, $p < 0.0001$)

A nationwide cross-sectional study conducted by Singh et al (COVAT study) among healthcare workers in India showed a significantly high seropositivity among people vaccinated with initially one dose of ChAdOx1 nCoV-19 (AZD1222) vaccine (COVISHIELD™) (86.8 vs. 43.8% respectively, $p < 0.001$) after the first dose. as compared to BBV152 (COVAXIN®) [15]. Vaccine safety among pregnant women was also established by a systematic review and meta-analysis conducted by Prasad et al which proved vaccine safety, a 15% decrease in the odds of stillbirth was associated with vaccination (vs. no vaccination) in pregnancy ($p = 0.035$) and decreased odds of birth asphyxia by 71% by virtue of vaccination (as opposed to no vaccination) with no higher risk of obstetric complications ($p > 0.05$) among vaccinated women as compared to non-vaccinated women [16].

In our study we additionally documented the effect of prior BCG vaccination on patient outcomes. All patients vaccinated with the BCG Vaccine had less generalised weakness, nausea, a low respiratory rate, low pulse(in all $p < 0.001$) compared to those who were not vaccinated with BCG. These effects are postulated to have occurred due to transcriptional, epigenetic and metabolic reprogramming of the myeloid cells in the BCG-vaccinated individuals. The epigenetic changes are manifested as chemical modifications of the histone, resulting in enhanced chromatin accessibility, easier transcription of genes important for antimicrobial responses and improved cell function [17]. In a global retrospective analysis by Madan et al, countries with a high burden of tuberculosis had a lower incidence of COVID-19, irrespective of the BCG vaccine status of the country. On the other hand, in countries with a lower burden of tuberculosis, BCG vaccine administration showed a significantly lower incidence of COVID-19 ($p < 0.001$), suggesting some protective mechanisms in TB-endemic areas [18]. Ozdemir et al have shown proportionately less cases, milder illness and a lower death rate in BCG vaccinated population as compared to BCG non-vaccinated across countries and hemispheres [19].

Through this prospective study, demographic factors like increased age ($p = 0.007$), no vaccination against COVID-19($p < 0.001$), history and longer duration of hypertension ($p < 0.001$; $p = 0.003$ respectively), a high CRP level in blood ($p < 0.001$), a lower oxygen saturation on room air ($p = 0.036$) and the requirement of a ventilator for respiratory support ($p < 0.001$) to be a strong predictor of poor patient recovery and outcome.

V. LIMITATIONS

This study, has a smaller sample size due to a reduction in the number of people willing to test themselves for the disease and limited access to other hospitals actively involved in management of COVID-19 affected patients on a larger scale. This study was conducted as a prospective analysis of patients in the second wave of COVID-19 infection in India; since then there have been many changes implemented to vaccination schedules, patient categorisation and screening coupled with the concept of herd immunity which could have changed patient outcomes which may or may not be coherent with the findings of our study.

VI. CONCLUSION

Our study along with many others conducted among different populations in many parts of the world proves vaccination to have reduced disease severity and improved outcomes among patients affected with COVID-19. Vaccines have also been argued upon to have resulted in several serious adverse effects, however, it must be well understood and impressed upon the public that vaccine development is a dynamic process which entails careful post-marketing surveillance of the product and persistent efforts to avert any such mishappenings.

Although primordial prevention in the form of self-protection, isolation and education of frontline workers, students in healthcare and the public is being conducted even today on a daily basis, given the rapid transmission and phylogenetic variations of the Sars-CoV2 virus, vaccination is imperative as a means of risk reduction in both the diseased and healthy population in the best interests of the healthcare facilities and the population alike.

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GLOBAL JOURNAL OF MEDICAL RESEARCH: K
INTERDISCIPLINARY

Volume 23 Issue 1 Version 1.0 Year 2023

Type: Double Blind Peer Reviewed International Research Journal

Publisher: Global Journals

Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Knowledge, Attitudes, and Practices in Adapting to Covid-19 Pandemic Conditions: A Cross-Sectional Survey among Mongolian Residents

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Keywords: COVID-19 pandemic, attitude, knowledge, practice, Mongolia.

GJMR-K Classification: DDC Code: 398 LCC Code: PH107



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Knowledge, Attitudes, and Practices in Adapting to Covid-19 Pandemic Conditions: A Cross-Sectional Survey among Mongolian Residents

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Abstract- This survey aims to compare the level of knowledge, attitudes, and practices of the population towards coronavirus infection with the results of the baseline survey result; to define the challenges faced by the participants and the behavioral changes when they have overcome and are adapting to the new style; to develop and disseminate evidence-based recommendations for decision-makers who are dealing with the pandemic. A total of 1896 people aged 15-60 years old participated in the study. The survey data were collected using quantitative (questionnaire) and qualitative (observation) methods. The survey questionnaire consisted of 45 questions of 6 chapters: demographic, knowledge, attitude and adaptation practice towards coronavirus infection, patient satisfaction with health care service delivery, and information demand. Using the previously developed guideline, the in-depth interview was conducted among three specific groups (specialists, general population, and teenagers). There are positive changes in personnel hygiene, wearing masks, and ventilation that were practiced while implementing preventive measures against coronavirus infection. Most of the qualitative survey participants correctly understood that adaptation means following strictly preventive measures and continuing everyday life.

Keywords: COVID-19 pandemic, attitude, knowledge, practice, Mongolia.

I. INTRODUCTION

The first internal incidence of COVID-19 was reported on 11 November 2020 in Mongolia. At this moment, we conducted a knowledge, attitude, and practice survey on Coronavirus infection among the general population. The survey has found that 41.7 percent of the population wore masks incorrectly or exposed noses worn under the chin, 83.3 percent wore one mask throughout the day, one in two did not wash their hands properly, and two out of three participants did not use spacing at all. In addition, knowledge about

coronavirus infection in rural areas was generally poor, especially in Bayan-Ulgii aimag, indicating that targeted public health prevention activities may not have been adequately implemented ¹. As of September 21, 2021, 65.3 percent of Mongolia's population was vaccinated at full dose. However, as of COVID-19 confirmed cases, Mongolia is in the top five countries in the West Pacific ². This indicates that there is a lack of practice in the prevention of coronavirus infection in the population. Therefore, during this time when the spreading of coronavirus infection continues, it is needed to improve the prevention, response, and risk communication of Mongolians and ensure the adaptability of citizens. This survey will define how the existing situation has changed and the need to continue or further improve risk information communication strategy. Knowing what kind of information people receive, how much they have been perceived, their attitudes and attitudes, and how they adapt is essential for policymakers, health sector decision-makers, and public health professionals to develop and disseminate effective and targeted information for the population. Hence, it will be evidence of the need to change and adopt proper disease prevention practices.

II. METHODS

This cross-sectional survey data collection was conducted using qualitative (in-depth interview, focus group discussion, and desk review) and quantitative survey methods. In the baseline survey, we used the contextualized country context of the COVID-19 Readiness and Response Guidelines³ and Risk Information Communication Planning strategy⁴, which was developed by the WHO European region as a survey tool. In the follow-up study, we have been using the tools of the baseline study, such as questionnaires, interview guidelines, and an observations checklist to incorporate new knowledge and insights into the world, current vaccines, and coronavirus variants.

Data collectors were researchers and had trained in ethical issues during the data collection. The research methodology was approved at the Scientific Committee of the National Center for Public Health on

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November 9, 2021 (Protocol № 5) and the Medical Ethics Review Committee of the Ministry of Health on January 20, 2022 (Resolution №261) was issued the Ethical permission of the survey.

The sampling frame of this survey is residents of ger and apartment area of Songinokhairkhan, Chingeltei districts of Ulaanbaatar city, and indigenous people of representatives of Bayan-Ulgii aimag, border area residents of Selenge and Dornogobi aimag. The survey data were collected using quantitative (questionnaire) and qualitative (observation) methods. Using the previously developed guideline, the in-depth interview was conducted among three specific groups (specialists, general population, and teenagers). Observations were performed on the population's handwashing situation, duration, use of soap, wearing and removing masks, frequency, and social distancing behavior of people.

A total of 1896 people aged 15-60 years old participated in the study from 3 bordering provinces. Kazakh ethnic group in Bayan-Ulgii province, which make up 3.9 percent of the total population, was selected through targeted sampling methodology to determine whether cultural and religious factors influence attitudes towards spreading COVID-19.

The sample size was determined based on the assumption that the population's knowledge, attitudes, and practices on COVID-19 is 50.0% and calculated as 95% actual probability ($Z = 1.96$), error limit ($p = 0.05$), complex sampling coefficient (1.5). Considering the principles of gender balance in each age group, a total of 1,740 people participated in the survey, with an estimated 10 percent probability be that those selected would be excluded from the survey. The formula for calculating the sample size: The sample size of the two-stage household-population sample survey for a particular area or group of the population was calculated according to the following formula:

$$n = \frac{z^2 P(1 - P)N}{Ne^2 + z^2 P(1 - P)}$$

Herein,

$Z = 95\%$ confidence interval (1.96).

$P =$ baseline indicator prevalence percentage ($= 0.50$)

$E =$ acceptable margin of error (0.05)

$N =$ Population aged 15-60 in Songinokhairkhan and Chingeltei districts of Ulaanbaatar and Bayan-Ulgii, Selenge and Dornogovi aimag centers.

The sample size, which can be used to determine the purpose of the study, is performed according to the above conditions: The sample size was sampled using the previously given formula with the parameters $z = 1.96$, $P = 0.5$, and $e = 0.05$. The sample size in the Primary Sampling Unit (PRS) was estimated to 40, which is an optimal option in terms of distribution and representation. The total sample size for

each population group is 1,896 for a population aged 15-60 years.

20 individuals responded to the face-to-face interviews, including health sector specialists (Ministry of Health Director, Specialist, Director/Specialist, Aimag Special Committee Officer, Governor's Office staff, etc.) and 100 people aged 15-59 were interviewed. Also, 100 people of 20 households for observation responded to the qualitative survey.

In the second phase, the surveyed units were selected using a simple random sampling method from the population of 15-60-year-olds within the sampling range. In the final sampling phase, the Kish method randomly chose the individual from the selected household population aged 18-60. Only one person in the selected household, aged 15-60, was included in the survey. Individual and group discussions and observations were conducted to clarify issues raised in compiling survey data. The key informants of the qualitative survey were the head of the SEC, the directors of the Ministry of Health, the head of the NCCD/specialist, the relevant staff of the Aimag Emergency Commission, the governor's office, the health department, the NCCD and patients who covered from the COVID-19.

The data were collected using a previously developed questionnaire for face-to-face interviews with selected individuals from the target population. In qualitative research, data were collected through face-to-face interviews with key informants. The observation method determined whether participants washed their hands with soap for at least 20 seconds, covered their mouths (with elbow) when coughing or sneezing, wore face masks, and properly practiced social distancing. To maintain the high quality of data, a few measures were taken, such as minimizing coverage errors by preparing a complete list of sampling units and including selected units in the survey, minimizing errors in the information collected by gathering information with questionnaires and from selected areas and by consulting with the research supervisor and resolve any issues or difficulties encountered during the data collection process. The data collection was started after introducing the purpose and activities of the survey. After introducing the survey's purpose, effectiveness, and timing, a questionnaire and an interview with the person who agreed to participate were initiated.

The findings were presented by urban, rural, ger, apartment area, ethnic and age groups. Methodology for the classification of qualitative data has been created. A collection of codes was then established in accordance with the assessment criteria and all interviews were coded. Quantitative data analysis was conducted using SPSS version 23. The findings are represented in terms of the percentage of the population's knowledge and attitudes. Deviation values of 95% confidence interval (95%CI) were used to assess

the difference between the measurement of the accuracy of the results (distribution rate) and the groups (age, sex, location). The sampling errors that could change the accuracy of the results of this population-based survey were assessed by the dependent variables and the standard error of the results.

III. RESULTS

a) Social and Demographic Characteristics of Participants

A total of 1896 people were involved in the survey, and the coverage was 100%. 56.6% of total

participants (95%CI: 54.4-58.9) were from Ulaanbaatar and 43.4% (95%CI: 41.1-45.6) were from rural areas. The participants' average age was 35.1 ± 12.4 , the youngest was 15, and the oldest was 60.

Most of the participants were married (66.7%, 1265), belonged to the Khalkh ethnicity (79.3%, 1503), and were women (60.0%, 1137). As for living conditions, 37.9% (95%CI: 35.8-40.1) of the participants live in apartments, and 62.1% (95%CI: 59.9-64.2) live in ger areas (Table 1). 67.9% (n = 558) of the local participants and 57.7% (n = 620) of the UB participants lived in ger areas.

Table 1: The social and demographic parameters of the participants

№	The social and demographic parameters	Total		Male		Female	
		Num	%	Num	%	Num	%
1.	Location						
	Urban	1074	56.6	385	50.7	689	60.6
	Rural	822	43.4	374	49.3	448	36.3
2.	Place of residence						
	Apartment	718	37.9	306	40.3	412	36.2
	Ger	1178	62.1	453	59.7	725	63.8
3.	Age group						
	15-24 years	458	24.2	184	24.2	274	24.1
	25-34 years	530	28.0	234	30.8	296	26.0
	35-44 years	406	21.4	155	20.4	251	22.1
	45 and over	502	26.5	186	24.5	316	27.8
4.	Education						
	No education	26	1.4	9	1.2	17	1.5
	Primary school	37	2.0	13	1.7	24	2.1
	Middle primary school	166	8.8	77	10.1	89	7.8
	High school	546	28.8	240	31.6	306	26.9
	College	263	13.9	117	15.4	146	12.8
	High	858	45.3	303	39.9	555	48.8
5.	Nationality						
	Khalkh	1503	79.3	602	79.3	901	79.2
	Kazakh	313	16.5	134	17.7	179	15.7
	Others	80	4.2	23	3.0	57	5.0
6.	Marital status						
	Single	512	27.0	222	29.2	290	25.5
	Married/live in	1265	66.7	515	67.9	750	66.0
	Divorced/widowed	119	6.3	22	2.9	97	8.5
7.	Number of family members						
	1-2	288	15.2	112	14.8	176	15.5
	3-4	927	48.9	380	50.1	547	48.1
	5 or higher	681	35.9	267	35.2	414	36.4
8.	Employment status						
	Government organization	502	26.5	134	17.7	368	32.4
	NGO	64	3.4	28	3.7	36	3.2
	Private companies	225	11.9	147	19.4	78	6.9
	Self-employed	379	20.0	167	22.0	212	18.6
	Herder	171	9.0	96	12.6	75	6.6
	Student, student	289	15.2	103	13.6	186	16.4
	Pension/welfare	143	7.5	48	6.3	95	8.4
	Unemployed	123	6.5	36	4.7	87	7.7
	Total	1896	100.0	759	100.0	1137	100.0

The average number of family members was 4.06 ± 1.52 , with a minimum of 1 and a maximum of 16 members. Respondents who have 3-4 members in their family composed 48.9%. The study participants were

from 15 various ethnical groups. However, the Khalkh ethnicity represented 79.3% (95%CI: 77.5-81.2) of the total respondents, and 16.5% (95%CI: 14.7-18.2) were from the Kazakh ethnicity. If 20.0% of the respondents

were self-employed, 26.5% worked in government organizations and 15.2% were students.

In the baseline survey, 2.1 percent of the total participants were herders, and 10.7 percent were students, while in the follow-up survey, the number of these participants increased (herders 9.0%, 171, students 15.2%, 289). According to other participants, the representing number remained similar to the population of the baseline survey. 59.4 percent (1127) of the respondents said that the average household income has decreased, and 3.1 percent (59) remain the same. Of the total participants, 39.2 percent (95% CI: 37.0-41.3) were from Songinokhairkhan district, 17.4 percent (95% CI: 15.6-19.1) were from Chingeltei district, and 15.8 percent (95% CI: 14.2-17.4) were from Bayan-Ulgii aimag.

The majority of participants from Ulaanbaatar city were aged 25-34 and had a higher level of education. In terms of location, 57.7% (620) of them resided in the ger area. While participants of age 25-34 years in rural areas comprised 27.7% and 67.9% of them lived in ger areas.

The survey participants' sociodemographic pattern was similar to Mongolia's statistics, demonstrating that survey sampling has the power of the Mongolian population aged between 15-60.

b) Knowledge of COVID-19

Out of 14 knowledge questions that should be known about coronavirus infection, survey participants

had known in an average of 8.27 ± 3.73 (95%CI: 8.12-8.43) correct answers, which was lower than the results of the baseline study.

It has been defined statistically significant differences in knowledge of coronavirus infection on the location, gender, age group, marital status, education level, employment status, and type of housing of the surveyed participants. The average knowledge score for the urban population is approximately 8.44 ± 3.69 , which is 4 points higher than for the rural participants. The mean knowledge score for surveyed women (8.55 ± 3.62 , 95%CI: 8.34-8.77) was statistically significant 0.7 points higher than that of men (7.85 ± 3.85 , 95%CI: 8.10-8.77). Average correct answers of knowledge scores on coronavirus infection were higher among 15-24-year-olds (8.75 ± 3.54) and over 45 years of age group (8.35 ± 3.72). As the population's level of education increased, the average knowledge score on the coronavirus infection increased, and the statistically significant high of the participant with higher education levels was 8.81 ± 3.53 . The average knowledge score of infection was significantly high among employees of Government, Non-Government, private entities, and students were higher than the self-employer, herders, pensioners groups, and the unemployed participants. The knowledge score of the participants living in apartments (8.88 ± 3.50) was found to be 1.0 points higher than in the ger areas residents (Table 2).

Table 2: Social and demographic characteristics of the study participants, by average knowledge score

Selected indicators	Number	%	Average knowledge score, \pm SD 95%CI			P value
			Average	Min	Max	
Region						
Urban	1074	56.6	8.44 ± 3.69	8.24 ± 3.58	8.67 ± 3.80	0.003
Rural	822	43.4	8.04 ± 3.77	7.80 ± 3.64	8.31 ± 3.89	
Sex						
Male	759	40.0	7.85 ± 3.85	7.56 ± 3.73	8.10 ± 3.97	0.008
Female	1137	60.0	8.55 ± 3.62	8.34 ± 3.50	8.77 ± 3.73	
Age group						
15-24 age	458	24.2	8.75 ± 3.54	8.41 ± 3.33	9.09 ± 3.71	0.007
25-34 age	530	28.0	7.97 ± 3.79	7.65 ± 3.64	8.31 ± 3.93	
35-44 age	406	21.4	8.01 ± 3.83	7.63 ± 3.66	8.37 ± 3.99	
Above 45 age	502	26.5	8.35 ± 3.72	8.03 ± 3.56	8.67 ± 3.87	
Marital status						
Never married	512	27.0	8.49 ± 3.67	8.17 ± 3.51	8.80 ± 3.85	0.003
Married / living with a partner	1265	66.7	8.13 ± 3.74	7.92 ± 3.64	8.35 ± 3.82	
Divorced / Widowed	119	6.3	8.78 ± 3.81	8.10 ± 3.35	9.47 ± 4.14	
Education level						
No education	26	1.4	6.27 ± 4.04	4.77 ± 3.40	7.83 ± 4.52	0.023
Primary education	37	2.0	7.16 ± 4.20	5.77 ± 3.53	8.37 ± 4.72	
Lower secondary education	166	8.8	7.29 ± 3.89	6.71 ± 3.62	7.86 ± 4.14	
Upper secondary education	546	28.8	8.01 ± 3.76	7.69 ± 3.61	8.32 ± 3.91	

Selected indicators	Number	%	Average knowledge score, ± SD 95%CI			P value
			Average	Min	Max	
College	263	13.9	8.01 ± 3.81	7.51±3.58	8.48±4.01	0.026
Higher education	858	45.3	8.81 ± 3.53	8.57±3.39	9.05±3.67	
Work status						
Government employee	502	26.5	8.92 ± 3.55	8.59±3.37	9.21±3.72	
Non-government employee	64	3.4	8.47 ± 3.77	7.51±3.24	9.32±4.22	
A private company, enterprises	225	11.9	8.40 ± 3.83	7.88±3.56	8.90±4.06	
Self-employed	379	20.0	7.72 ± 3.64	7.39±3.62	8.07±3.69	
Herder	171	9.0	7.20 ± 4.12	6.57±3.84	7.83±4.34	
Student	289	15.2	8.79 ± 3.59	8.39±3.33	9.19±3.82	
Retiree	143	7.5	7.80 ± 3.85	7.17±3.55	8.44±4.12	
Unemployed	123	6.5	7.73 ± 3.82	7.07±3.48	8.39±4.12	
Ethnicity						
Khakh	1503	79.3	8.47 ± 3.66	8.29±3.56	8.64±3.75	0.023
Kazak	313	16.5	6.96 ± 3.85	6.50±3.63	7.38±4.04	
Other	80	4.2	8.27 ± 3.73	8.09±3.64	8.44±3.81	
Apartment type						
Apartment	718	37.9	8.88 ± 3.50	8.60±3.35	9.15±3.63	0.016
Ger districts	1178	62.1	7.89 ± 3.82	7.68±3.71	8.12±3.92	
Total	1896	100.0	8.27 ± 3.73	8.12±3.65	8.43±3.82	

Although the percentage of the surveyed participants is aware of the symptoms and prevention measures of COVID-19, the knowledge of the incubation period, the high-risk population and the transmission route are poor (Table 3).

Table 3: Comparison of the first and follow-up survey results of knowledge of coronavirus infection.

№	Knowledge questions	Answer's version	Percentage of participants, 95%CI		P value
			Baseline2020	Follow-up, 2021	
1.	How is COVID-19 transmitted?	When an infected person coughing, sneezing, and close contact with an infected person	58.1	47.8	0.000
			55.8-60.4	45.5-50.4	
2.	Do you know the duration of COVID-19 incubation period?	Yes, I know	25.6	64.3	0.000
			23.5-27.6	62.1-66.4	
3.	How is the most risky for COVID-19?	Elders, chronically ill person (heart, lung, diabetes, kidney)	41.9	37.3	0.005
			39.6-44.2	35.1-39.5	

c) Attitude towards COVID-19

54.5 percent of surveyed participants believed that the pandemic is "very dangerous". However, it has decreased by 25.6 percent compared to the baseline survey. The inadequate facilities for handwashing in markets and public centers, poor hand-washing facilities in large shopping malls, and additional funding for households to purchase masks and hand sanitizers are making trouble facing coronavirus infection prevention measures. Positive attitudes toward the right place at the onset of symptoms of COVID-19 and non-discrimination against infected people are more

prevalent in a population with a high average knowledge score.

d) Adaptation Practices toward COVID-19

Despite health care service demand, 23.2% of the survey participants (95% CI: 21.3-25.1) did not receive health care service in the last 6 months. Participants who did not receive medical care mentioned a fear of getting infected with COVID-19 (37.9%, 95%CI: 33.3-42.5) and hospital overcrowding (33.5%, 95% CI: 28.9-38.1). According to the location of surveyed participants infected with a COVID-19, their marital and employment status were statistically

significant. For example, participants who had COVID-19 living in urban areas were employees of government organizations, or self-employed. Whereas this indicator in rural areas was high among herders and employees of governmental organizations.

On average, 61.98 (95% CI:57.8–66.02) days after the last vaccination, people had been infected. 18.2 percent of the participants who had a COVID-19 (95% CI:15.4-21.4) became infected within 14 days of the last vaccination.

Of the participants who did not receive one, two, or three vaccine doses, 1,843 responded why they didn't get vaccinated. 47.5 percent of them said, "I got sick after taking....the dose", 19.9 percent said they did not get the vaccine due to negative information about the vaccine, and 12.0 percent did not get vaccinated due to their busy schedule. One in 10 surveyed participants (95% CI: 8.8-11.4) said they did not have personal hygiene hand sanitizers, wet wipes, paper tissue, and replacement facial masks.

According to the findings of the follow-up survey, hands washing frequency (50.5% to 83.2%), washing hands in the correct steps (21.4% to 39.1%), using soap regularly (26.0% to 53.2%), and spending 20 seconds when washing their hands (16.1% - 33.5%) were found that changes in handwashing behavior compare with the results of the baseline study (Figure 1). The practice of coughing and sneezing was defined by the observation method, and no changes in the baseline study results were observed in the follow-up survey. The frequency of cleaning and disinfection of the home and disinfectants (chloramine, javelin) has increased compared to the baseline survey results. The practice of wearing masks in the crowding places and

outdoors increased by 6.8 percent from the baseline survey. Compared to the baseline survey results, the follow-up survey (73.0%) had a better practice of wearing masks in the workplace or indoor space.

In the baseline study, the average duration to wear a mask was 29 hours, while in the follow-up survey, it was 4.2 hours, which shows improvement in the correct behavior. Compared to the baseline survey results, the frequency of cleaning and disinfection of the home and disinfectants (chloramine, javelin) has increased. Of those 63.9 percent of the surveyed participants (95% CI: 59.0-63.1) had declined frequent outings, 18.4 percent did not go out at all, 61.1 percent had been spent less time going to public entertainment and services, and 22.0 percent did not go to shows at all. Of those, 77.5 percent of participants (95%CI: 75.5-79.3) received information about the infection from television and 60.8 percent from social media. The lack of information on the infection in manuals, brochures, and newspapers is due to not developing information packages. Information on coronavirus infection was rarely available in newspapers and manuals (Table 4).

43.6% of survey respondents (95%CI: 41.3-45.8) demanded more information on the new vaccine. 41.2% (95%CI: 39.1-43.5) on the adaptation, and 40.1% (95%CI: 37.7-42.2) new variant of COVID-19. Most of the adolescents surveyed criticized the regular informing of the number of deaths and confirmation cases of COVID-19 as frightening. In the baseline survey, 42.4 percent of participants desired more information about the vaccine, while in the follow-up survey, 34.9 percent said they needed information about the future trend of COVID-19 infection.

Table 4: The main sources of information, by age group

No.	Information sources	15-24	25-34	35-44	45 <	P value
1.	Television	71.6	75.1	80.3	83.1	0.001**
2.	Newspaper/magazine	14.2	13.4	14.8	19.7	0.025
3.	Social network	73.6	72.1	55.4	41.6	0.001**
4.	Brochure, handbook	10.9	14.2	15.3	16.5	0.084
5.	Radio	10.7	13.0	14.8	18.9	0.003**
6.	Family, friends and colleagues	39.5	40.2	37.4	32.9	0.071
7.	Didn't get	1.7	2.3	3.0	1.6	0.492
	Total	458	530	406	502	

* **Statistically significant

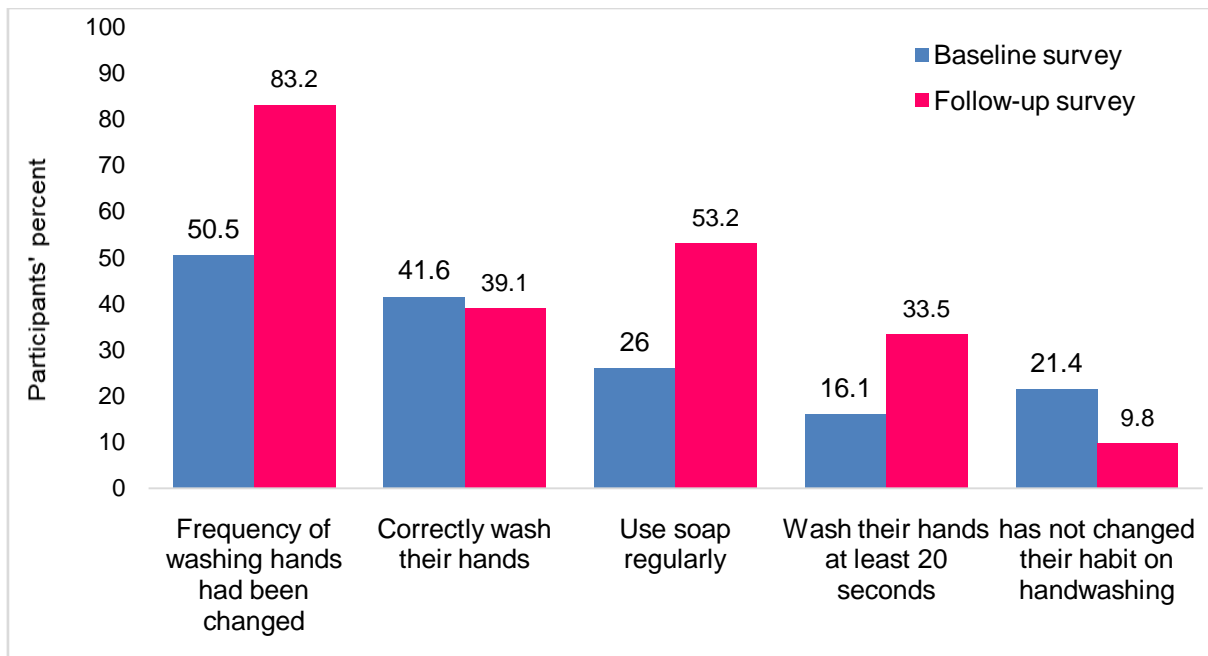


Figure 1: Changing habit on handwashing of participants, by percentage.

IV. DISCUSSION

Unprecedented measures have been adopted to control the rapid spread of the ongoing COVID-19 epidemic in China. An online sample of Chinese residents was successfully recruited via in Hubei, China. Among the survey participants (n=6910), 65.7% were women, 63.5% held a bachelor's degree or above, and 56.2% engaged in mental labor. The overall correct rate of the knowledge questionnaire was 90%. Nearly all of the participants (98.0%) wore masks when going out in recent days. In multiple logistic regression analyses, the COVID-19 knowledge score (OR: 0.75-0.90, P<0.001) was significantly associated with a lower likelihood of negative attitudes and preventive practices toward COVID-2019.⁵ According to the results, the majority of respondents (74.8–88.0%) were fairly or very confident about the level of knowledge. As for the attitude scale, the majority of respondents (82.0–92.4%) agreed or strongly agreed to hold a positive attitude toward the COVID-19 pandemic. They held the opinion that the outbreak deserved serious attention and had full confidence in the government's interventions. For the practice scale, there was also a majority of respondents (79.0–97.1%) reporting to be cautious in the prevention. The main reasons for barrier lay in limited knowledge (49.4%), influenced by the surrounding population (40.4%), limited or no access to COVID-19 information (34.8%), and attaching little importance to the outbreak (32.6%).⁶ In Tanzania, 472 adults participated in the survey. The levels of knowledge, attitude, and practices related to COVID-19 were found in 76.5%, 74.8%, and 58.1% of participants respectively. On performing multivariate analysis, odds of having good knowledge

regarding COVID-19 were almost 2 folds higher in participants who were females, with high education levels, those without partners, and those with stable income. Females were 1.5 folds more likely to have a good attitude toward COVID-19 and odds of good practice against COVID-19 were 3 folds higher in young adults compared to the elderly.⁷ A total of 872 subjects (female, 534; male, 338) were enrolled with ages from 17 to 25 years old of 10 universities in Shaanxi Province, China. Results showed that appropriate knowledge was acquired by 82.34% subjects; the levels were significantly higher in undergraduates from public universities and medical majors than those from private schools and non-medical majors (p<0.05). 73.81% of subjects reported positive attitudes; females showed significantly higher levels of positive attitudes than males (p<0.05). There was a positive correlation between attitude and practice (r = 0.319, p < 0.05) in the whole study group.⁸ In Liberia, the male participants, on average, achieved higher knowledge (52%) and attitude scores (72%), in contrast to females (49% and 67%, respectively). Radio (71%) was the most cited source for COVID-19 information, followed by social media (63%). After controlling for sociodemographic variables, adaptive regression modelling revealed that survey mode achieved 100% importance for predicting knowledge and practice levels with regard to COVID-19.⁹ In Uganda, 83.9% health care workers had sufficient knowledge, 78.4% had a positive attitude, and 37.0% had good practices toward COVID-19. Health care workers in Uganda have good knowledge and positive attitude but poor practices towards COVID-19. Differences in COVID-19 knowledge, attitude and practice between clinical and non-clinical people could

affect uptake of COVID-19 interventions including vaccination.¹⁰ In meta analysis review, 89.87% (95% CI: 67.71–97.40) understood about COVID-19 symptoms, 92.09% (95% CI: 84.32–96.18) knew about how it spreads, and 79.51% (95% CI: 59.38–91.15) knew about how to treat it. The public's perception of controlling COVID-19 is mixed, with only 44.16% (95% CI: 35.74–52.93) and 60.28% (95% CI: 49.22–70.38) believing the country would win the struggle against the pandemic and the infection will be successfully controlled, respectively. Although overall COVID-19 preventative practice was good, subgroup analysis found that men had a poor practice toward controlling the infection. The practice of avoiding crowded places (70.15%) and maintaining social distance (77.17%) was found to be satisfactory in institution-based studies.¹¹

Of the 2168 respondents, most were young adults (62.7%), females (62.4%), tertiary educated individuals (84%), non-health care workers (85.9%), and individuals who knew someone diagnosed with COVID-19 (75.2%). The mean score for knowledge was 10.0 ± 1.52 (maximum score = 12); correct response rate for each question ranged from 54.2% to 99%. The mean score in terms of attitude was 1.3 ± 0.85 (maximum score = 2); 68.7% respondents agreed that control over COVID-19 would finally be achieved; and 62.3% believed that Malaysia could conquer COVID-19. The mean score for practices was 5.1 ± 1.10 (maximum score = 6); 81.5%, 88.1%, and 74.1% respondents avoided crowded places, confined spaces, and conversations in close physical proximity, respectively. Furthermore, 94.2% wore masks when leaving home; 89.0% practiced hand hygiene; and 83.8% adhering to COVID-19 warnings. Small but significant correlations were found between knowledge and attitude ($r = 0.078$, $p < 0.001$) as well as between knowledge and practices ($r = 0.070$, $p = 0.001$)¹²

A study in Iran found that although overall the knowledge of COVID-19 was about 90% among participants, single men has shown significantly low score¹³ similar to our findings. Most Malaysians were aware of preventive measures such as avoiding public gatherings (83.4%) and practicing hygiene (washing hands) (87.8%). This trend also found in study that the majority of the population had a reduced their visits to households and outdoor activities.¹⁴ According to our country, the current survey is the second survey on coronavirus infection in Mongolia; it aims to create conditions and practices for the government and public health organizations to implement preventive measures against infectious diseases.

V. IMPLICATIONS FOR BEHAVIORAL HEALTH

Out of 14 knowledge questions that should be known about coronavirus infection, survey participants had known in an average of 8.27 ± 3.73 (95%CI: 8.12-

8.43) correct answers, which was lower than the results of the baseline study. The average knowledge score of the surveyed participants of the follow-up survey (9.23 ± 3.2 , 95%CI: 9.09-9.38) was smaller than the baseline survey by 0.96 percent. It might be due to the new variant of coronavirus, and its changes in the incubation period, clinical symptoms, and preventive measures. The mean knowledge score of women in the baseline survey (9.43 ± 3.14) and the follow-up survey (8.55 ± 3.62) of coronavirus infection was significantly higher than that of men ($p=0.0001$). As the population's level of education increased, the average knowledge score on the coronavirus infection increased, and the statistically significant high of the participant with higher education levels was 8.81 ± 3.53 ($p=0.0001$). The average knowledge score of the employed population was statistically higher than that of the herders, the self-employed, the unemployed, and the retired group of people in both surveys. In the first (8.94 ± 2.61) and follow-up (6.96 ± 3.85), survey results show that the average knowledge score of Bayan-Ulgii aimag was 0.29 and 1.31 lower than the average knowledge score of the total surveyed participants. The incubation period has changed due to the new variant of the SARS-CoV-2 virus. Therefore, 66.4 percent of the respondents said they did not know the incubation period, 14.4 percent more than the baseline survey results. In the baseline study, most of the participants said that wearing a mask (93.9%), keeping a distance between people (81.1%), and washing their hands with soap for at least 20 seconds (79.1%) would prevent infection. According to the follow-up survey findings, wearing a mask (75.1%), keeping distance between people (68.8%), and washing hands with soap for at least 20 seconds (64.9%) decreased by 12.3-18.8 percent, respectively, and 83.9 percent were vaccinated.

According to the baseline survey findings, 80.6 percent (95%CI: 78.2-81.9) of surveyed participants believed that pandemic is "very dangerous". It was 54.5 percent (95%CI: 52.2-56.7) has decreased by 26.1 percent compared to the baseline survey.

In addition, 23.0 percent of participants (95% CI: 21.1-24.9) responded that their relationship would change if they found out that someone had been cured of COVID-19, whereas in the baseline survey, it was 90.2 percent (95% CI: 88.8-91.6). This suggests that the baseline survey participants considered the pandemic "very dangerous" and discriminated against those who fell ill and recovered. However, in the follow-up survey result, this decline may be due to the ability of Mongolians to adapt quickly to anything.

Our survey has found that many positive changes in the handwashing practice of the population have been made. In the baseline study, 1 in 5 participants said there was no change in handwashing habits, but this follow-up survey dropped to 1 in 10 participants. Compared to the baseline survey results,

the frequency of handwashing increased by 32.7 percent, washing with soap regularly increased by 27.2 percent, and the time spent on washing hands at least 20 seconds increased by 17.4 percent. There is a tendency among adults to become positive behaviours if they continue to implement IEC/BCC strategies that promote positive change in the practice of handwashing.

The practice of avoiding touching the eyes, nose, and mouth with dirty hands decreased by 16.3 percent from 66.9 percent (95% CI: 64.7-69.2) in the baseline study to 50.6 percent (95% CI: 48.3-52.8) in the second study ($p = 0.0001$). The preventive measure for the infectious intestinal disease is to wash hands with soap and water before preparing food and drink, before

eating and drinking, and after using the toilet. Therefore, below shows the incidences of intestinal infectious diseases (salmonellosis, dysentery, hand, foot and mouth disease, food poisoning) registered nationwide in 2018-2021.

In 2021, when the coronavirus infection outbreak was reported, 1,017 cases of intestinal infections were registered, of which 732 (71.9%) were cases of dysentery. Nationwide, 9572 cases were registered in 2018 and 8497 cases in 2019, but in 2020 it reached 5113, which is 1.7 times less than the previous year, and in 2021 it was declined by 5 times. This indicates the positive change in the handwashing behaviour of the population¹⁵.

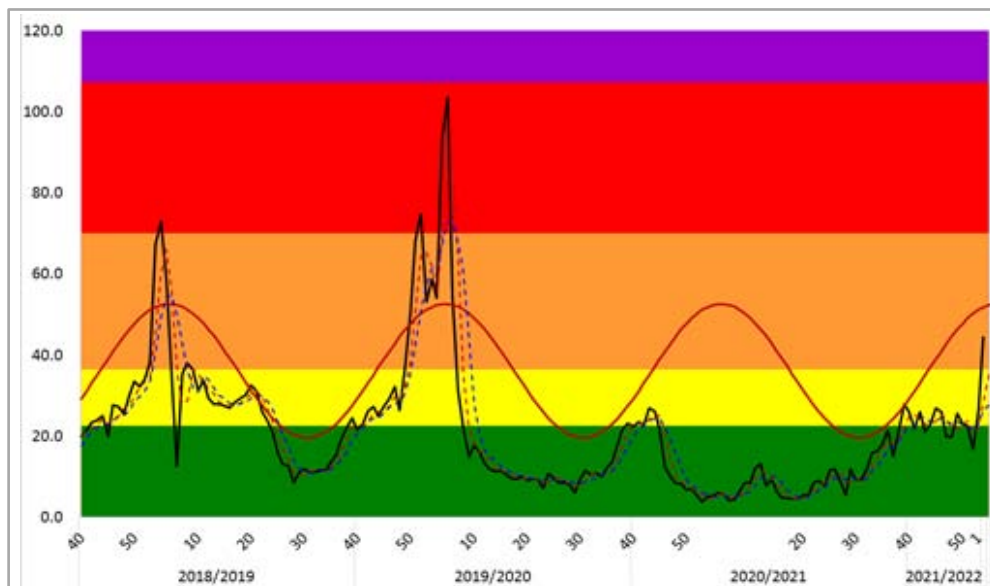


Figure 2: Tendency of influenza and influenza-like illness, by 10000 population.

Of those, 79.2 percent of survey participants (95%CI: 77.4-81.0) reported that coughing and sneezing in their elbows or with paper tissue when they were not covered mouth has been increased by 2.6 percent from the baseline survey (76.6% and 95% CI: 74.6-78.6). There is an increased awareness of the risk of coronavirus infection through coughing and sneezing and improving correct habits.

The importance of wearing masks to prevent coronavirus infection is reflected in the declining incidence of influenza and influenza-like illness reported in Mongolia.

Every year in our country, seasonal influenza is registered as an outbreak among the general population, increasing the workload of hospitals and healthcare service providers by 2-3 times. No influenza outbreaks have been reported in 2020 due to a comprehensive public health measurement taken during the pandemic since December 2019.

In the last 4 years, influenza and influenza-like illnesses were registered in 2016 and the outbreak was

prolonged for 5 weeks, B and AH1 virus were registered and was lasted for 20 weeks, AH1 and AH3 virus outbreak was extended for 19 weeks. While in 2020, AH3 and B virus registered, and the outbreak lasted only for 3 days.

During the 2016-2019 flu outbreaks, school holidays were somehow regulated, but there were no outbreaks as in 2020 and 2021. This is a positive impact that everyone is getting used to wearing a mask.

The importance of handwashing, masking, cleaning and using disinfection to prevent coronavirus infection was positively reflected in the declining incidence of intestinal infections, influenza, influenza-like illnesses, and acute respiratory infections in Mongolia.

Conflict of Interest Statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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GLOBAL JOURNAL OF MEDICAL RESEARCH: K
INTERDISCIPLINARY

Volume 23 Issue 1 Version 1.0 Year 2023

Type: Double Blind Peer Reviewed International Research Journal

Publisher: Global Journals

Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Waldenstrom Macroglobulinemia's Immunophenotypes and its Relation with Others Hematopathies

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Abstract- Waldenstrom's Macroglobulinemia (MW) is characterized by a type of mature B-cell non-Hodgkin lymphoma with proliferation of lymphoplasmocyte elements in the bone marrow and presence of monoclonal immunoglobulin M gamopathy. Given the rarity of the disease, the wide spectrum of hematopathies can mask the diagnosis of this disease. Therefore, the identification of immunophenotypes is one of the main medical challenges for making an early diagnosis. The present study brings a retrospective and descriptive essay, based on systematic reviews around the main biological markers used to make the diagnosis of patients with Waldenstrom's Macroglobulinemia, through the active search for original articles in the Pubmed, Science direct, Scielo, UpToDate and Portal Capes databases. Six articles with a specific theme were selected, categorized according to the differential diagnoses of Waldenstrom's Macroglobulinemia.

Keywords: *lymphoma, non-hodgkin; immunoglobulin m; immunophenotyping.*

GJMR-K Classification: *DDC Code: 616.4107 LCC Code: RC645.7*



WALDENSTROMMACROGLOBULINEMIASIMMUNOPHENDYPESANDITSRELATIONWITHTOTHERHEMATOPATHIES

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Waldenstrom Macroglobulinemia's Immunophenotypes and its Relation with Others Hematopathies

Nichollas de Lorenzi Carvalho ^α, Alexandre Lemos de Souza ^σ, Andre Chaves Calabria ^ρ,
Claudia Marchezan Spaniol ^ω & Gabrielle Ferreira [¥]

Abstract- Waldenstrom's Macroglobulinemia (MW) is characterized by a type of mature B-cell non-Hodgkin lymphoma with proliferation of lymphoplasmacyte elements in the bone marrow and presence of monoclonal immunoglobulin M gamopathy. Given the rarity of the disease, the wide spectrum of hematopathies can mask the diagnosis of this disease. Therefore, the identification of immunophenotypes is one of the main medical challenges for making an early diagnosis. The present study brings a retrospective and descriptive essay, based on systematic reviews around the main biological markers used to make the diagnosis of patients with Waldenstrom's Macroglobulinemia, through the active search for original articles in the Pubmed, Science direct, Scielo, UpToDate and Portal Capes databases. Six articles with a specific theme were selected, categorized according to the differential diagnoses of Waldenstrom's Macroglobulinemia. Among the articles analyzed, it is known that monoclonal IgM, detected by immunofixation electrophoresis, has a higher diagnostic value in MW compared to other hematopathies. In addition, genetic mutations in MYD88 and in the CXCR4 receptor are frequently found in this pathology, corroborating the possible specificity of these findings in the diagnosis of affected patients. The identification of other specific immunophenotypes, according to the literature, is verified through flow cytometry. Current data point to the MYD88L265P mutation and monoclonal IgM as the main biomarkers, accompanied by the CD19, CD20, CD22 and CD79a immunophenotypes. The CXCR4 mutation is still uncertain, so it needs long-term studies to assess its predictive value in MW.

Keywords: lymphoma, non-hodgkin; immunoglobulin m; immunophenotyping.

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I. INTRODUCTION

Lymphomas are a group of disease characterized by the presence by malignant cells lymphoids that accumulate in the lymph nodes and could be divided in Hodgkin and non-Hodgkin lymphons¹. Among the non-Hodgkin has a group of neoplasms of cells mature T and the neoplasms group of cell mature B, being the Waldenstrom's Macroglobulinemia (WM) one of their examples.

The bone marrow has a physic microenvironment consisting of a range of different cells, including hematopoietics, blood, osteoblasts, osteoclasts, endothelial cells, besides chemokines, growth factors, extracellular matrix and mesenchymal cells². These, characterized by a heterogenous population of auto-renewable cells established by different markers, such as Nestine³, neural-glia antigen⁴ and leptin receptor⁵. Mesenchymal and hematopoietic cells' association leads to secretion of support factors and chemokine binding 12 (CXCL 12), angiopoietin and stem cell factor (binding SCF). In addition, endothelial cells also provide support and maintenance to hematopoietic cells, through secretion of the same factors mentioned above, as well as fibroblast growth factor (FGF2) and Delta-like 1, encouraging the process of supporting medullar microenvironments⁴.

This medullar microenvironment are divided into endosteal niche and vascular niche⁶. First is localized in the interface between bone marrow cells and osteoblasts and they stimulate and regulate the function of hematopoietic cells through a direct connection between the two cells or by via paracrine, where there is cytokines production by the osteoblasts which will act on their cognate receptor in the target cell. Notwithstanding, vascular niche is composed of the sinusoidal capillaries and surrounding hematopoietic cells, facilitating their dissemination into the vascular system. This characteristic is considered important in the study of infiltrative hematopoietic, because the physiological conditions of this niche facilitate the development of the pathological mechanism^{6,7}.

In view of the medical difficulty of performing a consistent diagnostic confirmation of this pathology, as it is the same to several other modular neoplasms, this

research's objective was to investigate the pathogenesis of Waldenstrom's Macroglobulinemia and the typical immunophenotypes involved, relating the markers expressed in this pathology and their early diagnosis.

II. MATERIALS AND METHODS

This research is about a retrospective and descriptive trial based on systematic reviews around the main biological markers used to make the diagnosis of patients with Waldenstrom's Macroglobulinemia.

The research planning and development took place between October 2022 and December 2022, through the active search for original articles in the databases Pubmed, Science direct, Scielo and UpToDate using the descriptor "Lymphoma", "immunoglobulin", "diagnosis", separated by semicolons, in Portuguese and English.

Articles published between 2000 and 2020 were selected to address similar topics and explore the differential diagnoses of several etiologies of non-Hodgkin lymphoma and other bone marrow hematopathies to perform comparative analysis

between the different markers and diagnostic methods through review, clinical trials or case studies. The articles were evaluated according to the updates on the subject, predominantly their year of publication, whether they were in Portuguese or English and the quality of the indexed database. The researches that explored similarity with the proposed theme, as well as the pathogenesis and diagnostic criteria of the different gammopathies were included. Articles that did not correspond to the mentioned factors were excluded from the study.

III. RESULTS

Six articles were found with the specific theme, categorized according to the several etiologies that permeate the bone marrow hematopathies that resemble Waldenstrom's Macroglobulinemia.

The articles were summarized according to the author, year of publication, the hematopathy and the biomarkers used for the diagnosis and will be presented in table 1.

Table 1: Waldenstrom's macroglobulinemia and its main differential diagnoses

Author	Year of publication	Hematopathy	Biomarkers and diagnostic technique
Andrade ⁸	2009	Monoclonal Gamma disease of Undetermined Significance	IgG or IgA serum levels >3mg/dL or monoclonal proliferation <10% of plasma cells in the bone marrow; differs from multiple myeloma by the absence of lesions in peripheral organs.
Calheiros et al ⁹	2010	Multiple Myeloma	Expression of myeloid markers (CD117++, CD33++, CD28++, CD56++, CD13++) on the surface of myelomaplasmocytes by immunohistochemistry or flow cytometry methodology.
Rajkumar et al ¹⁰	2014	Multiple Myeloma	Monoclonal IgM plasmocytes presence in 10 to 60% and/or serum monoclonal protein (IgG or IgA) >30g/L by immunohistochemical biopsy analysis.
Treon et al ¹¹	2014	Waldenstrom's Macroglobulinemia	Mutation in the MYD88L265P gene, identified by the allele-specific polymerase chain reaction technique (PCR-AE); mutation in the CXCR4 terminal in DNA analysis of bone marrow aspirate and sequencing by the Sanger method.
Rodrigues et al ¹²	2016	Chronic Lymphocytic Leukemia	Presence of $5 \times 10^9/L$ monoclonal $CD5^+/CD23^+$ B lymphocytes in peripheral blood, using the flow cytometry technique.

<p><u>Dimopoulos;</u> <u>Kastritis</u>¹³</p>	<p>2019</p>	<p>Waldenstrom's Macroglobulinemia</p>	<p>Biopsy shows medullary infiltrate with >10% monoclonal IgM and infiltration by clonal lymphoplasmocyte cells, detected by immunoassay electrophoresis.</p>
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IV. DISCUSSION

MW is a rare condition, representing approximately 2% of cases of Non-Hodgkin's Lymphoma¹⁴, with a higher prevalence in adult Caucasian male patients, around the seventh decade of life and has an incidence of 3-4/1,000,000 cases per year^{4,15}.

Histologically, it is characterized by proliferation of lymphoplasmocyte elements in the bone marrow and the presence of monoclonal immunoglobulin M (IgM) gamopathy^{1,2}. Although the presence of this serum paraprotein is related to lymphoplasmocyte lymphoma (LPL), it is not a typical marker of this pathology. Based on the bone marrow involvement status, LPL is categorized into the subtypes: Waldenstrom's Macroglobulinemia and non-MW LPL⁴.

Normally, MW shows itself as an indolent disease, although there is considerable heterogeneity in its clinical manifestations when present. In about 25% of the patients are asymptomatic and with almost 40 to 70% develop symptoms within 3 and 10 years after diagnosis, respectively⁵. Among the main signs and symptoms, anemia is prevalent in most patients due to insufficient erythropoiesis due to infiltration of the medulla and decreased erythrocyte survival related to IgM hemolysis. 25% of patients have lymphadenopathy and/or hepatosplenomegaly⁵. Another recurrent manifestation in patients with MW is the hyperviscosity syndrome, due to the involvement of peripheral blood, which leads to dizziness, pain, ataxia, visual disorders, deafness, nystagmus, mucocutaneous bleeding and, in some cases, damage to cognitive function and alteration of mental status^{4,5}.

In MW there is a molecular control with the malignant cells that internalize in the bone marrow. It is known that CXCL12 (stromal-derived factor) is highly expressed in the bone marrow of patients with MW and its action is aggravated by the mutation in the CXCR4 chemokine receptor. Increased CXCR4 and CXCL12 interaction promotes a significant homing of malignant cells from MW to bone marrow¹⁶, as is the case with Chronic Lymphocytic Leukemia (CLL). Alsagaby and Alhumaydhi, 2019, cited in their studies that the relationship between CXCR4 and CXCL12 expresses CLL identifying factors in marrow cells, such as prognostic markers CD38 and CD49d, produced by the malignant cells in CLL¹⁷ and other types of leukemia, ensuring their survival in the spinal cord environment. No retrospective study reported the presence of similar markers in Waldenstrom's Macroglobulinemia.

The migration of malignant cells in the stroma of bone marrow promotes the secretion of a number of monoclonal immunoglobulins. The MW studies with a typical finding of monoclonal IgM secretion by B lymphocytes, through the activation factor of B cells (BAFF)¹⁸ present in lymphoplasmocytic cells, which bind to the receptors present in the lymphocytes (BAFF-R), inducing its proliferation, in addition to the action of the chemokine ligand 5 (CCL-5), very much expressed in patients with MW, which stimulates the release of IL-6 by the malignant cells, which will act on the B lymphocytes in the secretion of IgM¹⁹.

The monoclonal immunoglobulin M detection in MW is performed by means of the immunoassay electrophoresis technique^{13,20} from bone marrow biopsy. The accuracy of the diagnosed is limited by the presence of spinal cord infiltrate with monoclonal IgM protein, associated with >10% of lymphoplasmocytic cells^{21,22}, demonstrating, in retrospective studies, sensitivity and specificity of 80.6% and 89.2%²³, respectively. Furthermore, a monoclonal IgM-free LPL, as well as the presence of IgM without histopathological findings of LPL in medullary biopsy, does not give parameters for MW as the main diagnostic assumption¹³, running with differential diagnosis for 377 monoclonal gammopathies, such as nodal lymphoma and Gamopathy of undetermined meaning (MGUS)²⁴, due to its histological characteristics similar to the findings mentioned above.

A similar case of this mechanism was studied in a work on Multiple Myeloma (MM) by Rajkumar et. al in 2014. In it, the author addresses monoclonal IgM secretion as low diagnostic value, since its sensitivity to monoclonal IgA and IgG is minimal and therefore of little value¹⁰. Dauen Ryu and collaborators, 2016, also stated that IgM secretion in the MM is a rare subtype of condition that presents a low prognosis (IgM-MM)²⁵. In addition, myeloma cells express aberrant phenotypes such as CD56+++ , CD117++ , CD33++ , CD28++⁹, documented by the incubation of bone marrow samples with monoclonal antibodies and immunophenotypic analysis in flow cytometry⁹, representing great value in the diagnostic identification of the MM.

Gammopathy of Undetermined Significance (MGUS) has high monoclonal sensitivity in IgG, found in approximately 70% of patients, followed by IgM (15%) and IgA (12%)²⁶. Andrade, 2009, addresses in his scientific study a pathological condition in which a MGUS subtype has serum IgM peaks and medullary findings very similar to MW and other lymphoplasmocytic lymphomas²⁷. In this case, the

differentiation occurs by the clinical history of the patient, showing absence of hyperviscosity in peripheral blood, hepatosplenomegaly and lymphadenopathy^{20,27}.

Studies have shown that monoclonal IgM secretion is not characteristic of Chronic Lymphocytic Leukemia (CLL)^{28,29}. Its gene expression is much greater in CD5⁺ B cells²⁸, leading to clonal expansion in the peripheral blood of adult patients. The differentiation between CLL and MW, besides the absence of monoclonal IgM, is given by clinical and laboratory variants, through the peripheral blood smear with visualization of small mature lymphocytes, increased nuclear density with aggregate chromatin, absence of visible nucleoli²⁹ and presence of at least 5x10⁹/L of B cells with CD5⁺ phenotype in the absence of splenomegaly, hepatomegaly and lymphadenopathy¹². The negativation of the FMC7, CD79b and CD22 fractions in leukemic lymphocytes allows their differential diagnosis with other monoclonal B-cell gamopathies³⁰. This finding is ratified by the study developed by EuroFlow group, through a cytochemical analysis with the combination of several appropriate monoclonal antibody markers, that identify the main markers expressed in CLL cells, such as CD5 +, CD23 + and the absence of FMC7 and CD22 verified by flow cytometry³¹.

It is noticeable that the flow cytometry techniques for the various neoplastic hematopathies of the bone marrow show a great advance in the confirmation of early diagnosis, compared to MW²⁴. The best accepted hypothesis for diagnostic differentiation today is the presence of a population of clonal lymphocytic and plasmocytic cells in the marrow in patients with MW, evidenced by the expression of CD19, CD20, CD22 and CD79a biomarkers, identified by immunohistochemistry or flow cytometry³². As previously mentioned, the presence of a CD22 positive helps in the diagnostic exclusion of other gamopathies, especially CLL, which does not present such a marker in laboratory tests.

This finding complements the analysis performed by B Paiva et. al, 2014, with 244 patients diagnosed with monoclonal IgM, 100 of them with symptomatic MW²⁴. Laboratory studies with malignant MW cells documented higher positivation in light chain B cells and a characteristic phenotyping in these patients (CD19 / CD20/ CD22 [+dim]/ CD25⁺ / IgM+) besides differing from other lymphomas by negativating the expressions CD5, CD10, CD11c or CD103c²⁴.

However, the great value findings in the identification of Macroglobulinemia are by genomic sequencing and identification of somatic mutations in the myeloid differentiation factor (MYD88)¹¹, due to the L265P mutation, which changes the position 265 of leucine in proline in MYD88³³. This mutation activates the kinase associated with IL-1 receptor (IRAK) and Bruton's tyrosine kinase (BRK) promoting the translocation of the

nuclear factor kB-p65 guaranteeing the development and growth of malignant cells¹¹. The studies conducted by Xinfang Yu and collaborators, 2013, demonstrated a low spectrum of this mutational change in different cancers, once ratified by Treon et. al, in 2012, which identified the presence of MYD88^{L265P} in 90% of patients diagnosed with MW included in the study³⁴. The detection of mutations in the LPL MW performed by Vinarkar et. al, 2018, showed a rate of 84.8% of MYD88-L265P patients positive by conventional PCR-AE³⁵ technique, Ondrejka et al and Maria et al, 2013, claimed 100% of MYD88-L265P mutational positivity using the same technique^{36,37}, corroborating the high specificity of this finding in the diagnosis of these patients.

At the same time, the MYD88-L265P mutation is accompanied by CXCR4^{MUT}, a genetic alteration in the chemokine receptor CXCR4³⁸, ensuring the migration of malignant lymphoid cells in the stroma of bone marrow¹¹.

Two classes of mutations are found in CXCR4: CXCR4^{NS} and CXCR4^{FS}, both equally distributed among patients with MW¹¹. Bone marrow and peripheral blood aspiration and analysis by the Sanger method performed by Treon et. al, 2014, in lymphoplasmocyte cells with CD19⁺ markers was the most reliable method for CXCR4 mutational identification¹¹. Another large-scale study presented by Ballester et. al, 2016, reported a high correlation MYD88-L265P and CXCR4^{MUT}, where a clinical trial was conducted with 8 patients with CXCR4 mutation, among which 7 had the diagnosis of MW confirmed by laboratory methods³⁹. Recently, an experimental study by Bárbara Muz and collaborators, 2019, demonstrated the identification of CXCR4^{MUT} through a ⁶⁴Cu (copper) radiomarker, associated with a CXCR4 inhibitor (AMD3100)⁴⁰. The detection of mutation in this gene by in vivo radiolabeling with PET/TC was effective, besides identifying high potential metastatic in patients diagnosed with MW. However, the CXCR4 mutation, although rarely, has also been found in patients with the congenital immunodeficiency syndrome associated with chronic leukopenia (WHIM)⁴¹, given its pleiotropic properties. Thus, reducing the specificity of the mutation of this gene in MW.

V. CONCLUSION

The Waldenstrom Macroglobulinemia diagnosis is one of the most current medical challenges of modernity, given the rarity of the disease. Laboratory and clinical findings show a potential path for specific diagnosis of this pathology, even though there is a broad spectrum of hematopathies triggered by bone marrow dysfunction that, in certain cases, can mask this path.

Immunophenotypes, in general, are the main markers for the differentiation between medullary neoplasms. According to the analysis of the subject, it is

evident that monoclonal IgM still shows itself as the biomarker of great accuracy in the diagnosis of MW, associated with greater expression of CD19, CD20, CD22 and CD79a, resulting from lymphoplasmatic infiltration. Together with these findings, the gene mutation MYD88L265P complements the diagnosis, due to the great specificity of the disease in question, obtained through gene sequencing.

Another mutation under study is the one in the CXCR4 gene. Although the above findings ratify the mutation hypothesis in this specific receptor, few studies have brought significant results correlated with its presence in Waldenstrom's Macroglobulinemia, emphasizing the importance of long-term research in this area to reach a concrete conclusion on the predictive value of the CXCR4 mutation in this pathology.

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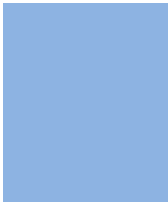
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1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Appealing Decisions

Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

Global Journals is in partnership with various universities, laboratories, and other institutions worldwide in the research domain. Authors are requested to disclose their source of funding during every stage of their research, such as making analysis, performing laboratory operations, computing data, and using institutional resources, from writing an article to its submission. This will also help authors to get reimbursements by requesting an open access publication letter from Global Journals and submitting to the respective funding source.

PREPARING YOUR MANUSCRIPT

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.



Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

- a) A title which should be relevant to the theme of the paper.
- b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
- c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
- d) An introduction, giving fundamental background objectives.
- e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
- f) Results which should be presented concisely by well-designed tables and figures.
- g) Suitable statistical data should also be given.
- h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

- i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
- j) There should be brief acknowledgments.
- k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



FORMAT STRUCTURE

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, "What words would a source have to include to be truly valuable in a research paper?" Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.



Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

PREPARATION OF ELETRONIC FIGURES FOR PUBLICATION

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

TIPS FOR WRITING A GOOD QUALITY MEDICAL RESEARCH PAPER

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

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10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.



20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.



The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."



Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

THE ADMINISTRATION RULES

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CRITERION FOR GRADING A RESEARCH PAPER (COMPILATION)
BY GLOBAL JOURNALS

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	C-D	E-F
<i>Abstract</i>	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
<i>Introduction</i>	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
<i>Methods and Procedures</i>	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
<i>Result</i>	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
<i>Discussion</i>	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
<i>References</i>	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring



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ISSN 9755896



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