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The Association between Obesity and Mitochondrial Dysfunction: A Mini Review

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ABSTRACT

In times where the prevalence of obesity increases steadily and has become one of the so called "top killers" of the world, it is necessary to understand more how obesity affects our body and more importantly why it affects our body in that manner. To do that this article will emphasize on the bidirectional relationship between obesity and mitochondrial dysfunction. Overall said it appears that in patients suffering from obesity the total number of mitochondria seems to decrease in the different tissues due to an increase in production of the Tumor necrosis factor alpha (TNFa), which stimulates the extrinsic apoptotic pathway. However, it is of high importance to notice that the effects of obesity differ from tissue to tissue (as discussed later). Likewise, the production of Reactive Oxygen Species (ROS) inside the mitochondria, seems to increase also. This increase in ROS is often also associated with damage of the mitochondrial DNA (mtDNA) leading to mutations that may affect important metabolic pathways in the human body. Following mutations in the mitochondrial DNA can also be inherited in a maternal fashion and can lead to metabolic disorders like diabetes. Moreover, it is important to mention that the effects of obesity will also differ from woman to men, because of hormonal reasons that cause different fat deposits in men (more visceral fat) compared to women, that tend to have higher fat deposits at gluteal and femoral subcutaneous regions. On the other hand, there is also a lot of evidence that supports the thesis of mitochondrial dysfunction leading to obesity. For example, in elderly people the volume of mtDNA decreases and may result also in metabolic changes. To conclude, this article gives some possible ideas on how mitochondrial dysfunction could be treated.

1 INTRODUCTION:

Obesity is referred as a medical condition involving excessive accumulation of adipose tissue in the body with a consequent elevated body mass index (BMI) [1]. It is a complex disease that presents a risk to health, since it increases the danger of contract certain diseases such as various Cardiovascular Diseases, Type 2 Diabetes, Sleep Apnea and Depression. Obese people can suffer from excess of fat, which is named adipose tissue. There are two main types of adipose tissue: White Adipose Tissue (WAT) that appears yellow and Brown Adipose Tissue (BAT) that appear "brownish" due to a more elevated number of mitochondria inside it in light microscopy. The role of the White Adipose Tissue is principally to store energy, while the Brown Adipose Tissue is mainly for energy expenditure [2]. The high caloric diet that is nowadays available in more civilized countries and a nutritional transition to processed foods, have become a major health risk, since many countries have witnessed a 2-fold or even 3-ford increase to the incidence of this disorder compared to 30 years ago [1].

Furthermore, other external aspects have been influencing this increase in the rate of incidence, such as more sedentary lifestyles, economic growth, industrialization and mechanized transport [3,4]. According to a study, in 2015-2016, the prevalence of obesity among adults (~40%) was higher than in youth (~20%) and higher among middle aged adults (~43%) rather than younger ones (~36%). A recent study in 2017 showed that the average prevalence of obesity is 31% and is associated with a double increase in the risk of

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coronary heart disease and a 1.5-fold increase in the risk of all-cause mortality [5]. Obesity is a clinical case that might be consequence of several different factors, one of these can be a defect in cells' mitochondria, a mitochondrial dysfunction.

Carl Brenda (1898) was the first to introduce the term "mitochondrion" to humanity. Mitochondrion stands for the greek words "mitos" (thread) and "chondros" (granule) [6]. The mitochondrion is a cell organelle whose function is the cells are known as the powerhouse since most of the metabolic pathways that produce energy occur inside it. Mitochondria are found floating in the cytoplasm of the cell and their number varies depending on cell type, function and energy requirement. Their structure is composed of an outer membrane, an inner membrane that folds the internal part, called matrix, creating structures called cristae. Mitochondria are filled with water and proteins, called enzymes, that catalyze (speed up) the metabolic reactions. Many important reactions are taking place at this organelle such as the Citric Acid Cycle (Krebs Cycle), the Fatty Acid Oxidation (β Oxidation), the Urea Cycle and the Electron Transport Chain. It is discovered lately that the mitochondria play also an important role in the Apoptosis and cell death [7,8,9].

More detailed the Fatty acids once are broken down to Acyl-Coenzyme A (Acyl-CoA) are traveling through the carnitine pathway in the mitochondrial matrix and entering the Krebs Cycle. Glycolysis, that converts Glucose to Pyruvate, has the same "ending titles" since Pyruvate is converted to Acetyl-CoA and enters the Krebs Cycle as well. Many Amino Acids enter the Krebs Cycle too and the end products of the Krebs Cycle are Nicotinamide Adenine Dinucleotide (NADH), Flavin Adenine Dinucleotide (FADH2) and Guanine Triphosphate (GTP). However, our cells need Adenosine Triphosphate (ATP), so those three products have to undergo the Electron Transport Chain (ETC) and convert to ATP. The ETC is composed by five complexes that use H2O and two electron transporters to convert the redox active coenzymes to ATP. If there is a decrease in O2 availability, there will be an activation of transcriptional responses to preserve tissue O2 supply and increase glycolytic activity. This results in the production of Reactive Oxygen Species (ROS) in Complex III of the ETC in mitochondria, leading to high levels of mitochondrial mutations and other alternations [10].

Mitochondria have their own DNA that has prokaryotic nature since it is circular, covalently closed and double stranded. The mitochondrial genome (mtDNA) is maternally inherited and has high possibility to be mutated because of the inability of the Polymerase γ to repair the possible mutations and the exposure to ROS. In the past 30 years more than 250 mtDNA mutations have been classified and only recently it has been possible to estimate a rate of incidence to mitochondrial disorders, which is approximately, in adults, 12.5 every 100.000 individuals, and one in 4300 people carries mitochondrial mutations [11].

2 CURRENT STATUS OF KNOWLEDGE:

Obesity and Mitochondrial Dysfunction

Mitochondrial Dysfunction can be caused by different pathways, substances such as ROS, and conditions such as Obesity. All three can be related to each other since the human metabolic pathways do not happen through one way, but through many different ways. Following there are three different pathways, through which is believed that Obesity can affect mitochondrial function.

Extrinsic apoptotic pathway

Obesity and high fat diet can cause mitochondrial dysfunction due to reduction of the mitochondrial numbers because of an increase in Tumor Necrosis Factor alpha (TNFa), that will lead to Caspase 8 activation and release of the Cytochrome C causing apoptosis [12]. However, in astrocytes TNFa enhances the expression of Intracellular Adhesion Molecule 1 (ICAM1) and Major Histocompatibility Complex class II (MHC class II) [13]. Alternations of the mitochondrial genome is another reason for the decrease in mitochondrial size and structure. Also, Enzymatic oxidative Capacity, since the level of mitochondrial biogenesis will be reduced [14,15]. Consequently, ROS will increase and oxygen consumption in adipose tissue will decrease, blocking this way fatty acid oxidation and resulting to lipid accumulation. In contrast, another study showed that decreased ROS levels in 3T3-l1 adipocytes due to pharmacological agents can lower mitochondrial membrane potential as well as IL6 (interleukin- 6 secretion). On the other hand, hyperpolarization of the mitochondrial membrane can cause increased ROS formation and decreased insulin sensitivity [16]. Therefore, mitochondrial dysfunction and obesity are bidirectional, meaning that obesity can lead to mitochondrial dysfunction and mitochondrial dysfunction can lead to further fat accumulation [17,18,19].

Genetical alternations due to increased ROS levels

Although mitochondria are in low-abundant levels in WAT, they play a crucial role in their metabolic pathways, implying that any mutation can affect them. During adipose tissue differentiation mitochondria number and activity increase. The ROS levels though, as well as the duration of their generation are important for the initiation either of a physiological or pathological response [18,19,20,21]. An experiment in the WAT of obese ob/ob mice reported that mtDNA was reduced. However, according to Dahlaman et al. (2006), obesity is not the main cause of mtDNA alternations, but diabetes [22].

Estrogen Hormones

In humans the control of fat distribution is determined by sex hormones. In general, men have less total body fat that is located mostly on the intra-abdominal region, whereas women have more total body fat that is located mostly in the gluteal and femoral subcutaneous regions. It is noticed that the fat distribution can differ in post- and premenopausal women [23,24]. According to some studies Estrogen plays a crucial role in the distribution of fat in menopausal women. However, other studies conclude that the reasons for increasing obesity in menopausal women are

not clear. The decrease in Estrogen levels during the climacteric phase of women, is associated with an increase on the abdominal fat, as well as a decrease of the subcutaneous fat [25]. Accordingly, increase of estrogen in men due to an estrogen therapy, can lead to increase of visceral fat [26,27]. Furthermore, high levels of 17-estradiol (E2) results in a high production of Pro-opiomelanocortin (POMC) causing hyperphagia. In addition to that, they stimulate the secretion of Neuropeptide Y (NPY), which reacts to the Arcuate nucleus (ARC) and Paraventricular nucleus (PVN) in Hypothalamus resulting in Appetite. All these effects, in long term, are followed by fat accumulation, which can lead to obesity and causing mitochondrial dysfunction [28,29,30,31]. Another study with mitochondria in cerebral blood vessels in humans showed that Estrogen increases mitochondrial efficiency, since E2-treatment in vivo elevates the levels of specific proteins, such as Cytochrome C and decreases ROS production. [32]

Mitochondrial Dysfunction and Obesity

The role of mitochondria in the metabolic pathways, as mentioned earlier is essential; hence any dysfunction of this organelle may lead to metabolic syndromes such as obesity. It is a bidirectional pathway, but mitochondrial dysfunction is to be affected by different factors that are associated to Obesity.

The effect of ageing on mitochondria

Changes elicited by the process of ageing include alterations in the process of mitochondrial respiration, changes in the mtDNA, alterations in structure and a lower ATP production [33,34,35,36]. These facts were underlined in study results from animal experiments and cell cultures, which results also added the fact that middle aged mitochondria showed an increase in activity, whereas old mitochondria showed a more depressed activity [37]. This increase in mitochondrial activity however is to compensate the reduction in mitochondrial efficiency, but on the other hand results in a further increase in ROS production. This foster further age-related mitochondrial dysfunctions, that can lead to further disease patterns such as obesity or diabetes Typ 2 [38,39]. However, a trail called the CALERIE reported that physical activity conjoined with calorie restriction seemed to increase the oxidative capacity of skeletal muscle and reduce the risk of cardiovascular disease by approximately 38% compared to the control group, by increasing the lifetime of mitochondria [40,41].

In addition to this, some other studies showed that different pharmacological impacts, including the drugs aspirin and metformin, which seemed also to increase the long-life ability of the mitochondria [42,43,44]. Many anti-ageing studies do not provide enough follow ups to fully validate the results. Also it is important to notice that the results of the CLAERIE study only included previously non obese survey participants,which makes it difficult to transfer those results to other population groups such as already obese people. For the pharmacological therapies, it is important to notice that the time the drug intervention is started and also the selection of survey participants may be crucial for the test results. However, all in all, it can be stated that ageing of mitochondria seems to play a very important role in causing mitochondrial dysfunctions and its associated diseases.

Maternally inherited mutations

Considering that mtDNA is inherited by the mother, mutations in mtDNA can be transmitted from the mother to her children. Mitochondrial DNA mutations can lead to Diabetes Mellitus (DM) that can be associated with other defects such as deafness [45]. In one experiment with 130 patients diagnosed with DM, family history of DM and 3 unrelated patients with mtDNA were screened using genetic diagnostic methods. First degree relatives, of the 3 patients with mtDNA mutation, had this specific mutation also observed. From those patients, most mothers had DM and some of them had sensory hearing loss. In addition to this study, another study concluded that mtDNA mutations of the mother can lead to maternally inherited diabetes and deafness and can be identified through mtDNA testing [46]. This suggests that mtDNA mutations causing diabetes, which can cause obesity, can be inherited maternally [47].

However, those mitochondrial mutations can be age-related changes that can mediate apoptosis and cause ROS induce damage. By the development of the mtDNA mutator mouse, with mutated mtDNA polymerase γ, a study showed that mtDNA mutations can be caused by ageing (as discussed before). Age related changes may lead to atherogenesis and maybe also diabetes [48]. All in all, maternally inherited mutations of mtDNA, ageing that causes mitochondrial dysfunction, deficiency of Estrogens in menopausal women and excess of fat can lead to mitochondrial dysfunction. This dysfunction can affect different organs and tissues of the human body.

Mitochondrial dysfunction in different tissues due to Obesity

Skeletal Muscle

In skeletal muscle excess of fat and especially excess of palmitic acid (PA), leads to mitochondrial fragmentation that is associated with the high levels of oxidative stress, low levels of ATP production and reduce glucose uptake stimulated by insulin [49]. This reduction in insulin sensitivity is associated with mitochondrial dysfunction and partial inability to oxidize fatty acids [50,51,52]. In obese and diabetic patients with type II Diabetes, a change in number and morphology of the mitochondria in the skeletal muscle is to be observed [53,54]. However, the relation between mitochondrial function and fatty acid oxidation is uncertain. According to other researches, while a decrease in fatty acid oxidation was observed in obese human skeletal muscle [55], an increase was found in several different High-Fat Fed mice models [56].

Brown Adipose Tissue (BAT)

In BAT, defects in fatty acid oxidation and abnormal glucose homeostasis due to mitochondrial dysfunction can lead to impaired thermogenesis. Additionally, in patients with specific mtDNA mutation following by mitochondrial dysfunctions, multiple symmetrical lipomatosis was observed [57]. However, evidence from other studies have shown that

mitochondrial activation in BAT is an efficient treatment for obesity prevention by energy expenditure, in alternative to drug therapy and surgery. Although recent studies in mice suggest that, WAT browning is a valid alternative to BAT thermogenesis and can result in resistance to diet-induced obesity and an improvement in metabolism [58], other studies reported that exposure to cold temperatures accelerates plasma lipid dispersion by triglyceride absorption into BAT, resulting into an enhance in dyslipidemia [59]. In addition to that, substances used to imitate the function of activated UCP1 (specialized uncoupling protein in BAT mitochondria), if exceeded, involves side effects such as hyperthermia and even death [60,61,62].

Heart

The effect of mitochondrial dysfunction in the heart is also perceivable. The heart has lots of mitochondria; hence is very vulnerable. As mentioned before, mitochondrial defects can disrupt signaling pathways and protein interactions, leading to increase production of ROS, which can cause cardiac senescence [63]. It is not clear yet, whereas, the mitochondrial dysfunction in the cardiac cells is related to ageing, but obesity can affect mitochondrial function, and this implies also to the heart, since it can cause cardiac failure [64]. Another research states that, the size and appearance of cardiac mitochondria, as well as, the mitochondrial dynamics is not as revealing as the proteins involved in regulating the fusion of cardiac mitochondria [65].

A study in high-fat diet mice showed an abnormal mitochondria density and morphology, abnormal expression of genes that are involved in mitochondrial dynamics, decreased mtDNA replication, low levels of Complex I-III and Citrate Synthase activity, as well as, decrease in mitochondrial respiration. Those findings showed a significant correlation to the fat deposition in the myocardium, and the cardiac hypertrophy and dysfunction that were observed in those mice [66,67]. The same study shows that mitochondrial dysfunction and heart failure can be caused by a chronic exposure to excesses of fatty acids [68]. However, this study was just performed with 40 male rates over a period of 28 weeks [66]. Evidence suggests that there are sex-specific differences between ventricular myocytes in older men and women, which affects the heat failure rate associated with reduced ejection fraction [66]. Moreover, another study confirms that the accumulation of fatty acid is not only a cause of cardiac dysfunction, including heart failure but is also a consequence of it [69].

Additionally, another study shows that a mtDNA mutation at position nt. 4300 of the tRNA gene is associated with hypertrophic cardiomyopathy [70]. Hypertrophic cardiomyopathy is the thickening of the ventricles' walls, which can block the blood flow out of the ventricle leading to even cardiac arrest [71]. Although this disease is heterogeneous, mitochondrial defects inherited by the mother should be considered in differential diagnosis according to Cascli et al.

Treatment

As mentioned earlier, mitochondrial dysfunction can be involved in many diseases, for example cardiac and skeletal myopathies, obesity and diabetes mellitus. One of the best ways to avoid those effects is exercise [72]. Endurance training, for example, improves the ETC activity, whereas resistance training can lead to a reduction of mutated mtDNA by stimulating the incorporation of satellite cells, which have low levels of mutated mtDNA, into existing muscle fibers. Another benefit is the increase in mitochondrial proliferation [69,70]. This theory is supported by another research that states that exercise can improve mitochondrial function while reduction mitochondrial inflammation [73].

But there are also different theories for treatments specific for cardiac malfunction. For example, one study states that, an mitochondria-targeted antioxidant would be a good option for treating a heart disease because the heart is sensitive to oxidative stress caused by the generation of ROS [74]. Another study suggests that, implanting autologously derived mitochondria helps with ischemia-reperfusion injury by enhancing the oxygen consumption, high-energy phosphate synthesis and the proteomic pathways, which is important for the post-infarct cardiac function [75].

Furthermore, Estrogen plays an important role in the development of obesity, studies have shown that Estrogen Therapy is beneficial in menopausal women, since it decreases visceral adipose tissue, fasting glucose serum and insulin levels [76,77]. The physiological form of Estrogen is E2, which is available as oral treatment but also as patches, creams and gels for subcutaneous absorption [78]. In over 100 randomized trials in menopausal women without diabetes, both oral and transdermal treatment increased lean body mass, improved insulin resistance and reduced abdominal fat [79]. However, since it is a selected group of women without diabetes there is no comparison to a group of women with diabetes, which would be the main target group for the treatment.

Lastly, low-carbohydrate diet especially in diabetic patients is significant. Usually diabetic people can be treated with sulfonylurea and insulin. Also, some articles suggest that nitric oxide (NO) deficiency is significant in mitochondrial dysfunction in diabetic patients. The amino acids Arginine and Citrulline can be used as a supplement because they act as NO precursors. However, this treatment is still "unofficial" for diabetic-obese people, but doctors apply it to patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELA) [80].

All in all, there is still absence of therapeutic measures for mitochondrial disorders. A lot of research needs to be done to give more and diverse treatment for the multifaceted mitochondrial dysfunctions [81].

3 CONCLUSION:

Mitochondrial dysfunctions and obesity are in very close association with each other (bidirectional). On one hand mitochondrial dysfunction can lead to obesity by the before mentioned pathway of ageing and maternally inherited mutations in the different tissues of the human body (e.g. heart, BAT or skeletal muscle). On the other hand, obesity can

also cause mitochondrial dysfunction through the extrinsic apoptotic pathway, due to genetical alterations caused by an increase of ROS levels or the influence of Estrogen levels.

All in all, even though there is an association between obesity and mitochondrial dysfunction, more research is needed to better describe the exact Pathway of both, obesity causing mitochondrial dysfunction and the other way around.

DISCLOSURE STATEMENT

The authors have nothing to disclose.

4 REFERENCES :

[1]. Engin A. The Definition and Prevalence of Obesity and Metabolic Syndrome. Obesity and Lipotoxicity. 2017;:1-17.

[2]. Lee, Park, Oh, Lee, Kim, Bae. The Role of Adipose Tissue Mitochondria: Regulation of Mitochondrial Function for the Treatment of Metabolic Diseases. International Journal of Molecular Sciences. 2019;20(19):4924.

[3]. Abel R, Sampathkumar V. Tamil Nadu nutritional survey comparing children aged 0–3 years with the NCHS/CDC reference population. The Indian Journal of Pediatrics. 1998;65(4):565-572.

[4]. Mendez M, Monteiro C, Popkin B. Overweight exceeds underweight among women in most developing countries. The American Journal of Clinical Nutrition. 2005;81(3):714-721.

[5]. Olszowy K, Dufour D, Bender R, Bekelman T, Reina J. Socioeconomic status, stature, and obesity in women: 20-year trends in urban Colombia. American Journal of Human Biology. 2012;24(5):602-610.

[6]. Ernster L, Schatz G. Mitochondria: a historical review. The Journal of Cell Biology. 1981;91(3):227s-255s

[7]. Starkov A. The Role of Mitochondria in Reactive Oxygen Species Metabolism and Signaling. Annals of the New York Academy of Sciences. 2008;1147(1):37-52.

[8]. Williams G, Boyman L, Chikando A, Khairallah R, Lederer W. Mitochondrial calcium uptake. Proceedings of the National Academy of Sciences. 2013;110(26):10479-10486.

[9]. Czabotar P, Lessene G, Strasser A, Adams J. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. Nature Reviews Molecular Cell Biology. 2013;15(1):49-63.

[10]. Bullon P, Newman H, Battino M. Obesity, diabetes mellitus, atherosclerosis and chronic periodontitis: a shared pathology via oxidative stress and mitochondrial dysfunction?. Periodontology 2000. 2013;64(1):139-153.

[11]. Doi H, Tagawa M, Shinohara K. Gaze direction modulates the disengagement of attention from facial expression in 10-month-olds. Emotion. 2010;10(2):278-282.

[12]. Doll D, Rellick S, Barr T, Ren X, Simpkins J. Rapid mitochondrial dysfunction mediates TNF-alpha-induced neurotoxicity. Journal of Neurochemistry. 2015;132(4):443-451.

[13]. Chao CC e. Glia, cytokines, and neurotoxicity. - PubMed - NCBI [Internet]. Ncbi.nlm.nih.gov. 2020 [cited 16 February 2020]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8581983?dopt=Abstract

[14]. Ritov V, Menshikova E, He J, Ferrell R, Goodpaster B, Kelley D. Deficiency of Subsarcolemmal Mitochondria in Obesity and Type 2 Diabetes. Diabetes. 2004;54(1):8-14.

[15]. Mogensen M, Sahlin K, Fernstrom M, Glintborg D, Vind B, Beck-Nielsen H et al. Mitochondrial Respiration Is Decreased in Skeletal Muscle of Patients With Type 2 Diabetes. Diabetes. 2007;56(6):1592-1599.

[16]. Bournat J, Brown C. Mitochondrial dysfunction in obesity. Current Opinion in Endocrinology, Diabetes and Obesity. 2010;17(5):446-452.

[17]. Lin Y, Berg A, Iyengar P, Lam T, Giacca A, Combs T et al. The Hyperglycemia-induced Inflammatory Response in Adipocytes. Journal of Biological Chemistry. 2004;280(6):4617-4626.

[18]. Talior I, Yarkoni M, Bashan N, Eldar-Finkelman H. Increased glucose uptake promotes oxidative stress and PKC-δ activation in adipocytes of obese, insulin-resistant mice. American Journal of Physiology-Endocrinology and Metabolism. 2003;285(2):E295-E302.

[19]. Boudina S, Graham T. Mitochondrial function/dysfunction in white adipose tissue [Internet]. The Physiological Society. 2019 [cited 27 November 2019]. Available from: https://physoc.onlinelibrary.wiley.com/doi/full/10.1113/expphysiol.2014.081414%4010.1002/%28ISSN%291469-445X%28CAT%29VirtualIssues%28VI%29women2015

[20]. Kusminski C, Scherer P. Mitochondrial dysfunction in white adipose tissue. Trends in Endocrinology & Metabolism. 2012;23(9):435-443.

[21]. Gao C, Zhu C, Zhao Y, Chen X, Ji C, Zhang C et al. Mitochondrial dysfunction is induced by high levels of glucose and free fatty acids in 3T3-L1 adipocytes. Molecular and Cellular Endocrinology. 2010;320(1-2):25-33.

[22]. Bournat J, Brown C. Mitochondrial dysfunction in obesity. Current Opinion in Endocrinology, Diabetes and Obesity. 2010;17(5):446-452.

[23]. Dahlman I, Forsgren M, Sjogren A, Nordstr ¨om EA, Kaaman M, ¨Naslund E, Attersand A & Arner P (2006). Downregulation ¨of electron transport chain genes in visceral adipose tissue in type 2 diabetes independent of obesity and possibly involving tumor necrosis factor-α. Diabetes 55, 1792– 1799.

[24]. Talior I, Yarkoni M, Bashan N, Eldar-Finkelman H. Increased glucose uptake promotes oxidative stress and PKC-δ activation in adipocytes of obese, insulin-resistant mice. American Journal of Physiology-Endocrinology and Metabolism. 2003;285(2):E295-E302.

[25]. Garaulet M, Pérez-Llamas F, Zamora S, Javier Tébar F. Comparative study of the type of obesity in pre- and postmenopausal women: relationship with fat cell data, fatty acid composition and endocrine, metabolic, nutritional and psychological variables. Medicina Clinica. 2002;118(8):281–286.

[26]. Toth MJ, Poehlman ET, Matthews DE, Tchernof A, MacCoss MJ. Effects of estradiol and progesterone on body composition, protein synthesis, and lipoprotein lipase

in rats. American Journal of Physiology. 2001;280(3):E496–E501

[27]. Elbers JMH, Asscheman H, Seidell JC, Gooren LJG. Effects of sex steroid hormones on regional fat depots as assessed by magnetic resonance imaging in transsexuals. American Journal of Physiology. 1999;276(2):E317–E325.

[28]. Litwak S, Wilson J, Chen W, Garcia-Rudaz C, Khaksari M, Cowley M et al. Estradiol Prevents Fat Accumulation and Overcomes Leptin Resistance in Female High-Fat Diet Mice. Endocrinology. 2014;155(11):4447-4460.

[29]. Šlamberová R, Hnatczuk OC, Vathy I. Expression of proopiomelanocortin and proenkephalin mRNA in sexually dimorphic brain regions are altered in adult male and female rats treated prenatally with morphine. Journal of Peptide Research. 2004;63(5):399–408.

[30]. Hill JW, Urban JH, Xu M, Levine JE. Estrogen induces neuropeptide Y (NPY) Y1 receptor gene expression and responsiveness to NPY in gonadotrope-enriched pituitary cell cultures. Endocrinology. 2004;145(5):2283–2290.

[31]. de Souza FSJ, Nasif S, López-Leal R, Levi DH, Low MJ, Rubinsten M. The estrogen receptor α colocalizes with proopiomelanocortin in hypothalamic neurons and binds to a conserved motif present in the neuron-specific enhancer nPE2. European Journal of Pharmacology. 2011;660(1):181–187.

[32]. Stirone C, Duckles S, Krause D, Procaccio V. Estrogen Increases Mitochondrial Efficiency and Reduces Oxidative Stress in Cerebral Blood Vessels. Molecular Pharmacology. 2005;68(4):959-965.

[33]. Navarro A, Boveris A. Rat brain and liver mitochondria develop oxidative stress and lose enzymatic activities on aging. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2004;287(5):R1244-R1249.

[34]. DeBalsi K, Hoff K, Copeland W. Role of the mitochondrial DNA replication machinery in mitochondrial DNA mutagenesis, aging and age-related diseases. Ageing Research Reviews. 2017;33:89-104.

[35]. Son J, Sarsour E, Kakkerla Balaraju A, Fussell J, Kalen A, Wagner B et al. Mitofusin 1 and optic atrophy 1 shift metabolism to mitochondrial respiration during aging. Aging Cell. 2017;16(5):1136-1145.

[36]. Harman D. The biologic clock: the mitochondria? Journal of the American Geriatrics Society. 1972;20(4):145–147

[37]. Baker D, Peleg S. Biphasic Modeling of Mitochondrial Metabolism Dysregulation during Aging. Trends in Biochemical Sciences. 2017;42(9):702-711.

[38]. Madreiter-Sokolowski C, Sokolowski A, Waldeck-Weiermair M, Malli R, Graier W. Targeting Mitochondria to Counteract Age-Related Cellular Dysfunction. Genes. 2018;9(3):165.

[39]. Alexeyev MF, LeDoux SP, Wilson GL. Mitochondrial DNA and aging. Clinical Science. 2004;107(4):355–364.

[40]. Psilander N, Frank P, Flockhart M, Sahlin K. Exercise with low glycogen increases PGC-1α gene expression in human skeletal muscle. European Journal of Applied Physiology. 2012;113(4):951-963.

[41]. Lefevre M, Redman L, Heilbronn L, Smith J, Martin C, Rood J et al. Caloric restriction alone and with exercise improves CVD risk in healthy non-obese individuals. Atherosclerosis. 2009;203(1):206-213.

[42]. Hawley S, Fullerton M, Ross F, Schertzer J, Chevtzoff C, Walker K et al. The Ancient Drug Salicylate Directly Activates AMP-Activated Protein Kinase. Science. 2012;336(6083):918-922.

[43]. Amigo I, Menezes-Filho S, Luévano-Martínez L, Chausse B, Kowaltowski A. Caloric restriction increases brain mitochondrial calcium retention capacity and protects against excitotoxicity. Aging Cell. 2016;16(1):73-81.

[44]. Madreiter-Sokolowski C, Sokolowski A, Waldeck-Weiermair M, Malli R, Graier W. Targeting Mitochondria to Counteract Age-Related Cellular Dysfunction. Genes. 2018;9(3):165.

[45]. Harman D. The biologic clock: the mitochondria? Journal of the American Geriatrics Society. 1972;20(4):145–147.

[46]. Alexeyev MF, LeDoux SP, Wilson GL. Mitochondrial DNA and aging. Clinical Science. 2004;107(4):355–364.

[47]. Larsson N. Somatic Mitochondrial DNA Mutations in Mammalian Aging. Annual Review of Biochemistry. 2010;79(1):683-706.

[48]. Chistiakov D, Sobenin I, Revin V, Orekhov A, Bobryshev Y. Mitochondrial Aging and Age-Related Dysfunction of Mitochondria. BioMed Research International. 2014;2014:1-7.

[49]. Jheng H, Tsai P, Guo S, Kuo L, Chang C, Su I et al. Mitochondrial Fission Contributes to Mitochondrial Dysfunction and Insulin Resistance in Skeletal Muscle. Molecular and Cellular Biology. 2011;32(2):309-319.

[50]. Lowell, B.B., Shulman, G.I. 2005. Mitochondrial dysfunction and type 2 diabetes. Science. 307:384-387.

[51]. Simoneau, J.A., Kelley, D.E. 1997. Altered glycolytic and oxidative capacities of skeletal muscle contribute to insulin resistance in NIDDM. J. Appl. Physiol. 83:166-171.

[52]. Petersen, K.F., et al. 2004. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N. Engl. J. Med. 350:664-671.

[53]. Kelley, D.E., He, J., Menshikova, E.V., Ritov, V.B. 2002. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. Diabetes. 51:2944-2950.

[54]. Bonnard C, Durand A, Peyrol S, Chanseaume E, Chauvin M, Morio B et al. Mitochondrial dysfunction results from oxidative stress in the skeletal muscle of diet-induced insulin-resistant mice. Journal of Clinical Investigation. 2008;.

[55]. SIMONEAU J, VEERKAMP J, TURCOTTE L, KELLEY D. Markers of capacity to utilize fatty acids in human skeletal muscle: relation to insulin resistance and obesity and effects of weight loss. The FASEB Journal. 1999;13(14):2051-2060.

[56]. Turner N, Bruce C, Beale S, Hoehn K, So T, Rolph M et al. Excess Lipid Availability Increases Mitochondrial Fatty Acid Oxidative Capacity in Muscle. Diabetes. 2007;56(8):2085-2092

[57]. Bournat J, Brown C. Mitochondrial dysfunction in obesity. Current Opinion in Endocrinology, Diabetes and Obesity. 2010;17(5):446-452.

[58]. Bartelt A, Bruns O, Reimer R, Hohenberg H, Ittrich H, Peldschus K et al. Brown adipose tissue activity controls triglyceride clearance. Nature Medicine. 2011;17(2):200-205.

[59]. Vegiopoulos A, Muller-Decker K, Strzoda D, Schmitt I, Chichelnitskiy E, Ostertag A et al. Cyclooxygenase-2 Controls Energy Homeostasis in Mice by de Novo Recruitment of Brown Adipocytes. Science. 2010;328(5982):1158-1161.

[60]. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nature Medicine. 2013;19(10):1252-1263.

[61]. Jheng H, Tsai P, Guo S, Kuo L, Chang C, Su I et al. Mitochondrial Fission Contributes to Mitochondrial Dysfunction and Insulin Resistance in Skeletal Muscle. Molecular and Cellular Biology. 2011;32(2):309-319.

[62]. Lee, Park, Oh, Lee, Kim, Bae. The Role of Adipose Tissue Mitochondria: Regulation of Mitochondrial Function for the Treatment of Metabolic Diseases. International Journal of Molecular Sciences. 2019;20(19):4924.

[63]. Tocchi A, Quarles E, Basisty N, Gitari L, Rabinovitch P. Mitochondrial dysfunction in cardiac aging. Biochimica et Biophysica Acta (BBA) - Bioenergetics. 2015;1847(11):1424-1433.

[64]. Sun N, Finkel T. Cardiac mitochondria: A surprise about size. Journal of Molecular and Cellular Cardiology. 2015;82:213-215.

[65]. Chen D, Li X, Zhang L, Zhu M, Gao L. A high-fat diet impairs mitochondrial biogenesis, mitochondrial dynamics, and the respiratory chain complex in rat myocardial tissues. Journal of Cellular Biochemistry. 2018;119(11):9602-9602.

[66]. Tocchi A, Quarles E, Basisty N, Gitari L, Rabinovitch P. Mitochondrial dysfunction in cardiac aging. Biochimica et Biophysica Acta (BBA) - Bioenergetics. 2015;1847(11):1424-1433.

[67]. Keller K, Howlett S. Sex Differences in the Biology and Pathology of the Aging Heart. Canadian Journal of Cardiology. 2016;32(9):1065-1073.

[68]. Fukushima A, Lopaschuk G. Cardiac fatty acid oxidation in heart failure associated with obesity and diabetes. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids. 2016;1861(10):1525-1534

[69]. Casali C, Santorelli F, Damati G, Bernucci P, Debiase L, Dimauro S. A Novel mtDNA Point Mutation in Maternally Inherited Cardiomyopathy. Biochemical and Biophysical Research Communications. 1995;213(2):588-593.

[70]. Hypertrophic Cardiomyopathy [Internet]. www.heart.org. 2019 [cited 27 November 2019]. Available from:https://www.heart.org/en/health-topics/cardiomyopathy/what-is-cardiomyopathy-in-adults/hypertrophic-cardiomyopathy

[71]. El-Hattab A, Zarante A, Almannai M, Scaglia F. Therapies for mitochondrial diseases and current clinical trials. Molecular Genetics and Metabolism. 2017;122(3):1-9.

[72]. Taivassalo T, Shoubridge EA, Chen J, Kennaway NG, DiMauro S, Arnold DL, et al. Aerobic conditioning in patients with mitochondrial myopathies: physiological, biochemical, and genetic effects. Ann Neurol. 2001 Aug;50(2):133–141.

[73]. Kang C, Li Ji L. Role of PGC-1α signaling in skeletal muscle health and disease. Ann N Y Acad Sci. 2012 Oct;1271:110–117.

[74]. Vieira-Potter V, Zidon T, Padilla J. Exercise and Estrogen Make Fat Cells "Fit". Exercise and Sport Sciences Reviews. 2015;43(3):172-178.

[75]. Kim H, Nilius B, Kim N, Ko K, Rhee B, Han J. Cardiac Response to Oxidative Stress Induced by Mitochondrial Dysfunction. Reviews of Physiology, Biochemistry and Pharmacology. 2016;:101-127.

[76]. Masuzawa A, Black K, Pacak C, Ericsson M, Barnett R, Drumm C et al. Transplantation of autologously derived mitochondria protects the heart from ischemia-reperfusion injury. American Journal of Physiology-Heart and Circulatory Physiology. 2013;304(7):H966-H982.

[77]. Estradiol acutely inhibits whole body lipid oxidation and attenuates lipolysis in subcutaneous adipose tissue: a randomized, placebo-controlled study in postmenopausal women. Gormsen LC, Høst C, Hjerrild BE, Pedersen SB, Nielsen S, Christiansen JS, Gravholt CH Eur J Endocrinol. 2012 Oct; 167(4):543-51.

[78]. Fat distribution and insulin sensitivity in postmenopausal women: influence of hormone replacement. Munoz J, Derstine A, Gower BA Obes Res. 2002 Jun; 10(6):424-31.

[79]. Effects of hormone replacement therapy on the endometrium and lipid parameters: a review of randomized clinical trials, 1985 to 1995. Pickar JH, Thorneycroft I, Whitehead M Am J Obstet Gynecol. 1998 May; 178(5):1087-99.

[80]. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE Diabetes Obes Metab. 2006 Sep; 8(5):538-54.

[81]. El-Hattab A, Zarante A, Almannai M, Scaglia F. Therapies for mitochondrial diseases and current clinical trials. Molecular Genetics and Metabolism. 2017;122(3):1-9.