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Inter-relationships of Pediatric obesity and mitochondrial dysfunction

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Abstract: Childhood (pediatric) obesity is becoming more common at an alarming rate. Obese children are more likely to develop insulin resistance, relative insulin insufficiency, and type 2 diabetes. Recent research suggests that mitochondrial dysfunction is related to, and may be predictive of, insulin resistance in adult relatives of type 2 diabetes patients. **Mitochondria** produce ATP, which is used to create energy, especially in muscle tissue, and they play a role in glucose and fat metabolism. Mitochondrial dysfunction has a role in the development of metabolic diseases. Affected tissues include adipose, liver, and skeletal muscle, which all contribute to food metabolism. Because cells require a balance between mitochondrial ATP generation through oxidative phosphorylation (OXPHOS) and proton gradient dissipation to avoid damage from reactive oxygen species (ROS), abnormal mitochondrial function leads to fat buildup and insulin resistance. Obesity, insulin resistance, and type 2 diabetes (T2D) are all caused by growth and transcription factors that influence mitochondrial gene expression. On the other hand, obesity and hypertension both impair heart mitochondrial biogenesis and function. By promoting the expression of chaperones, SIRT1, and antioxidants, moderate weight reduction reduces systemic inflammation and improves mitochondrial dysfunction. In this review, the variables that relate mitochondrial dysfunction to pediatric obesity were discussed.

Keywords: mitochondrial dysfunction; pediatric obesity; bariatric surgery; gestational diabetes

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Introduction

Obesity is a multifactorial disease described by a low-grade chronic inflammatory state caused by an excess of malfunctioning adipose tissue [1]. This low-grade chronic inflammatory state is strongly and persistently associated with excess body fat mass and is characterized by pro-inflammatory cytokine and chemokine release as a result of pro-inflammatory macrophage and other immune cell infiltration and activation [2]. A recent study from the USA found that by 2030, at least 55–60% of today's children will be obese [3]. A nutrient imbalance between energy input and output causes secondary mitochondrial dysfunction in this pathological condition [4], which may contribute to the increased risk of obesity-related diseases [5].

Mitochondria are key organelles for several aspects of cellular homeostasis, including cellular energy production via oxidative phosphorylation, apoptosis, and calcium regulation. Because of these several activities within cells, mitochondrial function is critical to cellular and metabolic health. Changes in mitochondrial function can cause a variety of disorders, including neurological, cardiovascular, muscular, hepatic, endocrine, and reproductive disorders [6].

Childhood obesity, also known as pediatric obesity, is caused by genetic predisposition, and some environmental factors like consumption of fatty foods and a high-sugar diet, as well as cigarette smoking and a lack of exercise. Obesity affects 34% of children in the United States, and it is a major public health concern due to the high rates of illness and mortality. Furthermore, obesity-related medical costs have risen, accounting for 40% of the healthcare budget in 2006 [7]. Children with obesity who were followed-up to adulthood were much more likely to suffer from cardiovascular and digestive diseases. In addition, the increase in body fat also exposes the children to an increase in the risk of numerous forms of cancer, such as breast, colon, esophageal, kidney, and pancreatic cancer [7]. Pediatric obesity has more than doubled in children and quadrupled in adolescents globally in the last 30 years [8]. In children with obesity, the inflammatory markers are elevated as early as in the third year of life [9]. This has been linked to heart disease later in life [10]. Long-term effects of such findings can result in cumulative vascular damage, which correlates with increased weight status [11]. **Figure 1.**

Mitochondrial dysfunction has a role in the pathophysiology of metabolic diseases. Affected tissues include those involved in metabolism, such as adipose, liver, and skeletal muscle. As previously mentioned, the cells require a balance between mitochondrial ATP generation via oxidative phosphorylation (OXPHOS) and proton gradient dissipation to avoid damage from reactive oxygen species (ROS). Abnormal mitochondrial function results in fat buildup and insulin resistance. The pathophysiology of obesity, insulin resistance, and type 2 diabetes is influenced by growth and transcription factors that regulate mitochondrial gene expression [4].

The main purpose of this overview is to focus on the link between mitochondrial dysfunction and childhood obesity.

Mitochondria (anatomy and physiology)

The TCA cycle and the electron transport chain enable the mitochondria to produce most of the body's cellular energy (>90%) in the form of ATP. Five multi-subunit enzyme complexes make up mitochondrial ETC, which are in the inner mitochondrial membrane (I, II, III, IV, and V). The ETC receives electron donations from NADH and FADH2 produced by the TCA cycle at Complex I (NADH:ubiquinone oxidoreductase) and Complex II (succinate dehydrogenase), respectively. After passing through Complex III (coenzyme Q: cytochrome c reductase), electrons are subsequently transferred to cytochrome c. Molecular oxygen binds and is reduced to water in Complex IV (cytochrome c oxidase) by the mobile electron carrier cytochrome c after it has undergone reduction. The mitochondrial membrane potential () is an electrochemical proton gradient that is produced when ten protons (H+)—two from Complex III, four from each of Complex I and Complex IV—are pushed from the matrix into the intermembrane space in response to electron transport. Since it connects electron transport (complexes I–IV) (and oxygen consumption) to the activity of Complex V (ATP synthase), where protons re-enter the matrix to dissipate the proton gradient, the protonmotive force (p) is a crucial part of the process of energy storage during OXPHOS [12]. **Figure 2**

ROS are continuously produced by mitochondria because of oxygen metabolism and excessive free radical generation. The antioxidant enzymes superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase are all part of the enzymatic defense system and act as a protective mechanism against this oxidative stress. Antioxidant compounds (e.g., glutathione (GSH), vitamins E and C, as well as many carotenoids and flavonoids) shield cells from oxidative damage. However, when the antioxidant defenses are overpowered, there is an excess of ROS, which results in oxidative damage to the mitochondria's proteins, DNA, and lipids [13]. Excessive ROS may damage DNA, RNA, lipids, and proteins under pathological circumstances, which causes their interactions to result in functional harm or irreversible alterations to the targets. ROS are currently thought to be the main agents of cell destruction. Additionally, oxidative stress can harm cells and possibly support cancer [14].

In addition to being the primary producers of ROS, mitochondria are also the primary targets of oxidative damage, which can decrease mitochondrial effectiveness and increase ROS production [15]. Additionally, peroxisomes play a role in the generation and removal of ROS. Numerous oxygen-consuming metabolic processes take place in peroxisomes. Hydrogen peroxide, which can oxidize several compounds, is produced because of oxygen consumption in peroxisomes [16]. Impairment of mitochondrial oxidative phosphorylation, a rise in the number of aberrant mitochondrial structures, and altered expression and activity of the respiratory chain complex are all results of peroxisome dysfunction [17]. Figure 3

Pathophysiology of childhood obesity

A significant variety of hormones, are released by the gastrointestinal system, and involved in the appetite control and energy balance [18]. Ghrelin is the sole known appetite-stimulating (orexigenic) gut hormone, produced by the stomach's oxyntic glands. Shortly before a meal, ghrelin levels rise. Other gut hormones that have been discovered so far are anorexigenic (decrease appetite and food intake). Peptide tyrosine tyrosine (PYY), pancreatic polypeptide, oxyntomodulin, amylin, glucagon, glucagon-like peptide-1 (GLP-1) and GLP-2 are only a few of them. PYY, for example, is a satiety signal and rises within 15 minutes after eating, resulting in a reduction in food consumption. The gastrointestinal tract is the body's biggest endocrine organ, releasing hormones that play critical sensing and signaling functions in energy balance management [19]. **Figure 4**

Obesity in children is a multifaceted disorder caused by genetic and non-genetic factors, as well as their complex interactions. Energy intake and expenditure are also influenced by genetics and societal variables (socioeconomic position, race/ethnicity, media and marketing, and the physical environment). Excess body fat appears to be the outcome of a complicated interaction between the environment and the body's genetic and epigenetic susceptibility to obesity. The development of childhood overweight or obesity is influenced by a number of variables or risk factors [20].

In populations at high risk of obesity and diabetes, gestational diabetes exposure is connected with an elevated risk of childhood and early adult obesity in the children [21]. Some studies have found that severe variation in maternal adiposity (achieved, for example, by bariatric surgery) impacts child obesity. The frequency of overweight and obesity among children of women who lost a lot of weight after surgery was comparable to the general population, with no rise in underweight [22]. Furthermore, higher birth weight is linked to both increased fat and increased lean mass in the progeny. Babies that are small for gestational age yet develop quickly may be at risk of childhood obesity [23]. **Table 1**

Gestational diabetes, Childhood obesity and mitochondrial dysfunction

Gestational diabetes mellitus (GDM) is a frequent pregnancy condition in which hyperglycemia develops spontaneously throughout the pregnancy [24]. Maternal overweight or obesity, a westernized diet with nutritional deficiencies, maternal age, and a family history of insulin resistance and/or diabetes are all risk factors. While GDM normally goes away after delivery, it can have long-term health implications for the mother, such as an increased risk of type 2 diabetes (T2DM) and cardiovascular disease (CVD), as well as future obesity, CVD, T2DM, and/or GDM in the child [25].

GDM has both short and long-term consequences. The fetus's endogenous synthesis of insulin and insulin-like growth factor 1 (IGF-1) is stimulated by the increase in placental transport of glucose, amino acids, and fatty acids stated earlier. These factors can combine to produce fetal enlargement, which can lead to macrosomia at birth [26]. Babies born during GDM pregnancies have a higher risk of obesity, T2DM, CVD, and other metabolic illnesses later in life. Even after controlling for variables like maternal BMI, children born to diabetic women have nearly double the chance of developing childhood obesity as children born to nondiabetic women [27]. As a result, females are more prone to have GDM during their own pregnancies, adding to a vicious GDM intergenerational cycle [28].

Dysregulation of mitochondrial function and biogenesis modulators in adipose tissue of obese children

Energy storage is dependent on adipose tissue. It's also a metabolically active organ that plays a part in glucose homeostasis and endocrine activities [29]. Obesity, on the other hand, can alter adipose tissue functions and cause an increase in the release of fatty acids, hormones, and proinflammatory molecules, all of which can contribute to obesity-related complications [30]. Several studies have shown that obesity reduces adipose tissue mitochondrial respiration, suggesting mitochondrial dysfunction [31]. Obesity and other metabolic disorders like type 2 diabetes and metabolic syndrome are linked to a mitochondrial overload of glucose and fatty acids, which results in incomplete substrate oxidation and increased production of intermediate products like diacylglycerol, which stimulates the production of reactive oxygen species (ROS) [32]. Reduced fatty-acid oxidation has been reported in animal models and in individuals with obesity as another manifestation of mitochondrial dysfunction [33].

It was reported that, changes in mitochondrial structure and function may have a role in the pathophysiology of obesity-related diseases [34]. Reduced mitochondrial mass and mitochondrial biogenesis (MB) genes, structural damage, and altered mitochondrial morphology were observed in severe obesity, as well as mitochondrial protein hyperacetylation [35], increased inflammation, ROS generation, and oxidative stress [36].

The major transcription factor, PPARƔ regulates MB in adipocytes [37]. The PGC-1 transcriptional factor family also has a role in the dynamic modulation of MB and respiratory performance [38]. Post-translational modifications evoked by intracellular energy state sensors like cAMP-activated protein kinase (AMPK) and NAD+-dependent deacetylase SIRT1 modulate the activity of PGC-1α [39]. SIRT1 stimulates the generation of adiponectin in adipose tissue, which improves metabolic efficiency [40]. SIRT1 expression is significantly decreased in adipose tissue from obese people, which has a negative influence on adipocytes' energy status [38]. SIRT1 interacts closely with AMPK and deacetylates several lysine residues in PGC-1α under normal circumstances, resulting in the promotion of lipid catabolism while inhibiting "inflammation" of white adipose tissue (WAT) [41]. The expression and function of MB regulators like NRF1, NRF2, and TFAM, which are involved in the replication and transcription of mtDNA, are decreased as a result of lower SIRT1 expression and an unregulated downstream effector [42].

In mice with cardiomyopathy, obesity leads to metabolic abnormalities such as insulin resistance and intracellular low-grade inflammation, as well as increased oxidative stress and mitochondrial dysfunction [43], [44]. Only diabetic mice had low amounts of ATP synthase and, complexes II and III in adipocytes when the expression of mitochondrial proteins in the liver, muscle, and adipocytes of normal, obese, and diabetic mice was compared. Furthermore, abnormal mitochondrial shape, reduced mtDNA content, and elevated rates of -oxidation and respiration were observed in obese and diabetic mouse adipocytes, indicating a significant mitochondrial malfunction. Obese mice had skeletal muscle that displayed altered mitochondrial dynamic behavior, including decreased mitochondrial respiratory capacity, low ATP content, increased fission (increased Fis1 and Drp1 protein concentrations), and reduced fusion (increased Mfn1 and Mfn2 protein concentrations) [45]. **Table 2.**

Bariatric Surgery for Pediatric Patients with Severe Obesity

Severe childhood and adolescent obesity is a growing public health concern in the United States. Unfortunately, there are few effective treatments for severe obesity. In the pediatric population, the use of metabolic and bariatric surgery provides evidence-based, effective treatment of extreme obesity and concomitant comorbid disorders. [46]. Bariatric surgery has emerged as one of the most successful and long-lasting treatment options for morbid obesity and associated comorbidities in terms of weight loss and glycemic control [47].

Surprisingly, weight loss produced by bariatric surgery has been demonstrated to promote mitochondrial biogenesis, whereas weight loss mediated by diet has not improved mitochondrial dysfunction [48]. Furthermore, bariatric surgery may be linked to a reduction in renal tubular injury, as measured by the level of kidney injury molecule-1 in obese patients [49]. Several studies have also found that bariatric surgery is superior to non-surgical therapies for improving glycemic and metabolic characteristics in people with T2DM who are obese [50]. In addition, in an obese rat model, bariatric surgery greatly reduced chromosomal damage [51].

Figures, Tables and Schemes

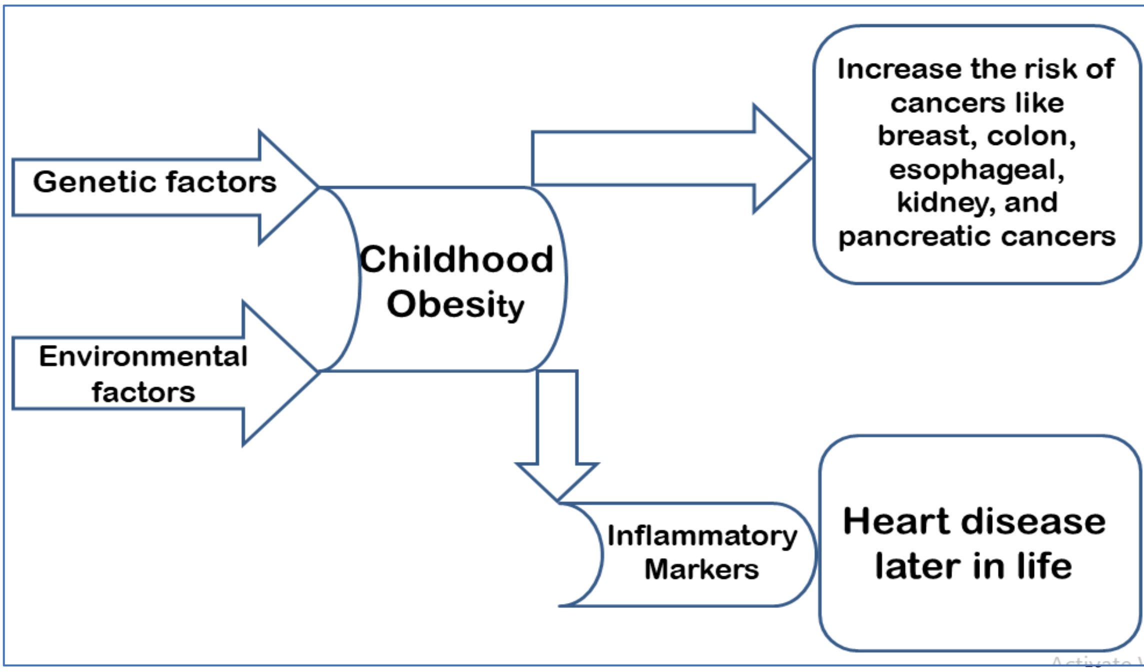

Figure 1. depicts the pathophysiology of childhood obesity and its adult consequences. .

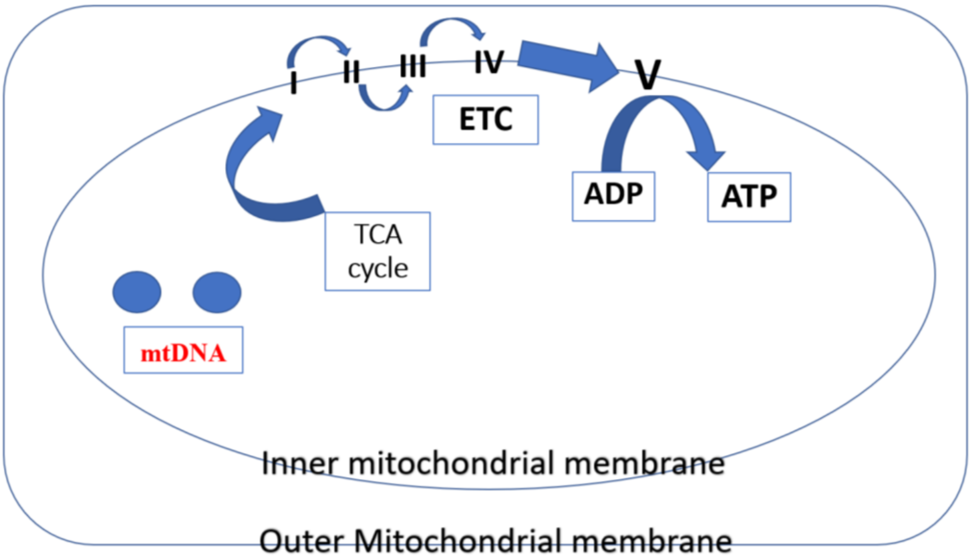

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Figure 2. In the mitochondria, several different protein complexes are involved in mitochondrial respiration: The inner mitochondrial membrane held I-4 complexes. These complexes produce a proton gradient (H+) by successively moving electrons (e). This gradient is subsequently utilized by Complex V (ATP synthase) to phosphorylate ADP to ATP.

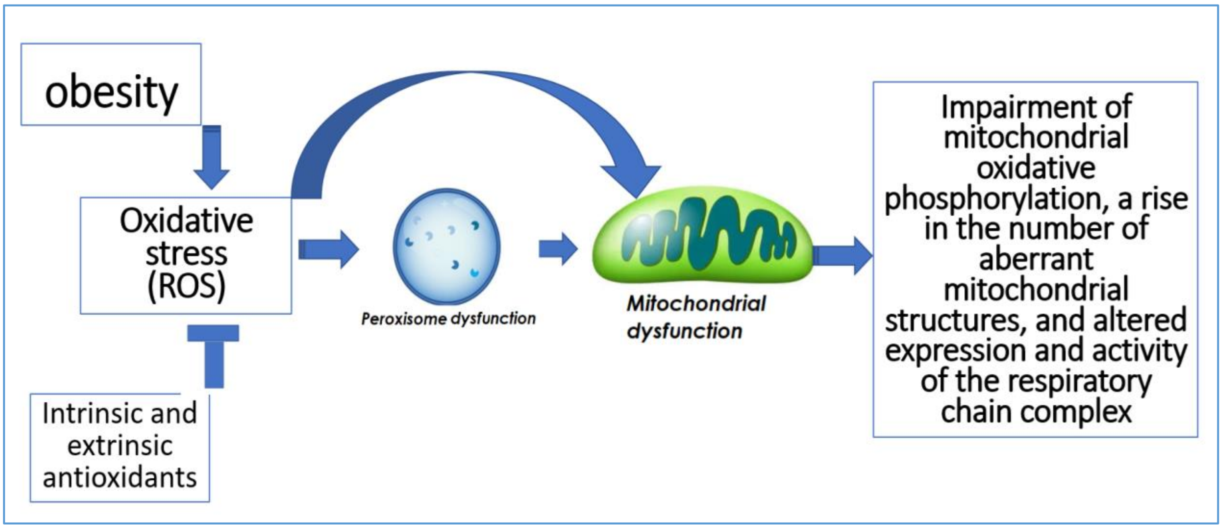

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Figure 3. The relation between oxidative stress, peroxisomal, and mitochondrial dysfunction.

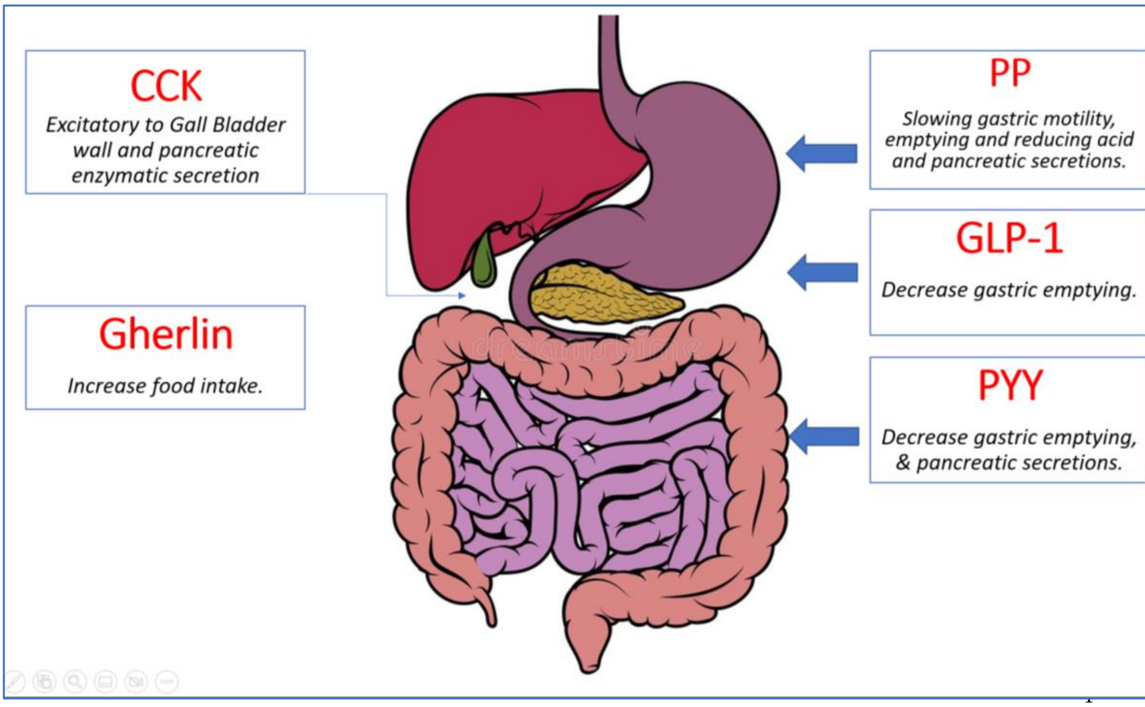

Figure 4. Summary of gut hormones involved in appetite regulation. Ghrelin, the orexigenic hormone in green, is released from the stomach and stimulates food intake. The anorexigenic hormones shown in red (Cholecystokinin (CCK), Pancreatic Polypeptide (PP), Peptide YY (PYY) and Glucagon-Like Peptide 1 (GLP-1)) are released from various organs in the gastrointestinal system and work together to decrease food intake by slowing gastric motility, emptying and reducing acid and pancreatic secretions [18].

Table 1. Summary of the common factors contributing in the development of pediatric obesity.

Factors	Common examples	Mechanism
Genetic factors	e.g. Prader-Willi syndrome,	Hypotonia, mental retardation, short stature, hypogonadism, hyperphagia, and obesity. Caused by a lack of expression of genes on chromosome 15q11-13 that are imprinted to be expressed only on the paternally inherited copy of the chromosome.
Endocrinal dysfunction	Thyroid dysfunction, growth hormone insufficiency or resistance, and cortisol excess Pseudohypoparathyroidism Polycystic ovarian syndrome (PCOS) is thought to be a result of, but also a contributor to, obesity.	Metabolic imbalances in the mentioned endocrinal disorders are the mechanisms of the obesity encountered in these disorders.
Hypothalamic disorders	Congenital or acquired	Infiltrative illness, tumors, or their treatment aftereffects commonly results in the development of an obesity syndrome marked by fast, unremitting weight gain, which may be accompanied by severe hyperphagia.

Maternal factors	Intrauterine prenatal diabetes exposure. Intrauterine exposure to increased mother adiposity. Babies that are small for gestational age yet develop quickly may be at risk of childhood obesity.	Excess fetal insulin secretion in gestational diabetes shares in the development of obesity in offspring.

Table 2. **Effects of obesity on mitochondrial structure and function in humans.**

Tissue	Possible changes in mitochondrial structure and function
Adipocytes	decreased levels of PGC-1 decreased oxygen consumption, citrate synthase activity, and mtDNA content
Subcutaneous adipocytes	Reduced mtDNA content, upstream regulator hypermethylation at 96 of 130 CpG sites, reduced mtDNA-encoded transcripts (12S rRNA, 16S rRNA, COX1, ND5, CYTB), and OXPHOS subunit proteins (complex III-IV)
Adipose derived stromal stem cells	TBX15 was one of the most significantly hypomethylated genes, indicating altered DNA methylation.
Skeletal muscle	TCA cycle and complex II proteins are expressed more, while ATP synthase and complexes I and III proteins are expressed less.

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