2021
8(4), 162-170

Chemical Biology
LETTERS

Obesity and Male Infertility: Energy Imbalance to Inflammation

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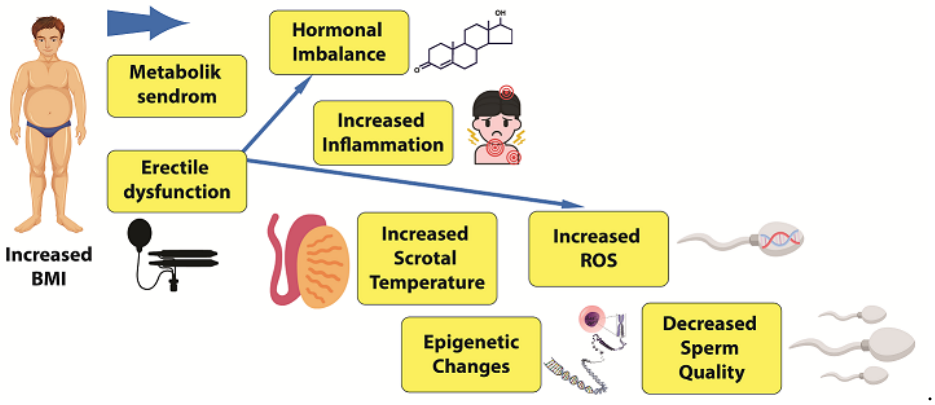
Submitted on: 19-July-2021, Accepted and Published on: 19-Sept-2021

Review Article

ABSTRACT



Obesity is an important health problem with an increasing frequency in the world. In recent years, obesity has been shown to be closely related to infertility in addition to causing many important additional and systemic health problems. The relationship between obesity and infertility is evaluated based on many complex mechanisms, such as inflammatory cellular response, endocrine factors released from adipose tissue, and epigenetic changes, as well as other known factors including increased scrotal temperature and hormonal imbalance. While increasing BMI negatively affects the known reproductive hormonal mechanism, on the other hand, adipose tissue acts as an endocrine organ and secretes several hormones called adipokines. These hormones affect spermatogenesis both central and testicular ways. Moreover, increased adipose tissue and BMI cause to rising scrotal temperature, and result in sperm DNA damage. Therefore, sperm DNA damage caused by both the negative effect of adipokines, increased scrotal temperature, and increased inflammatory response impairs sperm functional structure. In addition to all these factors, sexual dysfunction which develops due to hormonal imbalance as a result of excess weight and psychologic factors caused by a distorted body image, constitute an important obstacle to a healthy sexual life. As a result, obesity should be considered as a health problem that plays a role in male infertility with its multi-faceted interaction.

Keywords: adipokines, adipose tissue, inflammation, male infertility, metabolic syndrome, obesity, oxidative damage

INTRODUCTION

The World Health Organization defines infertility as the inability to conceive despite engaging in unprotected regular sexual intercourse for one year. Infertility affects approximately 13-15% of married couples.[1] In 50% of cases, the main reason is the male factor, and it is observed in 7% of all men.[1-4] There are several reasons for male infertility, such as genetic diseases, hormonal abnormalities, undescended testis, varicocele, testicular trauma, infection, and radiotherapy/chemotherapy.[5-7]

Obesity, defined as excessive adipose tissue accumulation, is a metabolic problem that occurs due to hereditary, nutritional and environmental factors. While obesity is expressed as a body mass index (BMI) over 30 kg/m^2, BMI over 35 kg/m^2 has been defined as morbid obesity.[8] Epidemiological studies have shown that the global incidence of obesity has tripled in the last 40 years. It is estimated that more than 40% of the world's population is obese, and more than 200 million men suffer from this problem.[9, 10] Additionally, increased body fat tissue results in clinically important in assessing the risk of obesity-related problems.[11, 12] The most common complications are cardiovascular diseases, type 2 diabetes mellitus, cancer in different organs, accelerated aging, and neurodegeneration. These conditions occur through complex and poorly understood different mechanisms, including hormonal imbalance, insulin resistance (hyperinsulinemia), hyperleptinemia, chronic systemic inflammation, and oxidative

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URN:NBN:sciencein.cbl.2021.v8.254
 ISSN: 2347–9825
https://pubs.thesciencein.org/cbl

stress.[13, 14] It has also been considered that some epigenetic and lifestyle changes are induced by obesity (Figure 1).

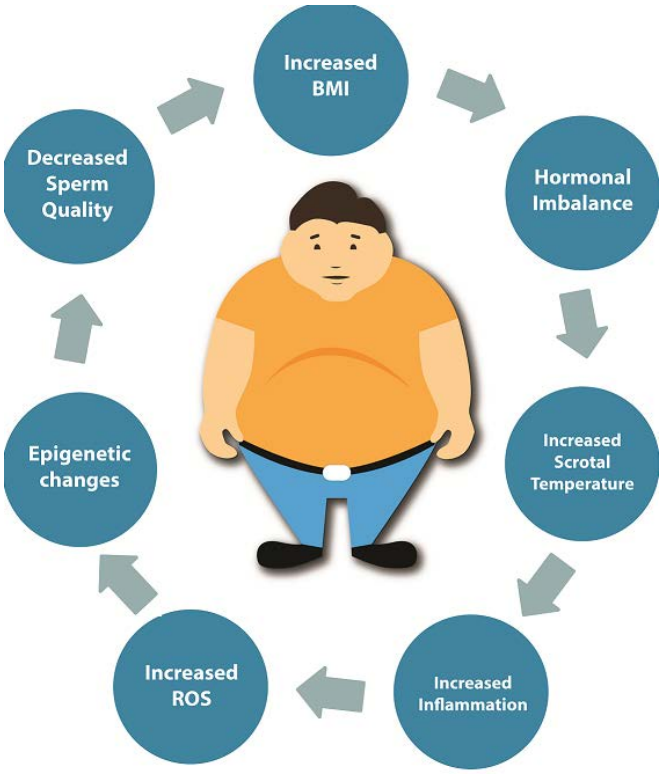

Figure 1. Effects of obesity on male reproductive system and sperm function

In the 16th century, Conrad Gesner, a Swiss botanist and doctor, described for the first time two separate types of adipose tissue as white and brown adipose tissue. It is accepted that white adipose tissue stores excess energy, especially in fish. On the other hand, it is believed that brown adipose tissue, which developed in the later stages of evolution, is responsible for energy storage and expenditure. Today, it is known that adipose tissue plays a role in the production of various substances, such as hormones and cytokines and in the functioning of the endocrine and immune systems.[15] Therefore, it plays an important role in the onset of puberty, sexual behavior, and seasonal regulation of fertility.

Recently, it has been stated that infertility may be another important health problem that occurs due to obesity. In a meta-analysis, it was reported that the probability of oligozoospermia and azoospermia gradually increased in proportion to weight when approximately 13,000 men were compared according to BMI.[16] This confirms the important role of obesity in male infertility and suggests that weight control can assume an important place in the treatment of this condition in the following years. In a more recent study, the rate of obesity in subfertile and fertile men was reported to be approximately 20%.[17] In another study conducted in the USA, it was shown that each 3 kg/m^2 increase in BMI increased the risk of infertility by 1.2 times.[16]

Despite the studies mentioned above, the relationship between obesity and infertility in men has not yet been clearly elucidated. In the complex pathophysiology of obesity, endocrine disorders and chronic inflammation take an important place. Various factors such as hormonal imbalance due to the disruption of the testosterone/estrogen balance, increased inflammatory response, high testicular temperature, elevated reactive oxygen products, tissue damage due to peripheral vascularization, and erectile dysfunction have been implicated in the etiology of obesity.[18-21] As a result of the induction of increased adipose tissue, proinflammatory responses mediated by Th1-lymphocyte and M1-macrophage develop, which leading to a chain of events beginning with the modulation of cytokines, adipokines and myokines, negatively affecting many systems in the organism.[22-25]

In this article, the mechanisms of obesity on sperm quality are briefly reviewed. Therefore, in addition to the known factors in the etiology of infertility, it will also give some information in the evaluation and interpretation of idiopathic male infertility, which today constitutes around 20 and 30 % of infertile men.[1]

Obesity and inflammation

Obesity is accepted as a chronic and systemic inflammatory disease. While the ratio of macrophages to total cells is only 10% in normal adipose tissue, it can be up to 50% in obese people.[26] Therefore, the hyperplasia of fat cells in adipose tissue is the first event that initiates metabolic inflammation. If the adipose tissue ratio exceeds its limits, apoptosis occurs. Esterified fatty acids produced by these adipocytes stimulate local macrophages, leading to the production of more esterified fatty acids, as well as more pro-inflammatory and inflammatory cytokines, chemokines, and acute phase reactants.[27, 28]

Cytokines are a group of proteins with molecular weights ranging from 5 to 20 kDa. Initially, it was considered that they were released by the immune system in cases of injury and inflammation.[29] However, it is now known that they play an important role in the regulation of the immune system and inflammation. Seminal plasma contains various cytokines originating from Leydig cells, Sertoli cells, testicular macrophages, epididymis, prostate, seminal vesicles, and male accessory glands, and these substances affect spermatogenesis, steroidogenesis, and sperm function.[30, 31]

Intercellular and vascular adhesion molecules are inflammatory factors and chemokines from which necrotic fat cells are secreted. This induces the proliferation and migration of monocytes and macrophages to adipose tissue.[28] Mainly, M1 macrophages secrete proinflammatory factors, and then activate the NF-κB pathway, which significantly increases the release of pro-inflammatory factors, such as TNF-α, interleukin-6 (IL-6), and interleukin-1β (IL-1β), and decreases anti-inflammatory factors. These events result in chronic inflammation.[28, 32]

As a result of the rapid increase in adipose tissue, local hypoxia develops due to insufficient blood flow, which is another factor that leads to chronic inflammation. The cell increases the expression of some local hypoxia agents, such as h*ypoxia inducible factor-1*α (HIF-1α), heme-oxygenesase-1 (HO-1), pyruvate dehydrogenase kinase-1 (PDK1) and vascular endothelial growth factor (VEGF) to protect itself against this hypoxic state.[33]

The testicular immune system has a special protection mechanism formed by a structure called the blood testicular barrier. However, in recent studies, it has been shown that some of the antigenic substances that occur during spermiation are excreted from the seminiferous tubules.[34, 35] Cytokines released by leukocytes in the testicular interstitium mediate the formation of immunity in the testis. However, cytokines are released in response to GnRH stimulation from these Leydig and Sertoli cells. Studies have shown that inflammatory cytokines reduce testosterone production by activating TLC2 receptors in Leydig cells in the testis.[35-37] On the other hand, in cases associated with aging, the increase in pro-inflammatory cytokine concentration leads to a decrease in testosterone.[38] Therefore, cytokines also play an important role in maintaining steroidogenesis and physiological testosterone levels in Leydig cells.

Obesity and Reactive Oxygen Species

In the case of a high carbohydrate or high fat diet, excess glucose and fatty acids form pyruvate, coenzyme A , and other reducing metabolites. Later, these substances enter the mitochondria for oxidation, increasing the production of reactive oxygen species (ROS).[39] It is suggested that a BMI of more than 25 kg/m^2 causes sperm DNA damage.[40] Obesity can lead to an increase in testicular ROS levels by different mechanisms. Increased fatty acid oxidation in mitochondria and peroxisome with adipose tissue deposition leads to higher ROS production. Therefore, higher ROS mediates oxidative damage to biomolecules including lipids, proteins and DNA. Moreover, in obese patients, oxidative stress increases due to chronic low-level inflammatory response, and various immune cells are activated to generate large numbers of free radicals. Oxidative stress further exacerbates cell oxidative damage and accelerates cell aging. Aging adipocytes recruit macrophages secrete a variety of proinflammatory cytokines, and stimulate inflammation.[41] In addition, since the level of orexins[42], which plays a role in the improvement of cellular oxidative damage, decreases in obese men, one of the protective mechanisms against DNA damage is impaired.[43, 44]

Interactions that occur as a result of increased ROS level stimulating the inflammatory response are discussed in detail in the next section.

Obesity, Scrotal Temperature and Spermatogenesis

Spermatogenesis is also affected by high scrotal temperature due to increased scrotal adiposity. Increased scrotal temperature in obese men results in increased cytokines and ROS levels in seminal plasma and decreased self-defense mechanism of spermatozoa.[20] In a recent meta-analysis, it was shown that all sperm parameters (volume, sperm count and motile sperm ratio) were reduced in obese men. Other researchers similarly showed that increased BMI and scrotal temperature negatively affected sperm maturation in the testis and epididymis of obese men.[45, 46]

Systemic inflammation caused by increased estrogen can affect steroidogenesis in Leydig cells. Steroidogenic enzymes, such as P450scc, 3βHSD, and 17βHSD, which mediate the uptake and synthesis of steroidogenic acute regulatory protein and cholesterol into cell mitochondria, are adversely affected by inflammatory cytokines, and as a result testosterone synthesis is impaired.[47]

Apoptotic balance is achieved by the activation of the Bcl-XL and Bax systems. Studies have shown that the disruption of the apoptotic balance is one of the important causes of male infertility.[48, 49] While Bcl-2 expression is suppressed in obese patients, Bax expression increases significantly. This leads to the activation of the caspase pathway. The existing hyperlipidemia state further increases the stress level and induces apoptosis in sperm cells with the increased expression of binding immunoglobulin protein.[43]

Obesity also negatively affects the testicular histological structure. The examination of obese men has shown that the diameter of their seminiferous tubules decreases, and epithelial cell atrophy and apoptosis develop. Germ cell counts are reduced, and Johnsen scores are considered low. The connection between Sertoli cells and sperm cells, and more importantly the connections that form the blood testicular barrier are weakened.[50, 51]

In addition to these systemic and local inflammatory changes, some hormonal disorders can also occur due to obesity. These problems occur both in the hypothalamo-pituitary-gonadal axis that controls the normal function of the reproductive system and in the form of hormonal changes arising from the adipose tissue itself. The main source of these hormonal problems is obesity-related inflammatory events.[11]

Effects of Obesity on Hormonal Regulation of Reproductive Axis

Sperm production in the testis is controlled by the effect of gonadotropin-releasing hormone (GnRH) released from the hypothalamus, and follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secreted from the pituitary gland. LH stimulates the production of testosterone in Leydig cells in the testis, and mature spermatozoa are produced from germ cells in seminiferous tubules under FSH control. Additionally, intratesticular testosterone plays an important role in spermatogenetic activity in the testis. Testosterone is metabolized to the active form in androgen-sensitive end organs and inactivated into 17-ketosteroids in the liver.[52-54]

Aromatase is a cytochrome P450 enzyme that converts testosterone to estrogen. While this enzyme is found in many cells and tissues, including Leydig cells, Sertoli cells, granulocytes, luteal cells, placental cells, neurons, fibroblasts, vascular smooth muscle cells, preadipocytes, chondrocytes, and osteoblasts in humans, it shows the most important activity in peripheral adipose tissue. Therefore, increased aromatase activity in obese males results in decreased testosterone levels and leads to male hypogonadism.[54-56]

Testosterone and estrogen have an effect on the secreted arcuate nucleus of GnRH and kisspeptin-1 (KISS1). They suppress the release of these hormones through a negative feedback effect. KISS1 is a peptide that promotes the hypothalamic neuroendocrine interaction between metabolic and reproductive functions. Moreover, it has been stated that these two hormones play a role in lipid metabolism via KISS1.[57, 58]

Different results have been reported in studies on serum hormone levels in obese men.[59-61] In some studies, it has been reported that the serum total and free testosterone levels decreased in proportion to BMI, whereas the LH levels remained normal.[15, 62] This has been attributed to the negative feed-back effect of the increased estrogen level on GnRH in obese individuals due to aromatase overactivity, which decreases testosterone synthesis in the testis. On the other hand, increased estrogen suppresses FSH secretion which controls spermatogenesis in Sertoli cells and decreases of spermatogenesis. Therefore, in obese individuals, hypogonadism develops due to either the aromatization of testosterone to estrogen with increased BMI or the central inhibition of KISS1 and GnRH.[54, 63]

In other epidemiologic studies, the serum LH, testosterone and sex-hormone binding globulin (SHBG) levels have been observed to be low in obese men. As an important finding, while the decrease in testosterone due to obesity is accompanied by a low LH level, age-related low testosterone level is accompanied by increased LH. Moreover, testosterone shows antioxidant activity that prevents β-cell apoptosis in pancreatic islets and has a protective effect against glucotoxicity damage in pancreatic β-cells.[64, 65] These effects may disappear with decreasing circulating testosterone levels and may explain the relationship between low serum testosterone levels and the development of insulin resistance and type 2 diabetes mellitus (DM). The relationship between testosterone and insulin has been known for a long time.[66] While insulin suppresses GnRH release centrally, it affects SHBG synthesis and Leydig cell function in the periphery.[67]

Effect of Hormonal Activity of Adipose Tissue on Reproductive Function

Adipokines are hormones produced by white adipose tissue, which is also considered as an endocrine organ, and play a role in energy regulation. Adipokines have important roles in the lipid and glucose metabolism and the control of inflammation and the immune system.[68, 69] These hormones control the functioning of the hypothalamo-pituitary-gonadal axis, and thus spermatogenesis. Leptin, adiponectin, ghrelin, orexin, and obestatin are among these adipokines with negative effects on reproductive hormonal balance **(Figure 2).**

Leptin is one of the most important adipokines released from adipose tissue and plays an important role in many systems, such as glucose metabolism, neuroendocrine systems, angiogenesis, puberty, and reproductive regulation.[70, 71] It is a 16kDa protein whose secretion is controlled by obesity genes (*ob genes*) and has an important effect on the organism's energy balance, food intake, and regulation of body weight.[21, 70] The arcuate nucleus of the hypothalamus is the most concentrated region where the genes controlling the leptin release of the brain are located. In response to insulin, leptin inhibits the release of neuropeptide Y (NPY) in the arcuate nucleus and increases proopiomelanocortin (POMC) expression.[72, 73] Normally, POMC neurons control food intake energy disbursement. Melanocyte-stimulating hormone also plays a mediator role in this process. Finally, NPY inhibits POMC neurons, and thus stimulates food intake. Moreover, with

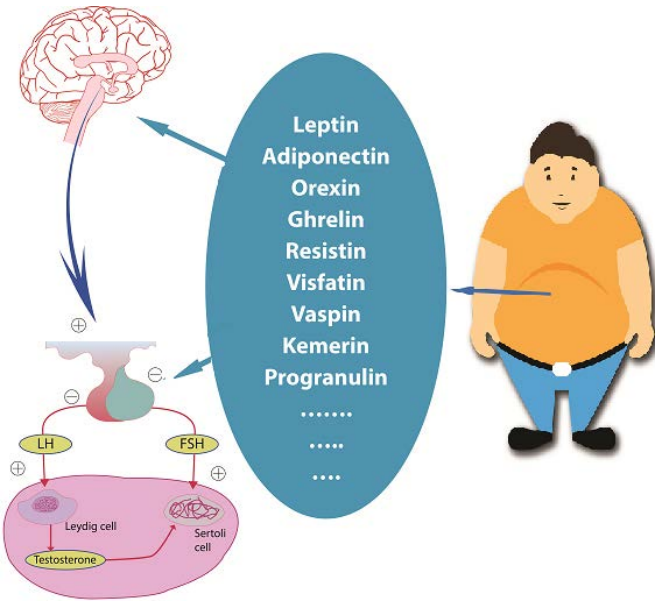

Figure 2. Adipokines released from adipose tissue and hormones affecting testicular function and reproductive system

the effects of these mediators, plasma insulin and corticosterone levels increase.[74, 75] As a result, the suppressive effect of leptin on NPY leads to the inhibition of food intake, increased thermogenesis, and decreased fat mass. Leptin gene knockout rats *(ob/ob -/-*) are infertile. Experimental studies have shown that the deletion of leptin receptors in forebrain neurons delays the onset of puberty in male and female mice.[62, 76, 77]

An increased leptin level with growing weight decreases food intake and increases energy expenditure. Serum leptin activity in the obese population is four times higher than in normal weight. Although leptin levels are high in obese individuals, sensitivity and resistance develop against its activity.[78] This is generally caused by impaired neural response to leptin. This results in leptin being incorrectly transported within the blood-brain barrier, reduced signal activation of leptin neurons in the arcuate nucleus and decreased central and peripheral leptin receptor expressions.[79, 80]

Leptin also affects testosterone production in the testis via its receptors in Leydig cells. It is considered that increasing leptin levels in the circulation in obese men lead to low testosterone levels due to leptin resistance.[81] White fat cells also secrete various other proteins, such as adipsin, adiponectin, obestatin, angiotensinogen, resistin, Tumor Necrosis Factor-α (TNF-α), and retinol-binding protein.[82, 83] An increased amount of adipose tissue causes an increase in serum estrogen levels, promotes chronic inflammation, and consequently contributes to leptin and insulin resistance. Since leptin is required to produce KISS1, these effects result in decreased KISS1 levels, negatively affecting the downstream signaling function, decreasing GnRH, luteinizing hormone and FSH release, and ultimately reducing testosterone production and affecting spermatogenesis. Thus, leptin also negatively affects the functioning of hypothalamo-pituitary gonadal axis through GnRH release and KISS1 and impairs spermatogenesis by disrupting hormonal imbalance.[70, 84]

Adiponectin is another hormone secreted by adipose tissue and controls insulin sensitivity, fatty acid oxidation, energy expenditure, and liver gluconeogenesis. In animal experiments, it has been shown that adiponectin inhibits the harmful effects of proinflammatory cytokines by suppressing NFkB in Leydig cells by down-regulating the expression of TNF-α, IL-6 and IL-18 genes.[85, 86] Unlike leptin, adiponectin levels are negatively correlated with BMI, particularly abdominal fat accumulation. Normal-weight and obese women have higher serum adiponectin levels than men. This is important in revealing the gender differences in the pathophysiology of obesity. In recent studies, the presence of adiponectin receptors in human and animal reproductive systems has been identified and shown to have significant effects on semen parameters.[87-89]

Orexins stimulate testosterone production by increasing steroidogenic enzyme activities in Leydig cells. It has been shown that orexin levels are low in obese individuals.[90-92] We previously mentioned that orexin had a protective effect against DNA damage. This effect is weakened in obese individuals due to its decreased level.

Ghrelin, also known as the hunger hormone, is a neuroendocrine peptide released from the gastrointestinal tract. Studies have shown that there is a relationship between impaired steroidogenesis and low serum testosterone levels and ghrelin.[92, 93] Although this effect is not yet clearly known, it is considered to be caused by the interaction at the receptor level. A relationship between ghrelin and spermatogenesis has not yet been demonstrated.[92, 94] However, the presence of ghrelin activation under LH control has been reported in Leydig cells, which has been associated with Leydig cell maturation. In a recent study, ghrelin was shown to have an inhibitory role in immature Leydig cell proliferation.[95] On the other hand, another study observed a positive correlation between testosterone and ghrelin concentrations.[96]

Resistin is another protein secreted by adipose tissue. It affects Leydig and Sertoli cells in testis under the control of gonadotropins.[97, 98] Resistin concentration is related to IL-6 and TNF-α levels and sperm quality. Inflammation and smoking increase the level of resistin.[99]

Visfatin is also secreted by visceral adipose tissue. The visfatin level is reported to be positively correlated with serum testosterone concentrations, BMI, and testicular weight and negatively correlated with serum glucose concentration. Many studies have shown decreased testicular visfatin expression in men with type-2 DM.[100] This finding suggests that adipokines and visfatin play a role in the deterioration of spermatogenesis in diabetic men.

In addition to the above-mentioned examples, there are also other adipokines, such as vaspin, chemerin, and progranulin, which are released from the testis and epididymis. Their roles have not yet been fully revealed, and their seminal plasma levels vary with BMI. However, there is no clear information concerning their effects on sperm parameters and the hypothalamo-pituitary-gonadal axis.[100]

Epigenetic Changes of Sperm in Obese Men

Recently, another factor affecting sperm parameters in obese men has been revealed as epigenetic changes due to obesity and lifestyle. Epigenetic changes result in DNA methylation, histone modification, and non-coding RNA changes, and ultimately impair sperm parameters. In a study, small non-coding RNAs were reported in obese male spermatozoa.[101] Later, Sourby et al. observed a lower methylation ratio in the MEG3, NDN, SNRPN and SGCE/PEG10 regions in obese men compared to the healthy control group.[102] Interestingly, it was also stated that due to epigenetic factors, there was an increase in the risk of obesity, metabolic syndrome, diabetes, and autism in the children of obese men. The same authors reported that improvement in the DNA methylation of ejaculate sperm started one week after surgery in cases that underwent bariatric surgery.[103] Moreover, they stated that if weight loss continued one year after surgery, the sperm epigenome returned to normal.

Obesity causes infertility with its systemic effects and leads to various health problems. Although it is associated with many health problems, metabolic syndrome and erectile dysfunction are the most important health problems associated with infertility.

In addition to changes in the sperm epigenome, male obesity has also been associated with worse ART outcomes. In a meta-analysis, the rate of infertility was found to be higher in obese men, while the rate of failed IVF was found to be higher.[104] More studies are needed to evaluate the relationship between obesity and epigenetic changes. Although it is now accepted that obesity plays a role in male infertility, achieving target weight before or before IVF treatment is planned in the future will be an approach not only for women but also for men.

Metabolic Syndrome and Infertility

Metabolic syndrome is a clinical condition characterized by complex metabolic, endocrine, cellular and molecular dysfunction. As a result of these events, insulin resistance, leptin resistance, systemic inflammation and immune dysregulation, oxidative stress and hypogonadism develop in men.[105, 106] In addition to BMI (over 30 kg/m^2), metabolic syndrome includes the following components: i) waist circumference greater than 94 cm (or 40 inches), ii) blood pressure higher than 130/85 mmHg, iii) fasting blood sugar higher than 100 mg/dl, iv) fasting high-density lipoprotein (HDL) level higher than 40 mg/dl, and v) fasting triglyceride level higher than 150 mg/dl.[107]

Previous studies have shown that in addition to the hormonal effects of obesity in metabolic syndrome, increased cholesterol levels negatively affect sperm quality (98). Furthermore, adipose tissue in obese men has been shown to contain higher levels of inflammatory molecules, such as TNF-α, IL-6, and CRP.[107] Specifically, TNF-α and IL-1 cytokines have been shown as major mediators of the inflammatory process. As a result of inflammation, increased levels of ROS lead to increased DNA damage in spermatozoa. Therefore, another negative situation in patients with metabolic syndrome is the increase in DNA damage in sperm.[108] Improvement in both inflammatory parameters and hormonal values in patients after bariatric surgery was reported

in previous study.[109] As a result, there is a significant development in the fertility status of the patients.

Therefore, it is considered that metabolic syndrome affects sperm parameters together with obesity and related conditions. However, more detailed studies are needed on this subject.

Obesity, Erectile Dysfunction and Male Infertility

Obesity also has negative effects on sexual performance. Erectile dysfunction is observed 1.5 times more frequently in obese men and occurs due to many factors.[110] In addition to hormonal anomalies, vascular anomalies and microvascular events caused by abnormal adipose tissue distribution and imbalance in the lipid metabolism can lead to erection problems in obese men.[111] The development of atherosclerosis, endothelial dysfunction, and consequently impaired release of some mediators, such as nitric oxide reduce erectile capacity. Low testosterone levels cause not only loss of libido but also insufficient response to drugs, such as PDE5i due to insufficient nitric oxide.[112, 113] As a result, obesity results in the development of sexual dysfunction and erection problems, as well as other factors leading to the development of ED, including hormonal anomalies, hypertension, diabetes, hypertension, and psychological disorders.

CONCLUSION

Obesity constitutes an important global health problem and causes infertility, as well as various other conditions. Hormonal factors and imbalance in the testosterone/estrogen ratio are not sufficient to explain the relationship between obesity and infertility since there are many other factors that play a role in this relationship. Obesity not only causes infertility but also negatively affects the results of assisted reproductive methods and can lead to various health problems in following generations. Therefore, the evaluation of metabolic factors in infertile cases and management of obesity, if present, are important for the treatment of infertility.

Conflict of Interest Statement

Authors declare no conflict of interest.

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