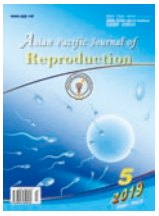

Review Article

Asian Pacific Journal of Reproduction

Journal homepage: www.apjr.net

doi: 10.4103/2305−0500.268133

Obesity, endocrine disruption and male infertility

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ARTICLE INFO

Article history:
Received 23 May 2019
Revision 20 June 2019
Accepted 26 July 2019
Available online 30 September 2019

Keywords:
Male infertility
Obesity
Semen quality

ABSTRACT

Obesity has become a global pandemic since the last few decades with prevalence in more than one-third of the population in the United States. Another concurrent global health concern is the declining trend in male fecundity in terms of semen quality. Male infertility etiology is multifactorial with obesity serving as one of the major causatives. An array of research is directed in unveiling the potential mechanism underlying the obesity-induced male subfertility or infertility. Obesity may alter the hormonal milieu of the hypothalamic-pituitary-gonadal axis, its crosstalks with other metabolic hormones, upregulates secretion of adipose tissue-derived hormones and other factors, thus influencing the endocrine regulation of male reproduction. Obesity may also directly impair testicular functions by inducing genetic and epigenetic alterations in spermatozoa, disrupting sperm morphology and functions. Given the complexity of the condition of obesity and the multivariate etiopathology of male subfertility/ infertility, this review is aimed to provide an updated concept on how obesity mediated hormonal modulation may affect male fertility parameters.

1. Introduction

Infertility is a public health issue affecting about 15% of all reproductive couples across the globe[1–4]. There has been a grown concern over the recent years regarding a worldwide declining trend in male fertility[5–7], with male-factor infertility responsible for 40%–50% of overall infertility in the world[8]. Some studies showed that sperm counts are decreasing by 1.5% with each and every year in the United States as well as in the other western countries[9]. Almost 70 million couples worldwide have been estimated to have fallen victim to subfertility or infertility[10]. The etiology of male infertility is not completely understood, and in most of the cases remain idiopathic[11]. Several environmental, physiological and genetic factors are been explained in this regard[12]. Increasing prevalence of metabolic syndrome (MetS) and higher BMI further increase the risk of reproductive dysfunctions[13]. There are emerging data suggesting a close association between MetS, especially obesity and male subfertility and/or infertility[14]. Improper lifestyle and dietary habits are the key role players in the accelerating global prevalence of obesity. Obesity refers to a pathophysiological state of increased visceral (abdominal) adiposity and is defined as a body mass index (BMI) of 30 kg/m^2 or more[15]. According to the 2016 World Health Organization (WHO) report,

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How to cite this article: Dutta S, Biswas A, Sengupta P. Obesity, endocrine disruption and male infertility. *Asian Pac J Reprod* 2019; 8(5): 195-202.

39% of the worldwide adult population possess BMI above the normal range (BMI between 18.5 to 24.9 kg/m^2)[16]. Obesity has been shown to afflict 35% of all adult population and about 50% of the aging population in the United States[17]. According to WHO, the universal pervasiveness of obesity has increased several folds during the last few decades[18]. Wang *et al* in the year 2011 predicted that by the end of 2030, United Nations obese people count will increase by another 65 million[19].

Obesity is presented with unusually high levels of lipids and/or lipoproteins in the blood leading to hyperlipidemia. The state of lipotoxicity in obese men is the main cause of cellular injury and tissue dysfunctions[20]. The risk factors for obesity tend to cluster the WHO Global Strategy on Diet, 2004. It presents a deviation from physiological homeostasis paving the way to several disorders and chronic diseases, including cardiovascular disease, diabetes, malignancies, neurodegenerative diseases among others. These are further associated with co-morbidities such as hyperinsulinemia, dyslipidemia, hypercholesterolemia, hyperleptinemia, hypertension, hyperglycemia, chronic inflammation, compromised reproductive functions[21,22]. The decline in male fecundity and a concurrent increase in the prevalence of obesity have led to an array of research interventions to unveil the mechanism underlying obesity-induced male subfertility or infertility[23].

Studies suggest that in recent years, a considerable number of infertile men undergo screening and treatment for obesity with the aim of ameliorating their reproductive functions[24]. It is mentionworthy that a well-defined J-shaped relationship has been proposed between increase in BMI and decline in semen parameters[25]. The prevalence of obesity in the reproductive age in the present years is reported to be three times higher in the last 30 years. This directly correlates with the increase in male infertility[26]. Studies also claim azoospermia and oligozoospermia rates in obese men are higher than in those with BMI within the normal range[27]. Moreover, every 3 kg/m^2 rise in BMI in the male partner is reported to decrease the chance of successful pregnancy by that couple by about 12%[28].

Semen quality in terms of sperm count, morphology, motility, vitality, and sperm DNA integrity, are reported to get compromised in obese men[24,27]. Obesity is associated with erectile dysfunction and low sperm counts[29]. Cross-sectional studies showed that about 20%-64% of obese men suffer from low total testosterone levels[30]. Several studies also have demonstrated that low testosterone positively correlates with insulin resistance and an increased risk for diabetes mellitus and MetS in men[31]. Conversely, it is evident that obese men with type 2 diabetes present with low testosterone levels (both total and free) as well as low sex hormone-binding globulin (SHBG)[32]. Among these people, insulin resistance is very common, so they have more circulating insulin in their blood. These may have inhibitory effects on spermatogenesis through sperm DNA damage that leads to infertility[33]. Obesity may also lead to genetic and epigenetic alterations in spermatozoa as well as impairment of the endocrine regulation of the male reproductive functions[24,34]. High-fat diet induces dyslipidemia which is responsible for the higher oxidative stress; this leads to altered sperm functions[35]. Besides decreased testosterone, progesterone and SHBG levels, obesity induced hormonal alterations may also include increased levels of estrogen, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin along with other metabolic hormones and factors[36,37]. Several studies showed the impact of obesity on the hypothalamic-pituitary–gonadal (HPG) axis and positive association with abnormal testicular homeostasis[38]. The low levels of androgen also have been found to be directly proportional to the degree of obesity[31]. Obesity-associated physical disorders such as increased scrotal temperature also contribute to impairing male reproductive functions[24].

The present review article presents an updated concept of the possible mechanisms of obesity-induced endocrine alterations that may affect male reproductive functions.

2. MetS and male infertility

MetS leads to disordered energy production, usage and storage. It is diagnosed if any three out of the following five conditions co-occurs: hypertension, obesity, high serum triglycerides, low high-density cholesterol levels and high fasting level of blood glucose. MetS has long been shown to positively associated with male reproductive dysfunctions such as hypogonadism and erectile dysfunction[39]. Obesity is a state well suited for several physiological dysfunctions, hormonal imbalances and chronic disorders like hyperglycemia, hyperinsulinemia, *etc*[40]. These detrimental bodily consequences in obese men serve as confounding factors impairing sperm quantity[40].

The physiological mechanisms that relate metabolic energy balance with reproductive functions essentially include the neuroendocrine crosstalks among metabolic hormones, HPG axis, other male reproductive hormones, and the neural circuitry. The neural entity that regulates energy homeostasis and metabolic rate may be referred to as the 'metabolic sensor' converting hormonal signals into neuronal impulses, to regulate the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator. GnRH is 'master' regulatory hormone initiating the orchestrated release and functions of pituitary gonadotropins and testicular sex hormones for the regulation of testicular functions to maintain proper semen quality[41]. The hormones that are markers of metabolic status, such as insulin-like growth factor-I, insulin, ghrelin, leptin, resistin, obestatin, and growth hormone, reportedly transmit signals of nutritional status to the hypothalamic centers. This may suggest a mechanism by which these hormones communicate and interfere with the HPG axis hormonal milieu, thereby modulating male reproductive functions[41,42].

3. Obesity and endocrine disruption in men

3.1. Obesity, HPG axis and reproductive hormones

The mechanisms associating obesity with male infertility are mostly unclear. The most acceptable mechanism may be the obesity-induced dysregulation of the HPG axis hormonal regulations over testicular functions. The pituitary gonadotropins, LH and FSH, are regulated by the pulsatile release of GnRH from hypothalamus. The LH acts upon Leydig cells, mainly to regulate steroidogenesis and the FSH acts on Sertoli cells, primarily to regulate spermatogenesis. Obese men possess an increased number and size of adipocytes, responsible for abnormally high levels of various adipokines, inflammatory mediators and other hormones. These adipose tissue-derived substances interfere with the intricate regulation of the HPG axis which probably partially explains the mechanism of obesity-induced male subfertility or infertility. Studies show that the obesity-related parameters such as BMI, total body fat, subcutaneous fat, and intra-abdominal fat positively correlate with reduced levels of testosterone and higher estrogen levels in men[43]. This may be due to over-activity of the aromatase cytochrome P450 enzyme in obese men, which is produced in excess by the white adipose tissue over the levels that are produced by the Leydig cells. This enzyme converts androgens to estrogens and attributes a high estrogen level seen in obese men[44]. Such alterations in sex hormones affect spermatogenesis and other androgen-dependent male reproductive functions. Estrogen, being more biologically active than testosterone, may elicit huge downstream impacts with very minute rise in its plasma levels, to disrupt testicular functions[45]. On contrary, complete reduction of estrogen level in the testes also affects normal steroidogenesis and spermatogenesis[46]. The presence of estrogen receptors in the male hypothalamus suggests that higher estrogen levels in obese men lead to low testosterone levels also *via* a negative feedback mechanism inhibiting the pulsatile GnRH release and subsequent release of LH and FSH[47]. This mechanism ultimately leads to insufficient gonadotropins for androgen production and spermatogenesis. Another hormone that mediates feedback inhibition FSH production is inhibin B, which is a growth-like factor secreted by the Sertoli cells. It also stimulates testosterone synthesis by the Leydig cells. Suppressed inhibin B production in obese men may be due to high estrogen level or any other mechanism indicating a direct disruptive effect of obesity on Sertoli cells[48].

3.2. Obesity, adipokines and metabolic hormones

Obesity presents complex bodily disorders that greatly impairs physiological hormonal milieu[49]. High deposition of white adipose tissue in obese men leads to elevated estrogen levels, a surge of adipose tissue hormones, affecting the endocrine support for steroidogenesis and spermatogenesis. As discussed earlier, the increased estrogen level is due to increased aromatase enzyme activities that convert testosterone to estrogen. Adipose tissue is the major energy source and acts as an endocrine gland in the human body. These tissues are able to synthesize various bioactive substances like adipokines that can elicit chronic low-grade inflammation and interrelate with a wide range of metabolic homeostasis[50]. Accretion of excess fat leads the liberation of free fatty acids into the circulation which is a decisive factor for insulin sensitivity[51]. Adipokines are the proteins secreted by the adipose tissues; physiological levels of adipokines are obligatory to retain metabolic functions.

Obesity induces adipose tissue hormonal release, such as that of ghrelin[52], leptin[53], orexin[54], adiponectin[55,56], obestatin[57,58] and other metabolic hormones[49,59], all of which find relevance in regulation of male fertility[60–62].

3.2.1. Leptin

Leptin mainly controls the satiety center and body weight *via* three different leptin-sensitive neurons of the hypothalamus: neuropeptide Y, γ-aminobutyric acid and proopiomelanocortin neurons[63]. Leptin can be able to cross the blood-brain-barrier and inhibits neuropeptide Y and γ-aminobutyric acid neurons, which concurrently acts on proopiomelanocortin neurons and promotes the sensation of satiety to increase the energy expenditure[64]. Thus, leptin, a regulatory adipose tissue hormone, balances food intake and energy utilization through the effects upon hypothalamic control. Leptin reportedly mediates both metabolic and neuroendocrine roles. Besides its functions in glucose metabolism, it can also regulate male sexual maturation and reproductive functions[65]. Research has conveyed that the obese mouse, devoid of a functional leptin gene, demonstrated reduced gonadotropin secretion which led to infertility, while exogenous leptin treatment successfully restored fertility[66]. Moreover, chronic administration of anti-leptin antibody to rats proved detrimental to LH secretion and reproductive functions. Leptin also plays a regulatory role in mediating normal spermatogenesis as leptin-deficient mice showed disrupted spermatogenesis, elevated expressions of testicular pro-apoptotic genes, thus inducing germ cell apoptosis[67]. There are a few reports that contradict the ameliorating effects of leptin on male fertility, which shows that it also has inhibitory effects on testicular functions at levels exceeding the physiological limit[68]. Leptin induces reactive oxygen species (ROS) generation in human endothelial cells by increasing mitochondrial fatty acid oxidation[69,70]. Leptin may also stimulate the HPG axis by increasing the release of GnRH, FSH, and LH[71]. It can impose its direct effect upon the gonads as its receptor isoforms are present in abundance in the gonadal tissue[71]. Serum adiponectin levels show an inverse relationship with both testosterone[72] and ROS levels[73].

Leptin may also modulate hypothalamic GnRH release *via* its influence on kisspeptin. The role of kisspeptin in the regulation of

reproduction is widely accepted. Lying in the arcuate nucleus of the hypothalamus, the kisspeptin may serve as a link between metabolic status and reproductive functions[74]. Kisspeptin has been reported to inhibit lipogenesis and induce lipolysis[75]. In MetS like obesity, there is a reduced expression of kisspeptin mRNA (*KISS1*) in the hypothalamus as well as in the adipose tissues[74]. Since kisspeptin stimulates the pulsatile hypothalamic GnRH release, its deficiency in obesity may lead to hypothalamic hypogonadism[74,75].

3.2.2. Orexin

Orexin (hypocretin) is another emerging adipose tissue hormone that reportedly stimulates testosterone production *via* inducing steroidogenic enzymes activities in Leydig cells[76]. Orexin also seems to attenuate oxidative cell damage[77].

3.2.3. Resistin

Resistin secretion from the adipocytes has been reported to get highly increased in obese men. Resistin may induce insulin resistance in obese men leading to type 2 diabetes[78,79]. According to the Endocrine Society Clinical Practice Guidelines (2010), men with type 2 diabetes are subjected to be screened for low levels of testosterone[80]. This is justified as obese men with type 2 diabetes may possess secondary hypogonadism due to central or peripheral insulin resistance. This condition is worsened by the actions of associated pro-inflammatory cytokines (interleukin 6 and tumor necrosis factor-alpha) upon the HPG axis[44]. Moreover, high insulin levels in obese men downregulate SHBG levels, which may be the reason for reduced testosterone functions from that required to mediate normal spermatogenesis. Since compensation of low SHBG levels has been shown ineffective over the low testosterone levels in the state of insulin resistance in obesity, it may be suggested that there is an autonomous direct impact of insulin resistance on Leydig cell for the production of testosterone[24,44].

3.2.4. Ghrelin

Ghrelin is referred to as the "hunger hormone". It is a neuropeptide produced by ghrelinergic cells in the gastrointestinal tract, and it is suggested to be associated with altered serum testosterone levels in obese men[81-83]. Ghrelin receptors are found in the testis, which play a significant role in steroidogenesis. However, the direct impact of ghrelin upon spermatogenesis is still contentious[81]. Ghrelin may induce overproduction of ROS and induce oxidative stress to influence normal testicular functions[84].

3.2.5. Adiponectin

Adiponectin has an opposite affiliation between obesity and insulin resistance. It primarily affects the liver, skeletal muscle and the vascular wall of the endothelial cells. Where it can stimulate the nitric oxide production which helps in angiogenesis[85]. It also helps in the management of obesity-related nonalcoholic steatohepatitis, a situation in which redness and gathering of fat and gristly tissues in the liver[86].

3.2.6. Vaspin

Vaspin is an adipokine that has a role in the progress of fatness, metabolic dysfunctions and insulin resistance. Visceral expression of *vaspin* mRNA significantly correlates with % of body fat, BMI and blood glucose level. It has sex reliant directive and are considerably higher in women than men[87].

Other recently discovered adipokines are apelin, acylation stimulating proteins, fatty acid-binding proteins, visfatin, omentin, chemerin, and plasminogen activator inhibitor-1.

All the above-discussed obesity-related hormones, discovered so far, are not enough to establish a clear mechanism of obesity-induced male subfertility or infertility. Further research is required to segregate an adipokine "from fat" that helps us to "fight against fat". In the 21st century, obesity is the emergent concern to all the developed and developing countries. Alterations in socio-economic status, unhealthy food habits, stressful lifestyle, and lack of physical activities might be the underlying causatives[88].

4. Obesity and semen quality

Human semen quality is a reliable predictor of male fecundity, which is undergoing a global declining trend[1-4]. Obesity and overweight along with the related allostatic load have widely been reported to be closely associated with an elevated occurrence of oligozoospermia and azoospermia[89]. Proper management and disciplined weight loss showed an impressive improvement in testosterone levels and semen parameters[90].

The most conventional and essential male fertility parameter is semen quality that comprises mainly of semen volume, sperm count, sperm morphology and sperm motility. In men, seminal fluid characteristics depend on their overall reproductive health and environmental cues. Semen parameters may get jeopardized even at the little deviation from homeostatic conditions. State of trauma, systemic illnesses, improper lifestyle, poor nutritional status, environmental stress and metabolic disorders like in case of obesity can adversely affect semen quality[27]. The association of high BMI with impaired steroidogenesis, spermatogenesis, and thereby deteriorated semen quality have been put forth but still require further elaborative research[24].

Obese men have been suggested to have three times more probability of sperm count less than 20 million/mL as compared to men with normal weight. This condition of decreased sperm count is termed as 'oligozoospermia'[45]. Chavarro *et al*[91] showed that men with higher BMI (>25 kg/m^2) had lower total sperm count compared to normal-weight men. The semen volume upon ejaculation also decreased with increase in BMI. A broad-spectrum study including

1 558 Danish military men also showed a negative correlation of increased BMI with total sperm count and concentration[92]. Obesity also affects sperm motility and morphology, while this mechanism is not yet completely understood[23]. Numerous studies have used these findings to suggest the disruptive impact of obesity upon male fertility[93,94].

5. Altered spermatogenesis in obese men

The seminiferous tubules maintain a dynamic yet steady balance between cell regeneration and apoptosis[95]. Following the first wave of spermatogenesis, a phase of germ cell differentiation occurs under intricate hormonal regulations. If the cell differentiation in this phase surpasses the physiological limit, they are directed to undergo apoptosis *via* the B-cell lymphoma-xL (Bcl-xL) and Bcl-2 associated X protein (Bax) systems[96,97]. Spermatogonial apoptosis may be triggered by specific physiological or pathological factors. The spermatozoa of artificial insemination were reported going through a high rate of apoptosis in conditions of obesity. Such immoderate obesity-induced germ cell apoptosis contributes to a majority of male subfertility or infertility[98]. Spermatogonial apoptosis is regulated by the conventional Bax and Bcl-2 homeostasis. Obesity disrupts the ratio of Bcl-2/Bax in the testis, increasing Bax and reducing Bcl-2 expressions. These alterations may induce the downstream apoptosis signaling caspases, especially triggering caspase 3 in spermatogonia[99]. Moreover, obesity-associated hyperlipidemia and lipid metabolic disorders trigger the endoplasmic reticulum to mediate spermatogenic cell apoptosis *via* high expressions of glucose-regulated protein 78 mRNA and protein[100,101].

6. Obesity on sperm chromatin fragmentation

Sperm DNA fragmentation (SDF) is an advanced sperm function determinant in the assessment of male infertility[102,103]. Obesity may severely affect SDF possibly by induction of oxidative stress. Very few studies have claimed the influence of obesity on sperm DNA integrity and their findings have disparities due to technical issues[91,104]. Increase in SDF level also corresponded to reduced pregnancy rates[102,105]. Kort *et al*[106] reported increased SDF in obese men by using sperm chromatin structure assay. Similar observations were reported by Chavarro *et al*[91] and Farriello *et al*[107] using the single-cell gel electrophoresis assay method (comet assay). La Vignera *et al*[108] used terminal-deoxynucleotidyl transferase-mediated nick end labeling assay with flow cytometry and found that obesity adversely affects sperm chromatin integrity. Similar reports were reported by a 3-year multicentre study on the association of BMI with sperm DNA integrity[109].

7. Obesity and micronutrient deficiency

Obese individuals practice an excess of dietary calorie intake but mostly suffer from micronutrient deficiencies, including those of vitamin D, vitamin C, biotin, chromium, and thiamine[110]. Metabolism in the body essentially needs certain micronutrients as co-factors, and these micronutrients especially vitamin D have beneficial effects on male fertility. It has been found to induce male reproductive hormone productions and improve semen quality. It is reported to contribute to the increased bioavailability of testosterone[111].

8. Conclusions

Obesity is presented with an array of pathological conditions. The increasing global prevalence of obesity together with the concurrent decline in male fertility arouses research interest to find any association between obesity and male infertility. The exact mechanism of obesity-induced male subfertility or infertility is far from complete understanding. Obese men have high adipose tissue deposition, which is considered as toxin depots and sources of several hormones and adipokines. These hormones may influence the HPG regulatory axis as well as directly testicular cells to impair male reproductive functions. This review article has discussed the endocrine crosstalks among the obesity-related hormones and male reproductive hormonal milieu that may partly explain the mechanism how obesity-mediated endocrine disruption adversely affect male reproductive functions.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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