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REVIEW ARTICLE **OPEN ACCESS**

Obesity and Male Infertility

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ABSTRACT
Obesity is an excessive accumulation of fat in the human body to the level that adversely affects his health. The increase in infertility cases occurs in parallel with the increase in the prevalence of obesity. A common finding in several previous studies is the inverse relationship between body mass index and male fertility. Obesity correlates negatively with semen volume, total sperm count, sperm concentration, vitality, normal morphology and motility. It increases sperm with DNA fragmentation. Obesity also reduces inhibin B and testosterone, elevates leptin and serum oestrogens, alters prolactin secretion and suppresses hypothalamic-pituitary-gonadal axis. The increase in the prevalence of obesity calls for greater awareness of its effects on male fertility, better understanding of underlying pathophysiology, and determination of suitable treatment.
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INTRODUCTION

World Health Organization (WHO) has defined overweight and obesity as an excessive accumulation of fat in the human body to the levels that can adversely affect his health. They are measured by body mass index (BMI) which can be calculated by dividing the weight by the squared height. A value between 25-30 kg/m^2 considered as overweight; whereas, a value more than 30 kg/m^2 is indicator of obesity (1). Obesity is a chronic complex disorder caused by interaction between endogenous and exogenous factors (2). Sedentary life style and unhealthy diet are common associations with obesity (3). Contemporary diet is an important determinant of obesity. The majority of obesity cases can be attributed to be diet-induced (4). World health organization estimated that in 2014 more than 1.9 billion of adults of age 18 years and older were overweight, from those more than 600 million were obese. Worldwide, 39% of adults were overweight and 13% were obese. This indicates that the prevalence of obesity in 2014 was more than the double of that in 1980 (5). The prevalence of obesity is higher in developed countries, with a percentage of more than 30%, than the developing countries in which the prevalence of obesity is 5% (6). Regardless of its cause, obesity is considered to be a chronic low-grade inflammatory condition manifested by high serum levels of several inflammatory biomarkers and high number of macrophages within the white adipose tissue (7). It is a predisposing factor to serious health problems such as diabetes mellitus, high blood pressure, ischemic heart disease, joint diseases, cancers and reproductive disorders (8). There is a growing evidence that the increase in infertility cases occurs in parallel with the increase in the prevalence of obesity (9). Even though the impairment of fertility is not the case in all obese men, 80% of men attending the fertility clinics are classified as overweight or obese, which suggests the association between obesity and male infertility (10). The prime goal of this review is to summarise the effects of obesity on male reproductive system and fertility.

EFFECTS OF OBESITY ON SEMEN QUALITY AND SPERM PARAMETERS

A common finding in several previous studies is the inverse relationship between BMI and sperm parameters (11). The predominant consensus is that obesity is associated with disturbances in semen and sperm analysis. However, there are controversies among the previously conducted researches about the sperm and semen parameters that have been affected by obesity. Experimentally, obesity induced in rats by high energy diet administration resulted in a reduction of sperm motility without noticeable

effects on the other sperm parameters (12). In mice, obesity resulted in a reduction of sperm motility associated with a reduction in post-copulatory plugs and pregnancy rates in female mice matted with those obese males (13). It resulted also in an impairment of preimplantation embryo development and implantation (14). Clinically, Chavarro et al. (2010) demonstrated that higher BMI is associated with a reduction in the volume of ejaculate and sperm count and an increase in sperm with DNA fragmentation with no effects on the other sperm parameters (15). Compared to these results, Jensen et al. (2004) reported that men with BMI of more than 25 kg/m^2 suffered from lower sperm concentration and lower total sperm count coupled with a fewer normal form of sperm; however, no effects of BMI were detected on semen volume and percentage of sperm motility (16). Kort et al. (2006) demonstrated that BMI is inversely related to the total number of normal motile sperm (17). All of the previously mentioned sperm parameters, apart from DNA fragmentation and semen volume, were found by Andersen et al., (2015) to be inversely related to BMI and they were severely affected in men with massive obesity (18). Palmer et al. (2012) reported that sperm concentration reduced with male obesity in 15 out of 23 of recent studies; whereas, sperm motility was reduced in 7 out of 19 studies. Pertaining to sperm morphology, normal morphology was reported to be reduced in 7 out of 16 studies (19). In a large meta-analysis based on 13077 men there was a negative association between BMI and sperm parameters with overweight and obese men showed the highest risk of abnormal sperm count in comparison to the normal weight men (20). In another large cohort study carried out by Belloc et al. (2014) on 10,665 men, BMI was negatively correlated with semen volume, total sperm count, sperm concentration, vitality and motility with no correlation was detected between BMI and sperm morphology (21). In contrast to aforementioned results, a meta-analysis and cross-sectional study were conducted by MacDonald et al. (2010, 2013) and cross-sectional study conducted by Aggerholm et al. (2008) to determine the association between BMI and male reproductive hormones and semen parameters, they ended up with the conclusion that no association was detected between BMI and semen parameters and if any, it was so marginal and below the detection limit in large population studies (22–24). Contradicting results were reported in another study carried out on 990 Chinese men where the authors suggested that being an overweight is a protecting factor against low sperm concentration and low total sperm count (25).

EFFECTS OF OBESITY ON MALE REPRODUCTIVE HORMONES

With the increase of adiposity, the activity of aromatase enzyme increases, which leads to the conversion of more androgen to oestrogen and as a consequence the level of oestrogen increases in obese persons (26). This can induce secondary hypogonadism via suppression of hypothalamic-pituitary-gonadal axis (27). Estradiol has an inhibitory feedback effect on the hypothalamic–pituitary axis that causes a reduction in the production and release of FSH with a subsequent shift of LH/FSH ratio towards LH predominance (28,29). Obesity particularly central obesity is associated with a reduction in testosterone level which is proportionate to the degree of obesity (30). The reduction of testosterone in obese men has two origins: 1) the reduction in sex hormone-binding globulin levels (SHBG), which is the main contributory factor for testosterone reduction in moderately obese men and 2) functional impairment at the pituitary gland level with a reduction in LH level and LH pulse amplitude. This can only be observed in massively obese men and it is the main cause for the decrease in the free testosterone and hypogonadism (31). Long term obesity can induce chronic testicular inflammation that affects Leydig cells steroidogenesis. This chronic inflammation manifested by an increase in testicular pro-inflammatory marker TNFα and the number of testicular macrophages (32). The reduction in testosterone with an elevation of oestrogen are associated with lower sperm count and infertility through disruption of hypothalamic-pituitary-gonadal axis or through the direct deleterious effect of oestrogen on spermatogenesis (10,30). The combination of decreased total as well as free testosterone, elevated serum oestrogens (both estrone and estradiol) concentrations and suppression of hypothalamic and pituitary functions are the characteristic hormonal profile of obese men and it is termed as hyperestrogenic hypogonadotropic hypogonadism (HHH) (33). This hormonal profile was confirmed by several previous studies. Chavarro et al. (2010) reported that, higher BMI associated with lower levels of serum testosterone, inhibin, sex-hormone binding globulin, FSH, and testosterone: LH ratio, and higher serum estradiol level (15). Similar results were observed in another cross-sectional study conducted on 1,558 Danish men. There was an inverse relationship between the BMI and serum testosterone, SHBG, and inhibin B; whereas, the relation was linear between the BMI and oestrogen level (16). Contradicting results for some if not all of the hormones of aforementioned obesity hormonal profile were reported in other studies. Andersen et al. (2015) demonstrated that there is no association between BMI and FSH or LH (18). MacDonald et al. (2010, 2013) in their meta-analysis and Aggerholm et al., (2008) reported that a strong evidence of negative relationship between BMI and testosterone and SHBG was found; however,

no relation existed between BMI and either of estradiol (increased only in some studies which does not reach the significant value), FSH or LH (22–24).

Leptin is another hormone produced by white adipose tissue and its level is commonly elevated in obese persons. High levels of leptin decreases testosterone production through its effect on hypothalamic-pituitary-testicular axis or through a direct inhibitory effect of leptin on Leydig cells function (19,34). It has a deleterious effect on sperm production and can induce apoptosis in germ cells (35). The deficiency in leptin receptors impairs sperm production and associated with increased DNA fragmentation (36). Accordingly, serum leptin mediates a link between obesity and male infertility (37).

Inhibin B is a hormone produced by Sertoli cells and plays an important role in the regulation of FSH secretion through a negative feedback mechanism. It is a potential marker for infertility status (38). Inhibin B level decreases with the increase of obesity in young adults. It was found to be 26% lower in the obese than the normal weight men, which reflects the suppression of Sertoli cells proliferation (39).

Another hormone is prolactin which is secreted by anterior pituitary gland (40). Its receptors are located on Leydig cells of the testes. prolactin at its normal level increases testosterone secretion; however, high level of prolactin reduces testosterone and leads to frigidity (41). Obesity is associated with altered prolactin secretion which indicates a dysfunction of hypothalamic-pituitary axis and leptin level which, in turn, affects male reproductive system (40).

Obesity and increased scrotal temperature

Excess fat accumulation in suprapubic and thigh areas is a leading cause to subfertility as a result of raised scrotal temperature (27). Sedentary lifestyle and reduced physical activity in obese individuals are another factors for high scrotal temperature, which subsequently leads to an impairment of sperm production and quality and reduced fertility (42). The optimum testicular function for spermatogenesis depends on the temperature that should be 2-8°C below the core body temperature. Men with increased scrotal temperature were found to have high percentages of immature and abnormal sperm in their ejaculate (43). Testicular hyperthermia can cause a transient reduction in relative testicular weight, disruption of spermatogenesis and induction of apoptosis, in addition to its effects on the expression of the genes involved in DNA repair and oxidative stress (44).

OBESITY AND DEOXYRIBONUCLEIC ACID FRAGMENTATION

Normal structure of sperm chromatin is crucial for transferring paternal genetic information to the offspring. It is well-known that disruption of chromatin integrity is correlated negatively with fertility (45). Sperm Deoxyribonucleic acid (DNA) damage causes conception failure, miscarriage, malformation and genetic diseases (46). Deoxyribonucleic acid fragmentation index (DFI) is the percentage of sperm in a semen sample that have raised level of breaks in their single or double strands of nuclear DNA. Its normal value is 3-5%; whereas, 25-30% DFI is a risk factor for infertility (11). Deoxyribonucleic acid fragmentation index is higher in overweight and obese men and it is an indicator of sperm chromatin disruption (17). Men with high DFI have reduced fertility associated with an increase in abortion rate in their partner (11).

INSULIN RESISTANCE AND MALE INFERTILITY

Insulin resistance is a common association with obesity (47). It is well-known that obesity particularly central obesity is a condition of insulin resistance and compensatory hyperinsulinemia (48). Diet-induced obesity induces macrophage infiltration in adipose tissue and causes a shift of adipose-resident macrophage from alternatively activated type (M2) to classical activated type (M1). This shift of the macrophages leads to an increase in the production of the pro-inflammatory cytokines; TNF-α and IL-6, and ROS which induce insulin resistance. Furthermore, the adipokine resistin constitutes another linkage between obesity and insulin resistance (49,50). Insulin resistance in established obesity is mediated mainly by pro-inflammatory cytokines; whereas, the initial stage of high energy diet-induced insulin resistance is independent of inflammation and mediated by lipid overload and lipotoxicity (51). There is also a positive association between oxidative stress and insulin resistance (52). There are controversies pertaining to the significance and strength of the association between insulin and testosterone (53). Insulin is deemed to have a regulatory role on serum testosterone concentration in men, with absence of insulin signalling in the central nervous system disrupts the process of steroidogenesis (54). Other studies suggested that testosterone plays a critical role in the regulation of insulin sensitivity with low testosterone level associated with increased insulin resistance (55). The positive association between low testosterone and insulin resistance was also demonstrated by Pitteloud et al. (2005) (56). Stellato et al. (2000) reported that low testosterone and sex hormone binding globulin (SHBG) are implicated in the development of insulin resistance and subsequently type-II diabetes (57). These results were supported

by Oh *et al.* (2002) who reported that low total testosterone level can predict insulin resistance and development of type-II diabetes (58). Tsai *et al.* (2004) demonstrated that the inverse association between insulin resistance and free and total testosterone, independent of SHBG, is mediated by body fat (53). While low testosterone is a predictive for development of type-II diabetes, the exact underlying mechanisms are not well-established. Insulin resistance could be a common underlying aetiology for both hypogonadism and type-II diabetes (27). On the other hand, testosterone administration to middle aged centrally obese men improved insulin resistance, increased insulin sensitivity, decreased fasting insulin, decreased visceral fat mass and decreased plasma cholesterol and triglycerides (59,60). Dhindsa et al. (2016) revealed that testosterone treatment in patients with type-II diabetes improved insulin sensitivity, reduced subcutaneous fat and increased lean body mass (61). Effects of testosterone on insulin resistance depends on the dose of testosterone (62). Marked insulin resistance was induced in male rats with either administration of high dose of testosterone or castration. Substitution of castrated rats with low dose of testosterone restored insulin sensitivity, which indicates that optimal insulin sensitivity is found in the physiological window of testosterone concentration (63).

OBESITY INDUCED-SLEEP APNOEA AND MALE INFERTILITY

Sleep apnoea is a disorder characterized by recurrent episodes of upper airway obstruction during sleep due to the repetitive collapse of pharyngeal airway resulting in hypoxia and hypercapnia (11). It is a common association with obesity particularly central obesity (64). Obstructive sleep apnoea is associated with a decrease in pituitary-gonadal function and a reduction in LH and testosterone. The reduction in testosterone is caused by obesity and to a lesser extent to sleep fragmentation and hypoxia (65).

OBESITY AND ERECTILE DYSFUNCTION

There is an association between obesity and erectile dysfunction. Up to 79% is the prevalence of overweight and obesity in men reported to be suffered from erectile dysfunction (66). It shares with the cardiovascular diseases in the common risk factors such as sedentary life style, obesity, smoking, hypertension and dyslipidaemia (67). Atherosclerotic obstruction of arterial inflow to the corporal bodies is the main cause of vasculogenic erectile dysfunction associated with these risk factors. The pathogenesis of atherosclerosis includes endothelial injury, vascular smooth muscle cell proliferation and cellular migration (68).

MANAGEMENT OF OBESITY-INDUCED MALE INFERTILITY

Treatment of obesity-induced male infertility can be accomplished through life style modification, pharmacotherapy or surgical intervention as illustrated in Figure 1 (11).

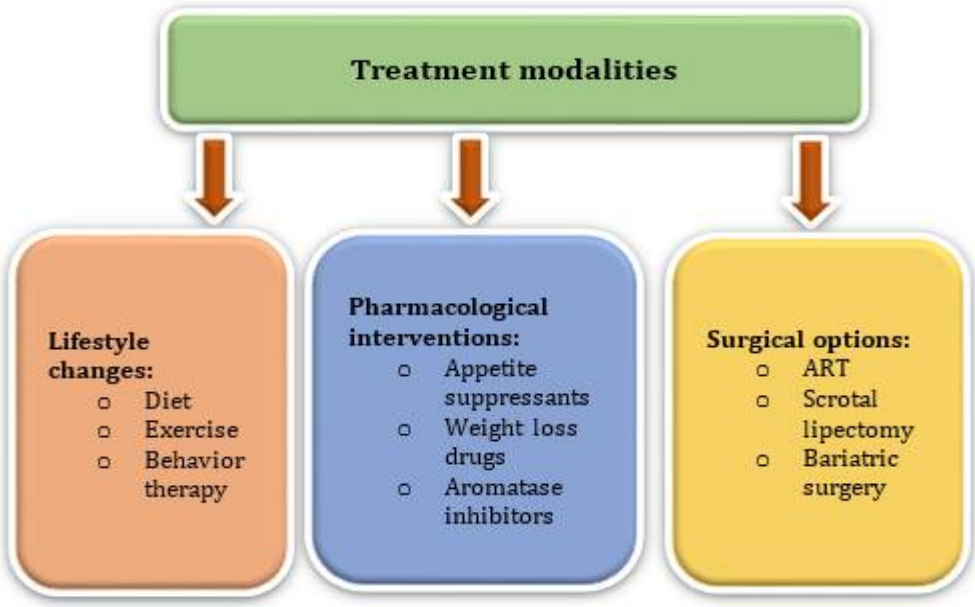

Figure 1: Management of Obesity-Induced Male Infertility

CONCLUSION

Obesity is an acknowledged risk factor for male infertility. The pathogenesis underlying obesity-induced male infertility is complex and multifactorial including hormonal disturbances, increased scrotal temperature, impairment of sperm parameters and erectile dysfunctions. Treatment modalities are life style changes, pharmacological and surgical options that may directed toward the obesity *per se* or toward the consequences of obesity as causes of male infertility.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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