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# Male Obesity and Reproductive Health

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## Abstract

Obesity has reached epidemic proportions globally, and all this evidence suggests that the situation is likely to get worse ahead. A combination of an increasingly sedentary lifestyle and unfavorable diet in the western world has resulted in increasing numbers of overweight and obese children and adults. According to the WHO, approximately 1.6 billion adults were classed as being overweight and 400 million adults were obese in 2005. Also gaining attention is the reported decline in semen quality and male reproductive potential over the past 50 years. Surprisingly, such decreases have not been reported in regions where obesity is less prevalent. Since this decline in fertility has occurred in parallel with increasing rates of obesity, the possibility that obesity is a cause of male infertility and reduced fecundity should be addressed. Effects of obesity on female fertility have been studied extensively. Weight loss in anovulatory women restores fertility and increases the likelihood of ovulation and conception. In contrast to the extensive knowledge of the effects of obesity on female fertility, male factor infertility as a result of obesity has been overlooked, even after the discovery of a threefold increase in the incidence of obesity in patients with male factor infertility, demanding the concern over male obesity with respect to infertility.

**Keywords:** obesity, reproduction, infertility, weight loss in men

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## 1. Introduction

Obesity has reached epidemic proportions globally, and all this evidence suggests that the situation is likely to get worse ahead. In developed nations such as Europe, the United States of America, and Australia, the prevalence is high and increasing, but in some developing countries, the situation is even worse.

A combination of an increasingly sedentary lifestyle and unfavorable diet in the western world has resulted in increasing numbers of overweight and obese children and adults. According to the WHO, approximately 1.6 billion adults were classed as being overweight and 400 million adults were obese in 2005 [1].

Also gaining attention is the reported decline in semen quality and male reproductive potential over the past 50 years. It is reported that the quality of semen has substantially declined, with the consequent negative effect of poor semen quality on male fertility conceivably contributing to an overall decrease in male reproductive potential. It is estimated by some studies that male sperm counts continue to decrease by as much as 1.5% per year in the USA; similar findings pertaining to other western countries have also been reported [2]. Surprisingly, such decreases have not been reported in regions where obesity is less prevalent [2]. Since this decline in fertility has occurred in parallel with increasing rates of obesity, the possibility that obesity is a cause of male infertility and reduced fecundity should be addressed.

Effects of obesity on female fertility have been studied extensively. Obesity in women is known to contribute to anovulation, a reduced conception rate and an increased risk of miscarriage and prenatal complication [3]. Weight loss in anovulatory women restores fertility and increases the likelihood of ovulation and conception [4]. In contrast to the extensive knowledge of the effects of obesity on female fertility, male factor infertility as a result of obesity has been overlooked, even after the discovery of a threefold increase in the incidence of obesity in patients with male factor infertility [5], demanding the concern over male obesity with respect to infertility.

## 2. Fertility

The term “fertility” is the natural capability of producing offspring, the capacity to conceive given unprotected intercourse, in contrast to demographic fertility, the actual number of children. Sometimes the alternative term “fecundity” is used for this purpose, but others use these terms the other way around. As a measure, “fertility rate” is the number of children born per couple, person or population. Fertility is difficult to study in humans. It can be looked at from a functional perspective, by the use of biomarkers, or from a mechanistic viewpoint. Functional fertility refers to how easy or difficult a couple find it to conceive, given that they are having unprotected intercourse, and tends to be assessed by looking at how long this takes, since more fertile couples tend to conceive more quickly.

Concern is increasing about impact of the environment on public health, including reproductive ability. Controversy has arisen from some reviews which have claimed that the quality of human semen has declined [6]. However, only little attention has been paid to these warnings, possibly because the suggestions were based on data on selected groups of men recruited from infertility clinics [7], from among semen donors [8], or from candidates for vasectomy [1]. It is, however, noteworthy that the lower reference value for a “normal” sperm count has changed from  $60 \times 10^6/\text{ml}$  in the 1940s to the present value of  $15 \times 10^6/\text{ml}$  [1]. As a decline in semen

quality may have serious implications for human reproductive health, it is of great importance to elucidate whether the reported decrease in sperm count reflects a biological phenomenon or, rather, is due to methodological errors.

## 2.1. Infertility

According to World Health Organization (WHO) and the American Society for Reproduction Medicine (ASRM) Practice Committee, infertility is the inability of the sexually unprotected, active couple to achieve pregnancy in 1 year [9]. Infertility is a major concern among married couples when they fail to achieve conception even after 1 year of regular unprotected intercourse [9]. About 25% of couples do not achieve pregnancy within 1 year, less than 5% remain unwillingly childless and 15% seek medical treatment for infertility. Approximately in 50% of the cases, the underlying etiology lies in men alone [10]. In addition, no causal factors are found in 60–75% of the cases in men, and therefore, the cause is idiopathic. Despite these statistics, male infertility has received little research and public health attention in comparison with female fertility.

Infertility can be permanent (irreversible) or subfertility which means the probability of spontaneous conception may be decreased. All men who are sterile would be considered infertile, but not all men who are infertile are sterile because an infertile man can father a child with medical help or with simple change in his life style. Infertility can either be primary or secondary; primary male infertility is when the man has never impregnated a woman, while secondary male infertility is when a man has impregnated a woman irrespective of the outcome of the pregnancy. Men with secondary infertility, in general, have better chance of future fertility. Reduced male fertility can be the result of congenital and acquired urogenital abnormalities, genital tract infections, increased scrotal temperature due to varicocele or occupational exposure, endocrine disruptors, genetic abnormalities and immunological factors.

## 3. Diagnosis of infertility in men

The most important steps in diagnosis of infertile men are a careful history taking and a physical examination. One-quarter of cases are related to the medical history of the patients. Specific childhood illnesses may result in problems in the reproductive system like delayed or failed testicular descend, post pubertal mumps-orchitis (mumps accompanied with swelling of one or both testis), time of puberty, surgical history especially around the reproductive tract, therapeutic medications, and systemic diseases.

Physical examination is the second step in diagnosing abnormalities that causes infertility in men. Measurement of height, weight, and blood pressure will also give some information about systemic diseases. Body hair distribution gives an indication of androgen production, breasts should be inspected for the abnormal enlargement in males known as gynecomastia.

## 4. Biology of obesity

In a world where food supplies are intermittent, the ability to store energy in excess of what is required for immediate use is essential for survival. Fat cells, residing within widely distributed adipose tissue depots, are adapted to store excess energy efficiently as triglyceride and, when needed, to release stored energy as free fatty acids for use at other sites. This physiologic system, orchestrated through endocrine and neural pathways, permits humans to survive starvation for as long as several months. However, in the presence of nutritional abundance and a sedentary lifestyle, and influenced importantly by genetic endowment, this system increases adipose energy stores and produces adverse health consequences.

### 4.1. Definition and measurement

Obesity is a medical condition in which excess body fat, or white adipose tissue, accumulates in the body to the extent that this accumulation of fat might adversely affect health. Although often viewed as equivalent to increased body weight, this need not be the case—lean but very muscular individuals may be overweight by numerical standards without having increased adiposity. Body weights are distributed continuously in populations, so that choice

Classification	BMI (kg/m <sup>2</sup> )	
	Principal cut-off points	Additional cut-off points
<b>Underweight</b>	<18.50	<18.50
Severe thinness	<16.00	<16.00
Moderate thinness	16.00–16.99	16.00–16.99
Mild thinness	17.00–18.49	17.00–18.49
<b>Normal range</b>	<b>18.50–24.99</b>	<b>18.50–22.99</b> <b>23.00–24.99</b>
<b>Overweight</b>	<b>≥25.00</b>	<b>≥25.00</b>
Pre-obese	25.00–29.99	25.00–27.49 27.50–29.99
<b>Obese</b>	<b>≥30.00</b>	<b>≥30.00</b>
Obese class I	30.00–34.99	30.00–32.49 32.50–34.99
Obese class II	35.00–39.99	35.00–37.49 37.50–39.99
Obese class III	≥40.00	≥40.00

Source: Adapted from WHO, 1995, WHO, 2000 and WHO 2004. BMI - Body Mass Index.

**Table 1.** The international classification of adult underweight, overweight and obesity according to Body Mass Index (BMI).

of a medically meaningful distinction between lean and obese is somewhat arbitrary. Although not a direct measure of adiposity, the most widely used method to gauge obesity is the body mass index (BMI), which is equal to weight/height<sup>2</sup> (in kg/m<sup>2</sup>). An individual can be defined as being overweight if their BMI is 25–30 kg/m<sup>2</sup>, and obese if their BMI exceeds 30 kg/m<sup>2</sup>. The WHO Expert Consultation concluded that the proportion of Asian people with a high risk of type 2 diabetes and cardiovascular disease is substantial at BMI's lower than the existing WHO cut-off point for overweight (= 25 kg/m<sup>2</sup>). However, the cut-off point for observed risk varies from 22 to 25 kg/m<sup>2</sup> in different Asian populations and for high risk; it varies from 26 to 31 kg/m<sup>2</sup>. The Consultation, therefore, recommended that the current WHO BMI cut-off points (**Table 1**) should be retained as the international classification. However, the distribution of body fat specifically in the central abdominal region has also been used to diagnose a patient as obese. However, these definitions should only be considered as guidelines, as the risk of developing chronic diseases increases progressively when the BMI increases above 21 kg/m<sup>2</sup> [11].

Other approaches to grade obesity include anthropometry (skin-fold thickness), densitometry (underwater weighing), computed tomography (CT) or magnetic resonance imaging (MRI), and electrical impedance. A BMI of 30 is most commonly used as a threshold for obesity in both men and women. Most but not all large scale epidemiologic studies suggest that all-cause, metabolic, cardiovascular morbidity, and cancer begin to rise when BMIs are  $\geq 25$ . Most authorities use the term overweight (rather than obese) to describe individuals with BMIs between 25 and 30. A BMI between 25 and 30 should be viewed as medically significant and worthy of therapeutic intervention in the presence of risk factors that are influenced by adiposity, such as hypertension and glucose intolerance.

#### 4.2. Prevalence

According to the World Health Organization (WHO), obesity is one of the most common, yet among the most neglected, public health problems in both developed and developing countries. According to the 2012 WHO World Health statistics report, one in six adults is obese and nearly 2.8 million individuals die each year due to overweight or obesity globally.

Selected statistics on overweight and obesity from most recent national prevalence surveys in adults for both developed and developing countries illustrates several well-known features of the pandemic: (1) that the highest rates of obesity are concentrated in several of the Pacific Islands with record rates in Nauru where 79% of adults were recorded as obese (BMI > 30 kg/m<sup>2</sup>) in 1994; (2) the lowest rates are in the lesser developed countries of Asia where India records just 0.5% obesity, China, Japan, and the Philippines record 3%, and Singapore records 6%; (3) that rates in Europe and North America are generally high but with some striking contrasts (for instance, 15% of Canadians are obese compared with 28% of US citizens, and 21% of Germans are obese compared with only 5% of Norwegians); (4) that rates are high in many Middle Eastern countries though again with considerable heterogeneity (for instance, Iran has 10% of obese adults, whereas Bahrain has 29%); and (5) that rates in Africa are very variable and reflect the stage of transition of each country.

### 4.3. Physiological regulation of energy balance

There has been a belief that adipose tissue is merely a storage site for energy, but the fact is that adipose tissue plays an active role in energy homeostasis and various processes [12]. There are two types of adipose tissue present in mammals: brown adipose tissue (BAT) and white adipose tissue (WAT). BAT plays an important role in energy metabolism in many mammals. While as white adipose tissue is used to store energy in the form of lipids, BAT expends stored energy as heat. The predominant type of adipose tissue in mammals is white adipose tissue (WAT). WAT is comprised mostly adipocytes, surrounded by loose connective tissue that is highly vascularized and innervated, fibroblasts, adipocyte precursors and contains macrophages, and various other cell types. The largest WAT depots are found in the subcutaneous region and around viscera. WAT can store enormous amount of triglycerides vital for survival. The concurrent rise in insulin, glucose, and lipids during and after meals stimulates triglyceride formation and storage in liver and WAT. Conversely, during fasting, the insulin also falls triggering glycogen breakdown and lipolysis through activation of the sympathetic nervous system and elevation of glucagon, epinephrine, and glucocorticoids to maintain glucose supply to the brain and other vital organs. Fatty acids released from adipose tissue during fasting are partially oxidized by muscle and liver, generating ketones that serve as alternate source of energy for the brain and peripheral organs.

Evidence suggests that body weight is regulated by both endocrine and neural components that ultimately regulate the energy intake and expenditure. This energy regulatory system has to function normally because even small imbalances between energy intake and expenditure will ultimately have large effects on body weight. It is not easy to monitor this regulation system by calorie-counting in relation to physical activity. Rather, body weight regulation or dysregulation depends on a very complex interaction of hormonal and neural signals.

If a person tries to alter his weight by changing the diet, there will be physiological changes. With weight loss, body will compensate with increase in appetite and decrease in energy expenditure. If the person does overfeeding, appetite falls and compensatory energy expenditure increases. This latter compensatory body mechanism frequently fails, and allows the obesity to develop when food is consumed in excess and physical activity is limited. Adipocyte derived hormone leptin plays a major regulatory role which acts through a complex brain circuits (predominantly in the hypothalamus) to influence appetite, energy expenditure, and neuroendocrine function. Appetite is integrated in brain especially in hypothalamus, influenced by many factors. Neural afferent signals, hormones, and some metabolites act on hypothalamic center as stimulants. Vagal inputs from gut are particularly important in modulating the hypothalamic center especially gut distention. Hormonal signals include leptin, insulin, cortisol, and gut peptides like ghrelin. Ghrelin is secreted in the stomach and stimulates feeding and peptide YY (PYY) and cholecystinin which is made in the small intestine can signal the brain either directly or via the vagus nerve. Metabolites, like glucose, can influence appetite, as seen by the effect of hypoglycemia which induces hunger; however, glucose is not normally a major regulator of appetite. These diverse hormonal, metabolic, and neural signals act by influencing the secretion and inhibition of various hypothalamic peptides.

There is continuous energy expenditure in the body which includes the following components: resting or basal metabolic rate (BMR), energy cost of metabolizing and storing food, thermic effect of exercise; and adaptive thermogenesis. Normally, the basal metabolic rate accounts for ~70% of daily energy expenditure, whereas other physical activity contributes 5–10%. Thus, a major component of daily energy consumption is fixed (~70%).

Leptin influences the metabolic activity of BAT acting through the sympathetic nervous system that heavily innervates this tissue. BAT deficiency in rodents causes obesity and diabetes, while as stimulation of BAT with a specific adrenergic agonist ( $\beta$ 3agonist) protects against diabetes and obesity. BAT also exists in humans (especially neonates) although less in percentage, but its physiologic role is not yet established. Beige fat cells, which resemble BAT cells have been recently described, in expressing UCP-1. They are scattered throughout the white adipose tissue, but their thermogenic potential is still uncertain.

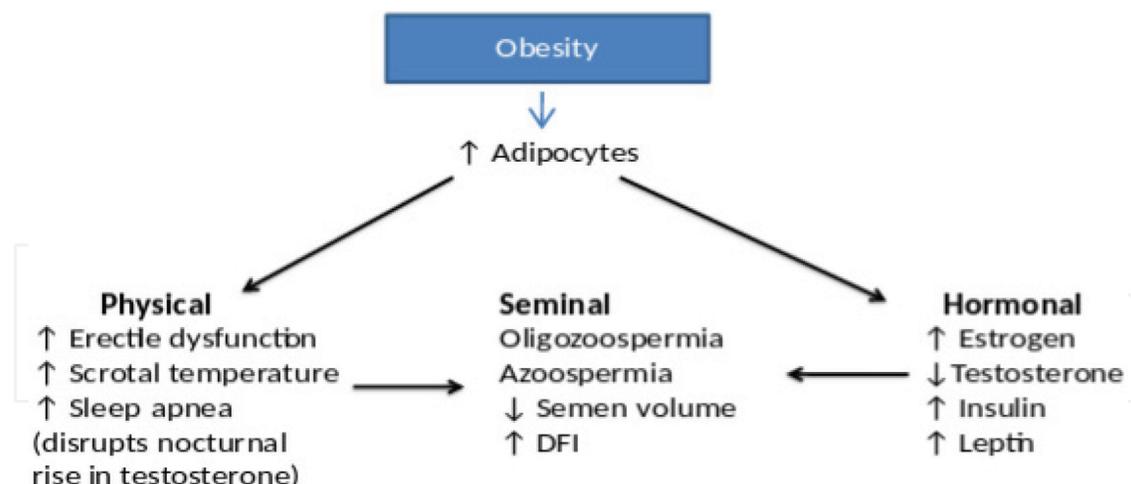
#### 4.4. The adipocyte and adipose tissue

White adipose tissue carries out a much more integral role other than maintaining physiological homeostasis, regulating metabolism and storing energy. It constitutes up to 20% of male bodyweight and the constituent cells contain a single, large fat droplet [12]. It comprises lipid-storing and lymphocytes, making it an important mediator of inflammation and metabolism [13]. Adipose tissue mass increases by enlargement of adipose cells in volume through lipid deposition, as well as by an increase in the number of adipocytes. Apart from this obese adipose tissue is also infiltrated by macrophages. Adipose cells are derived from a mesenchymal preadipocyte which involves a series of differentiation steps mediated by a cascade of specific transcription factors. Peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), a nuclear receptor is one of the key transcription factor that binds the thiazolidinedione class of insulin-sensitizing drugs used in the treatment of type 2 diabetes.

#### 4.5. White adipose tissue as an endocrine organ

It is now well known that adipose tissue is highly active and complex metabolic and endocrine organ [14]. Apart from adipocytes, adipose tissue also contains connective tissue matrix, nerve tissue, stromovascular cells, and immune cells [14]. Adipocytes express and secrete several endocrine hormones such as leptin and adiponectin, although many secreted proteins are derived from the nonadipocyte fraction of adipose tissue [15]. These components function in a well-coordinated integrated unit, making adipose tissue a true endocrine organ. All the proteins secreted by adipose tissue are represented by their respective receptors. Adipose tissue is classified under two broad categories: (1) secreted proteins that have metabolic effects on distant cells or tissues and (2) enzymes involved in the metabolism of steroid hormones.

The discovery of the protein hormone leptin confirmed the endocrine role of white adipose tissue [16]. Apart from leptin, white adipose tissue also secretes a number of adipocyte derived proteins; angiotensinogen, resistin, adipsin, acylation-stimulating protein, adiponectin, retinol-binding protein and tumor necrosis factor, among many others, are also secreted [17]. Therefore, accumulation of excessive fat characteristic of obesity can result in the altered release of adipose derived hormones and proteins (**Figure 1**).



**Figure 1.** Impact of adipocytes on male fertility. Obesity results in increase in size and number of adipocytes, which can result in physical and hormonal changes altering seminal parameters.

#### 4.5.1. Protein Leptin

Protein leptin is mainly synthesized in white adipose tissue and studies document a strong positive correlation between the levels of serum leptin and percentage of fat in body. Leptin is encoded by the *ob* gene, that is secreted by adipocytes is basically a 16 kDa adipokine. Leptin is secreted by adipocytes during the fed state and it causes stimulation of satiety center in the brain. Although leptin is mainly produced by adipose tissue, but a small amount can also be synthesized by the placenta, gastric fundic epithelium, intestine, mammary epithelium, brain, and skeletal muscles [18]. Leptin is a potential satiety stimulus. Apart from this Leptin also has a role in neuro endocrine system regulation, angiogenesis, hematopoiesis, and reproductive functions [19]. Obese individuals have higher serum leptin levels than nonobese individuals [13].

Although leptin plays an important role in energy regulation by controlling food intake and energy expenditure via hypothalamus. Leptin secretion increases with increase in white adipose tissue. Thus, change in leptin concentrations in obese men can alter normal physiological functions. Majority of obese individuals with elevated levels of serum leptin has leptin resistance in which there is no mutations in the leptin receptors. Mutation in *ob* gene can result in leptin deficiency which can also lead to obesity. Leptin is important for normal functioning of reproductive system [20]. The presence of leptin receptors in testicular tissue especially plasma membrane of sperm and leptin in semen has proven a link between this hormone and male reproductive function [18]. Excess concentrations of leptin from adipose tissue in obese men can have deleterious effect either directly on sperm or indirectly via HPG axis. Increased levels of leptin might suppress the testosterone secretion by inhibiting the Leydig cell function. Testosterone therapy has been proven to decrease leptin secretion, but its effects on semen parameters are not reported. By decreasing elevated leptin levels, it might be possible to reverse some of the potential effects of excess leptin on sperm membrane functioning and HPG axis to restore normal spermatogenesis and sperm function. Obesity is associated with increased leptin production subsequently high plasma leptin concentration [21].

#### 4.5.2. Adiponectin

Adiponectin is exclusively produced by mature adipocytes and its serum concentration is about 1000 times the concentration of other polypeptide hormones [22]. In contrast to leptin, adiponectin concentration is higher in women than men. In male obesity, leptin is increased while as adiponectin concentration decrease. Adiponectin increases in response to severe weight loss [22]. A longitudinal study revealed a strong relation between low adiponectin level and development of the metabolic syndrome [23]. Decreased adiponectin has been associated with insulin resistance, dyslipidemia, and atherosclerosis in humans [22]. Injection of recombinant adiponectin peripherally stimulates oxidation of fatty acids which results in decrease of body weight, specifically WAT [24]. Leptin is positively associated with increase in WAT mass while as adiponectin is negatively associated with WAT mass [25].

#### 4.5.3. Resistin secretion and insulin resistance

WAT secretes another adipose tissue-specific factor resistin, which is reported to induce insulin resistance. There is a strong association between obesity and type 2 diabetes. Almost 80% of men with type 2 diabetes men are also obese. Owing to a higher number of adipocytes in obese men, resistin secretion increases leading to type 2 diabetes [26]. Because of insulin resistance in type 2 diabetes males, high levels of insulin are present in the bloodstream leading to hyperinsulinemia. Hyperinsulinemia is known to have an inhibitory effect on normal spermatogenesis and can be linked to decreased male fertility. Insulin levels have also been shown to influence the levels of sex hormone binding globulin (SHBG). SHBG is a glycoprotein that has a strong affinity toward sex hormones, specifically testosterone and estradiol. Impaired levels of SHBG affect the levels of sex hormones. High circulating insulin levels inhibit the secretion of SHBG in the liver. Weight loss has been shown to increase SHBG levels by decreasing the insulin secretion [27]. In obese males, testosterone is converted to estrogen owing to the presence of high levels of enzyme aromatase present in the membranes of adiposites, the decrease in SHBG means that less estrogen will be bound, resulting in more biological active, free estrogen which can have an inhibitory effect on gonadotrophic secretions. This failure to maintain homeostatic levels of gonadotropins and sex hormones might further affect the negative feedback effect of elevated total estrogen levels. Even if the levels of SHBG are unaffected, an independent impact of insulin resistance on testosterone production can still be demonstrated [28]. Therefore, the levels of SHBG can be considered only as a marker of altered hormone profiles in obese infertile men. Both testosterone and SHBG are negatively correlated with insulin levels in the bloodstream, even after adjusting for BMI and WHR values [29]. Such an inverse relationship is due to the ability of high levels of insulin to inhibit hepatic SHBG synthesis in the liver.

## 5. Obesity and infertility

Obesity and nutritional habits are mainly associated with significant disturbance in the plasma hormonal milieu, such as a decrease in total and free testosterone levels, decreased gonadotropin levels, decreased binding capacity of sex hormone-binding globulin, and hyperestrogenemia

[30]. All these alterations might affect the male reproductive system and gamete quality. In support of this idea, some studies have documented a decrease in sperm quality associated with increased BMI [31]. Infertility may be more prevalent among men with elevated BMI's. About 40% of men presenting to one infertility clinic were overweight [32]. However, the relationship between male obesity and other fertility parameters has not been well established. Besides lifestyle changes, the genetics also plays a role in increasing obesity. India and most of Asia-Pacific population have mutation of MC4R genes which essentially puts them into high risk population [33].

It is unclear to what extent obesity affects a man's reproductive potential. There may be a causal link between male obesity and disturbed reproductive hormonal milieu reflecting on semen quality. However, they may also share a common etiological factor.

### 5.1. Proposed mechanisms

The main cause of obesity epidemic is sedentary lifestyle and/or increased caloric intake. More often, these factors occur in conjunction with an unfavorable genotype that predisposes the individual to obesity. Although all these factors might explain the growing numbers of obese adults, there is less evidence explaining how exactly obesity causes male infertility. The mechanisms responsible for effects on male fertility are mostly ambiguous. Although several mechanisms have been proposed, but the most important mechanism is the contribution to the dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis, one of the most important hormonal axis to regulate spermatogenesis.

#### 5.1.1. Aromatase overactivity

As already mentioned above that obesity is associated with an increased number and size of adipocytes, so abnormal levels of adipose derived hormones and adipokines related to reproductive hormones. These abnormal levels of hormones may impact on fertility by many proposed mechanisms. Obesity has been associated with low levels of free and total testosterone in men, and most infertile obese men present with a decreased ratio of testosterone to estrogen. This decrease is explained by over activity of the aromatase cytochrome P450 enzyme, which is present at high levels in the cell membrane of white adipose tissue and is responsible for a key step in the biosynthesis of estrogens by converting testosterone to estrogen. Owing to the high bioavailability of these aromatase enzymes, high levels of estrogens in obese males result from the increased conversion of androgens into estrogens. Dysregulated levels of sex hormones can affect HPG axis which can cause further detrimental changes in both spermatogenesis and other aspects of male reproduction. Since estrogen is biologically more active than testosterone, a small change in the levels of circulating estrogen can, therefore elicit large downstream effects on gonadotropin secretions which can affect spermatogenesis. High levels of circulating estrogen have been shown to have direct deleterious impact on spermatogenesis in animal models. The discovery of estrogen receptors in the male hypothalamus has indicated that estrogen might control the secretion of testosterone levels through a negative feedback mechanism [34]. Estrogen also acts negatively on the hypothalamus to regulate the release of gonadotropin releasing hormone (GnRH) as well as the release of luteinizing hormone (LH) and follicle stimulating

hormone (FSH) from the anterior pituitary gland. Estrogen agonists have been shown to have an inhibitory effect on androgen biosynthesis. This observation indicates that normal levels of estrogens are vital for regulating the HPG axis, suggesting that any amount of excess or deficient levels of estrogen could be detrimental to spermatogenesis.

#### *5.1.2. Environmental toxins and oxidative stress*

Most of the environmental toxins are fat soluble and might disrupt the normal reproductive hormone profile because it has been proved that such toxins are endocrine disruptors and affect male fertility. Their accumulation not only around the scrotum and testes, but also elsewhere in the body can have deleterious effect on spermatogenesis. As morbidly obese males present with excess fat around the scrotal region, the environmental toxins that accumulate in the white adipose tissue might have a direct deleterious effect on spermatogenesis in the testes. Such toxins have been reported to be associated with decreased sperm production and thus decreased male reproductive potential, irrespective of the location of fat in the body [30].

Reactive oxygen species (ROS) is the other toxic compound that can affect sperm quality. ROS are highly reactive and unstable molecules that may result in oxidative stress on sperms and that can induce significant cellular damage throughout the body including sperm cell membrane. It is documented in many studies that obesity and several of its causative agents, namely insulin resistance and dyslipidemia, are associated with increased oxidative stress. Mitochondrial DNA is very sensitive to ROS, which can lead to DNA damage and plasma membrane integrity of sperm.

#### *5.1.3. Erectile dysfunction*

Erectile dysfunction is significantly associated with obesity. Overweight or obese patients attending to infertility centers make up 76% of men who report erectile dysfunction and a decrease in libido [35]. Many studies have reported an association between erectile dysfunction and an increase in BMI. Disturbed hormonal milieu is the basic cause of erectile dysfunction and obesity. Erectile dysfunction is highly common in men with obesity associated with type 2 diabetes. Improved diabetes control and weight loss have been found to improve erectile function.

#### *5.1.4. Elevated scrotal temperature*

Excess fat deposition around the scrotum and in the upper parts of thighs cause increase in scrotal temperature impairing the spermatogenesis. Many reports consider heat as one of the potential cause of sperm impairment affecting the semen quality overall. Frequent fever and varicocele also leads to the generation of excess heat [35]. Even moderate elevation of scrotal temperature above physiological range affects the quality of semen parameters [36].

#### *5.1.5. Sleep apnea*

Obese people are often suffering from sleep apnea which is characterized by disturbed sleep owing to repeated episodes of upper airway obstructions leading to hypoxia. Patients with sleep

apnea have lower mean levels of testosterone and LH owing to disrupted nightly rise in testosterone levels compared to lean patients. So, it is concluded that disturbance in sleep is associated with HPG axis disturbance consequently leading to decrease in testosterone secretion which is further decreased in obesity and ultimately leading to compromised spermatogenesis.

## 6. Obesity and reproductive disorders

In morbidly obese men, plasma testosterone and sex hormone binding globulin (SHBG) are often reduced and plasma estrogen levels are increased due to the overactivity of the aromatase cytochrome P450 enzyme, responsible for the biosynthesis of estrogen, highly expressed in white adipose tissue. Due to high bioavailability of these aromatase enzymes in obese males, androgens are converted to estrogen resulting in high levels of plasma estrogen levels and low levels of testosterone. Although in majority of men libido, potency, spermatogenesis and masculinization may not be affected, but few obese men get affected. Some of them may show signs of gynecomastia. Total testosterone is mainly decreased in morbidly obese men because of decreased SHBG. Most obese men seeking infertility treatment present with a decreased ratio of testosterone to estrogen.

Total body fat, intraabdominal fat and subcutaneous fat have all been associated with low levels of free and total testosterone in men, and most obese men seeking infertility treatment present with a decreased ratio of testosterone to estrogen [28]. Dysregulated levels of sex hormones especially testosterone can cause negative impact on both spermatogenesis and other aspects of male reproduction. Estrogen is biologically more active than testosterone. A small change in the levels of circulating estrogen can, therefore, elicit strong down regulating effects on hypothalamus as well as pituitary, which can lead to decreased secretion of gonadotrophins which can lead to suppression of spermatogenesis.

### 6.1. Male obesity and reproductive hormones

It is understood from various studies that obesity affects the hormonal regulation of spermatogenesis via hypothalamic pituitary gonadal (HPG) axis deregulation. It is also documented that increased male body mass index (BMI) is associated with decreased plasma concentrations of sex hormone binding globulin (SHBG) and SHBG bound testosterone.

The Sertoli cell has very important role in spermatogenesis as it is the only somatic cell responsible for upbringing of sperm from germ cell stage to mature spermatozoa. Testosterone is important for the normal functioning of Sertoli cells, which in turn plays a major role in spermatogenesis. Decreased concentration of testicular testosterone leads to the retention and phagocytosis of developing spermatozoa and reducing sperm counts [37]. Changes in testosterone metabolism through 5-reductase activity have been reported as the major cause in male obesity.

Other hormones like FSH, LH, inhibin B and SHBG involved in the regulation of Sertoli cell function and spermatogenesis, have all been observed to be lower in obese males compared with normal weight males. In obese males total and free testosterone blood concentration

levels progressively decrease with increasing body weight, mostly associated with a progressive decrease of SHBG concentrations. Spermatogenesis and fertility are not necessarily being impaired in obese men as all obese men are not suffering from systemic syndrome. However, these hormones levels have been described as being reduced in subjects with massive obesity [38].

The absence of clinical signs of hypogonadism in obese men can be explained by the fact that the fraction of free testosterone represents only 2% of total testosterone. Obesity predominantly affects circulating bound testosterone, owing to the decrease levels of SHBG production.

Some studies reported reduced levels of principal metabolites, such as androsterone glucuronide, and 5-androstane-3,17-diolglucuronide, particularly in the presence of massive obesity. On calculation, it was noticed that conversion rates from precursors, chiefly testosterone and DHEAS, was found to uniquely depend on decreased precursor levels rather than on altered 5-reductase activity. Although testosterone levels are negatively associated with obesity, it is still unclear whether they correlate with fat distribution in male obesity.

As mentioned above, both SHBG and testosterone are negatively correlated with insulin levels. Such an inverse relationship is due to the inhibitory effect of insulin on hepatic SHBG synthesis. Therefore, reduced levels of testosterone in obese males appear to be caused by several complementary factors, including reduced gonadotropin secretion and the negative effects of insulin on SHBG and testosterone itself.

## 6.2. Male obesity and semen parameters

### 6.2.1. Altered semen parameters

Obesity does not just only alter the physical manifestations and sexual function but can affect spermatogenesis in most of men leading to infertility. Obesity does not affect the fertility of men without systemic syndrome like hyperinsulinemia. There have been several studies trying to entangle the relationship between obesity and infertility and most of the studies show an inverse correlation between the two.

### 6.2.2. Sperm count and concentration

It is well documented in both humans as well as in animal models that obesity has a negative impact on semen parameters (count, motility and morphology). A recent systematic review found a J-shaped curve correlation with male BMI and abnormal sperm count, overweight and obesity was also associated with higher rates of oligozoospermia and azoospermia through evaluation of 21 studies [39]. The previous systematic review conducted in 2010 stated that there is no such effect [40].

### 6.2.3. Sperm morphology

Measuring differences in the morphology of sperm can be difficult due to high individual variability within individual patient samples. However, most studies have shown no correlation

between obesity and abnormal sperm morphology. Some studies have shown that BMI is negatively correlated with sperm morphology [31], while as other studies reported no change [41].

#### *6.2.4. Male obesity and DNA fragmentation*

In recent years DNA integrity has gained importance in evaluating the potential of sperm to generate a healthy pregnancy. Reactive oxygen species (ROS) is known as one of the main contributing factor for sperm DNA impairment. It is also well documented that obese infertile men have higher levels of ROS compared to normal weight men and fertile obese men. Sperm is deficient in antioxidant defense mechanism so highly susceptible to ROS.

Hyperinsulinemia has an inhibitory effect on normal spermatogenesis directly as well as indirectly to affect male fertility. In a study it was presented that, in a group of diabetic men, semen parameters (concentration, motility and morphology) did not differ from the control group, but the percentage of nuclear and mitochondrial DNA damage in the sperm was significantly higher in diabetic group. This high sperm DNA damage can impair male fertility and reproductive health. A study found that increased BMI is accompanied by higher DFI, demonstrating that obesity might be the cause of compromised DNA integrity [42]. Males presenting with a high DFI will have reduced fertility or repeated miscarriages as a consequence.

## **7. Male obesity and hypogonadism**

Alterations in gonadotropin secretion have also been documented in male obesity. Gonadotropin (FSH and LH) levels are usually normal or slightly reduced in mild obese men. Obese men with high BMI values may show a reduction of LH secretion, probably due to impaired secretion of GnRH at hypothalamic level. The absence of clinical signs of hypogonadism can be explained by the fact that the Free testosterone fraction represents only 2% of total testosterone, which could be the reason for absence of hypogonadism signs. Obesity predominantly affects circulating bound testosterone, owing to the concurrent decrease of SHBG production.

### **7.1. Decreased inhibin B**

The most accurate marker for spermatogenesis is inhibin B, and it can be used to predict the fertility of obese individuals. Normal values of inhibin B reflects normal sertoli cell function and associated spermatogenic activity. Decreased inhibin B levels are indicative of subnormal spermatogenesis. Animal studies revealed that inhibin B levels correlate positively with sertoli cell number and function, and indicate that reduced levels of inhibin B in obese men are likely to signify fewer or unhealthy sertoli cells than in men of normal weight. The consensus is that obese men have significantly lower inhibin B values than normal BMI men.

### **7.2. Decreased testosterone: estrogen**

Obese infertile men show typically a decrease in the testosterone: estrogen ratio. It was documented in a study that obese men had 6% higher levels of estradiol and 25–32% lower

levels of testosterone compared to normal weight men [30]. The severity of obesity determines the degree to which levels of estradiol are increased and testosterone decreased. The increased conversion of testosterone into estrogens, a characteristic of obesity, suppresses the function of the pituitary gland by disturbing normal feedback in the testis.

## 8. Discussion

High BMI is not only associated with increased risk of cardiovascular disease [43] and type 2 diabetes [44], but also with other endocrine symptoms including changes in reproductive hormones. Obesity has been implicated to have direct and indirect impacts that could reduce male fertility including decreased sperm motility and increased DNA fragmentation [45].

Weight reduction among men with obstructive sleep apnea secondary to obesity increased testosterone levels. Physical inactivity negatively impacts on erectile function, and exercise interventions have been shown to improve sexual responses. A reduction in caloric intake has also been found to improve erectile function in men with aspects of the metabolic syndrome, including obesity and diabetes.

Hormonal alterations and diminished sexual quality of life have both been reported to improve after gastric bypass surgery [46]. Even though natural weight loss and even gastric bypass has shown promising results in terms of restoring fertility and surgical treatment has been shown to restore reproductive hormones to normal levels, some studies indicate that gastric bypass procedure and the drastic weight loss might induce secondary infertility.

Excess adiposity leads to increased aromatization of androgens in the adipose tissue leading to higher circulating estradiol levels [47]. Hyperinsulinemia, secondary to obesity related insulin resistance, decreases SHBG production in the liver [48]. Low testosterone levels are thought to be the result of decreased SHBG binding capacity [49], direct action of leptin, and other adipocyte derived hormones on Leydig cells [50].

Further, testosterone increases after weight loss in massively obese men [51]. The observed lower testosterone:LH ratio among the most obese men also suggests decreased Leydig cell function among these men and is consistent with a report of impaired LH-stimulated testosterone production among morbidly obese men [18]. The consistency of these findings across studies and the reversibility of this pattern following weight loss suggest a causal role of increased body weight on the hormonal pattern described above.

Weight loss should be considered during the initial work up with the infertile couple and advised before initiating the ART treatment to improve the pregnancy chances. Physiological levels of reactive oxygen species (ROS) are necessary to maintain normal sperm function but if reactive oxygen levels increase they lead to deteriorating function or reduced survival [52]. Oxidative stress has long been implicated as the major etiological factor in sperm DNA damage. In contrast to somatic cells, sperm are very vulnerable to oxidative stress [53] due to their unique membrane structures combined with limited antioxidants or protective enzymes [54].

Additionally, it has been claimed that rather than the overweight per se, the metabolic syndrome (MetS) could be the underlying mechanism of a high DFI in obese men. MetS and several of its components like abdominal obesity, insulin resistance and dyslipidemia, are associated with a systemic proinflammatory state and increased oxidative stress. Thus, among overweight subfertile men, those having both subnormal testosterone levels and associated low grade systemic inflammation [55], due to their overweight, MetS or both, might be over represented. Consequently, this could lead to increased DFI in this subgroup.

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