Chapter 26
The Role of Obesity in ROS Generation and Male Infertility

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Abstract
Aim: To discuss the relationship between obesity and male infertility, specifically exploring the role of reactive oxygen species (ROS) production in obesity and the subsequent generation of oxidative stress, as well as abnormal hypothalamus-pituitary-gonadal regulation associated with obese males.


Results: Both enhanced ROS generation and abnormal hormonal regulation due to obesity are strongly correlated to suboptimal semen quality and, thus, reduced male reproductive potential.

Conclusion: The continuing rise and prevalence of both obesity and declining male sperm count all over the world call for additional research and a greater awareness to obesity as a potential etiology of male infertility.

Keywords Male infertility • Obesity • Reactive oxygen species • Oxidative stress • Hormones
26.1 Introduction

With the onset of sedentary lifestyles, high-fat diets, and a general decline in physical activity, much evidence suggests that obesity is becoming a global pandemic \[1, 2\]. Obesity is reaching unprecedented levels in the Western world. One study revealed a prevalence of obesity in the USA of 19.8% \[3\], while another indicated a staggering 30% \[4\]. Reports have already shown that the world’s overweight population has grown greater than its underweight population \[4\]. The World Health Organization (WHO) predicts that by 2015 approximately 2.3 billion adults will be overweight and that an additional 700 million will suffer from obesity \[5\].

Simultaneous to this alarming trend, there has been an apparent progressive increase in infertility rates over the past few decades. It has been indicated that 15% of all couples of reproductive age are infertile \[6, 7\], and up to 50% of all cases are believed to be due to the male factor alone \[8\]. Although still highly debated, the increased prevalence of overweight and obesity may account for the declining sperm counts over recent decades. According to a study conducted in 2000 by Swan et al., male sperm counts have been dropping by as much as 1.5% annually in the USA, as well as in other Western countries \[9, 10\]. Since these declines were not present in regions where obesity was less prevalent \[9\], this may further suggest a potential link between altered lifestyles, obesity, adverse health outcomes and, now, semen quality and male infertility \[11\].

As obesity trends continue to increase and expectation levels show no signs of decline, the interaction between obesity and fertility has received astonishing attention \[3, 4\]. Nevertheless, obesity and its effect on sperm count has just recently been documented \[11, 12\]. Studies have shown a negative correlation between obesity and various sperm parameters in the general population \[11, 12\]. Some have suggested a relationship between body mass index (BMI) and male infertility \[13, 14\]. Evidently, there has been a higher probability of abnormal spermatozoa and infertility found in obese men \[1\].

Furthermore, obesity has been shown to be associated with significant disturbances in the hormonal milieu, which can adversely affect the reproductive system \[15, 16\]. These reports have illustrated that fat tissue accumulation in men causes subsequent lowered serum levels of total and free testosterone while simultaneously elevating estrogen serum levels \[15, 16\]. A study demonstrated that such fat accumulation resulted in oxidative stress (OS) from a dysregulation of adipokine and reactive oxygen species (ROS) production \[17\]. Interestingly, data has been in agreement with recent studies suggesting that systemic OS correlates with BMI \[18, 19\]. The relationship of increasing levels of obesity and male-factor infertility calls for greater clinical awareness, as much evidence suggests that obesity may play a significant role with the rising subfertility rates.

The aim of this review is to discuss the relationships between obesity and male infertility. Moreover, it specifically explores the role of ROS production in obesity and its subsequent generation of OS, thereby directly and indirectly linking the effects of obesity on male reproductive potential.
26.2 Obesity

Obesity is a medical condition related to an excess accumulation of white adipose tissue in the body, which has the potential to inflict adverse health effects. The principal cause for this state is an energy imbalance between the body’s energy intake and expenditure (Fig. 26.1). Excess energy is stored predominantly in the form of triglycerides and deposited in adipose tissue. Triglycerides play a vital role in metabolism serving as energy sources and for systemic transporters of dietary fat. Consequently, this fat accumulation and response to adipocyte hypertrophy has been suggested to compromise adipose tissue function and incite structural alterations to other organs [20]. The excessive fat accumulation in adipose tissue, liver, and other organs predisposes the onset of metabolic abnormalities that are often accompanied with hypertension, impaired glucose tolerance, insulin resistance leading to hyperinsulinemia, and dyslipidemia. Thus, obesity has been considered a chronic disease linked to a widespread range of physical, genetic and hormonal disorders.

Traditionally, obesity has been defined as a body weight of at least 20% above the weight corresponding to the lowest death rate for individuals of a specific height, gender and age, as well as additional specific requirements [21]. However, its present characterization has been more broadly classified as abnormal or excessive fat accumulation [10].

Several means of measuring obesity are currently utilized. The most accurate yet impractical measurements are to assess the weight of an individual underwater or to use an X-ray test called dual energy X-ray absorptiometry. Additional modes of evaluation include skinfold and waste to hip ratio (WHR) measurements, bioelectrical impedance analysis, and the risk factors associated with comorbidities. Two of the more common and simpler methods include the measurement of BMI and waist circumference.

BMI is a simple weight to height ratio that is defined as an individual’s weight (kg) divided by the square of their height (m²). There has been much controversy over the BMI ranges and cutoff points to deem an individual obese. The WHO has considered the normal range to lie between 18.5 and 24.9 kg/m², the risk of comorbidity to increase between 25 and 29.9 kg/m², and the onset of obesity to occur over 30 kg/m² [22]. In order to achieve optimum health, the median BMI for the adult population has been found to be in the range of 21–23 kg/m², while individuals should maintain a BMI in the range of 18.5–24.9 kg/m² [22]. These BMI values are age-independent and the same for both sexes [22]. Nevertheless, this may not represent the same degree of obesity in different populations due in part to different body proportions. A shortcoming of BMI as a measurement tool has been its overestimate in mesomorphic individuals. Hence, since calculations tend to diverge from accurate values, BMI values allow only for an estimate, at best.

The quantification of waist circumference has been believed to be more accurate and convenient marker of obesity. This measurement that is unrelated to height makes an approximate index of intra-abdominal fat mass and total body fat.
It has actually shown much of a correlation to BMI and risk factors of chronic diseases. A waist circumference ≥102 cm in males and ≥88 cm in females have been indicative of metabolic complications [22].

26.3 Obesity and Male Infertility

BMI has been found to be associated with altered sperm parameters in numerous reports. In a recent study investigating factors related to semen quality, the prevalence of infertility in obese men was found to be three times greater than in male partners of couples with idiopathic or female-factor infertility [12]. Moreover, sperm density and total count was shown to have a statistically significant negative correlation to increasing BMI [12]. Another study looked at normozoospermic partners in an infertile population and reported a reduction in sperm concentration among men with BMI greater than 30 kg/m² when compared to leaner members of the study group [23]. Kort et al. further examined the relationship between sperm parameters and BMI in a generally overweight selection of subjects [24]. After 520 semen samples were subjected to analysis, semen quality and the number of normal sperm per ejaculate exhibited declines with increasing BMI [24]. On the other hand, when obesity was expressed as a measurement of WHR, the similar trend between obesity and impaired sperm parameters was not seen [25]. This further illustrates...
the inconsistency in obesity measurement techniques. Since an overwhelming evidence indicates that altered spermatogenesis and abnormal sperm parameters—reduced total sperm count and concentration—are correlated to the findings in obese males and that subfertility and infertility of couples are certainly related to such conditions [26], it may be postulated that obesity may induce semen abnormalities via the generation of ROS, dysregulation of the hypothalamus-pituitary-gonadal (HPG) axis, and/or physical manifestations (Fig. 26.2).

### 26.3.1 Reactive Oxygen Species

OS results from an impairment of a biological system’s ability to reduce the formation of highly reactive species, repair detrimental damage, or reach a balance between ROS and antioxidants. Much research has focused on the etiology of OS, its link to male infertility, and its pathophysiological effects on male reproduction. Disturbances in reductases and functional redox state conditions disrupt cellular homeostasis. Numerous studies demonstrate a multitude of adverse effects induced by its causative factor—ROS. Environmental toxicants have been verified to impair a cell’s reductive environment by decreasing its reduction potential, leading to subsequent reverse catalysis by oxioreductases, and possibly damaging cell membrane proteins, lipids and DNA [27]. Even moderate levels of OS may trigger molecules to initiate a cascade of reactions, thereby inducing programmed cell death (apoptosis) [28].

There are two general forms of free radical species: ROS and reactive nitrogen species (RNS). ROS are the more common free radicals with oxygen centers,
whereas RNS are often considered to be a subclass thereof. Free radicals generated during oxygen reduction reactions of natural aerobic metabolic pathways typically form ROS. The three major forms of ROS are the superoxide anion ($O_2^{-•}$), hydrogen peroxide ($H_2O_2$), and the extremely reactive hydroxyl radical ($OH^{-•}$). These highly reactive pro-oxidant species can interact with antioxidants in order to maintain homeostasis. In the case of any imbalance between pro-oxidants and antioxidants, OS commences.

Of the inspired oxygen, 98% is reduced during lipolysis and ATP production, while the other 2% is incompletely reduced [29]. However, since many ROS are byproducts of aerobic cellular metabolism during oxidative phosphorylation in the mitochondria, any impairment due to OS may result in ATP depletion and potentially initiate cellular degradation [27]. Moreover, the mitochondria of spermatozoa have been found to be the primary source of ROS in infertile men [30]. The majority of ROS generated occurs at complexes I (NADH-Q dehydrogenase) and IV (conversion of ubiquinol to ubisemiquinone to ubiquinone) of the electron transport chain [31]. Since molecular oxygen is the final electron acceptor at complex IV in the formation of water, an extra electron may be captured during ATP generation becoming a major source of ROS - namely, superoxide anion [32]. This free radical can further propagate a series of reactions impairing cellular function and ultimately semen quality.

Many studies have pointed to ROS as independent biomarkers of semen quality due to their potential to cause suboptimal reproductive function [27, 33]. As highly reactive free radical oxygen molecules seek stability by attacking their neighboring stable species to obtain an electron, the targeted molecule itself becomes an unstable free radical, thereby generating a cascade of reactions. Consequently, structural and functional cellular damage may arise, both of which have been linked to irregular sperm function and motility via mitochondrial genome impairment [34, 35]. Extensive research supports the free radical-induced pathological effects on DNA damage, lipid peroxidation (LPO), and apoptosis in spermatozoa [28, 36].

Nevertheless, low levels of ROS are necessary in maintaining cellular homeostasis with their counteracting scavenging species, antioxidants, as well as in processes of the immune system, redox signaling and sperm maturation [33]. However, only a few studies have specifically discussed the physiological roles of free radicals in sperm function. The most well-documented ones have revealed their importance in controlling sperm maturation processes, capacitation, hyperactivation, acrosome reaction, and sperm–oocyte fusion; others have expressed ROS to be essential signal-transduction biomolecules and components of the complex cascade pathways in spermatozoa [36].

### 26.3.1.1 Sources of ROS

There are several sources of ROS, both endogenous and exogenous, found in the seminal plasma that can exert their effects on spermatozoa. Numerous studies report leukocytes and spermatozoa as the two main sources of free radicals found in semen [27, 34].
Leukocytes are the predominant source of endogenous ROS during sperm maturation, as well as one of the main mechanistic agents in combating pathogens \[37, 38\]. Moreover, leukocyte production is enhanced in obesity and participates in inflammatory pathways that are activated in adipose tissue of obese individuals \[39\]. Plante et al. demonstrated a positive correlation between levels of ROS and the degree of leukocyte contamination \[30\]. In times of infection or disease, peroxidase-positive leukocytes generate high levels of ROS through the nicotinamide adenine dinucleotide phosphate (NADPH) pathway \[40, 41\]. Subsequently, this elevated production of ROS during times of defense has been shown to have adverse effects on sperm function \[42\]. Furthermore, reports reveal signs of decreased motility and fertilization capacity from a lack of antioxidant-defense mechanisms in the testis and epididymis, rendering sperm extremely susceptible to infection \[43–45\].

Spermatozoa are an additional source of free radicals located in the semen. Normally, the cytoplasm is extruded during spermatogenesis. However, if spermatogenesis is impaired by any means, proper cytoplasm extrusion may not occur, and sperm are left arrested in an immature and functionally defective state. This defect ultimately results in increased ROS production through activation of the NADPH system, providing electrons for free radicals to initiate a series of events, eventually activating NADPH oxidase. Hence, there are two primary mechanisms by which spermatozoa may generate ROS: either (1) at the plasma membrane level through NADPH oxidase or (2) at the mitochondrial level through a NADH-dependent oxidoreductase system.

Exogenous sources of ROS also have a major influence on sperm quality and function through the production of ROS in pathological amounts. A few of these sources include industrial compounds, smoking, alcohol, spinal cord injury, and varicocele \[36\]. A majority of ROS comes from fat-soluble environmental toxins, allowing for a large accrual in white adipose tissue of obese males. Much evidence indicates that environmental pollutants increase ROS in the testes \[34\]. Accumulations of these highly reactive, unstable molecules cause the propagation of free radical reactions that have been proven disruptive to male reproductive function.

Furthermore, as lipophilic-toxin contaminants intensify in the scrotum of obese males, they may in turn cause direct effects on spermatogenesis and may be potentially linked to infertility. One such toxin, phthalate, a compound found in plastics and beauty products, was reported to induce sperm DNA damage and impair spermatogenesis \[46, 47\]. Studies also revealed elevated OS levels in male testes due to heavy metals (e.g. lead), pesticides, and sulfur dioxide (a common food preservative) \[48–50\]. Free radical generation and decreased antioxidant capacity have shown links to nicotine, a component of cigarettes, as well as cigarette smoke \[51, 52\]. Furthermore, evidence suggests that cigarette smoke, an environmental toxin, decreases sperm parameters—motility, morphology and concentration—all of which adversely affect male reproductive potential \[52, 53\]. A large amount of alcohol (ethanol) consumption plus a poor nutritional diet—often found in obese individuals—contribute to symptoms of elevated ROS with a simultaneous decrease in antioxidants \[54\]. The production of such reactive species further implies an additional pathway to stimulate substantial cellular damage to proteins, lipids and
DNA. Interestingly, it has been reported that over 90% of men with spinal cord injury are infertile due to possible elevated ROS levels resulting in poor semen motility and morphology [55, 56]. Other attributing factors include impairments in erectile and ejaculatory function. However, the more immotile sperm does not seem to be caused by lifestyle factors, such as elevated scrotal temperature, ejaculation frequency, and method of bladder management, and thus, may rather be related to factors within the seminal plasma [57]. Additionally, it has been reported that varicocele is a contributing factor of elevated levels of ROS [58]. Varicocele is a medical condition characterized by abnormal dilation and venous tortuosity in the pampiniform plexus around the male spermatic cord. Greater concentrations of nitric oxide (NO), a RNS, have been found in infertile men with varicocele [59]. Moreover, augmented xanthine oxidase activity, a source of superoxide, was observed [60]. This enhanced enzymatic activity and NO production appears to increase ROS, subsequently impairing sperm function [60]. Higher grades of varicocele in men have shown elevated levels of ROS in their semen, serving as biomarkers of OS from ROS-induced LPO and DNA damage, both of which decrease semen function and contribute to male infertility [61, 62].

However, the prevalence of varicocele does not appear to be proportional to BMI. In a clinical study, Handel et al. suggested this might be due to the increased adipose tissue in obese males preventing compression of the left renal vein or, simply, a decreased detection from the accumulation of adipose tissue in the spermatic cord [63]. Although studies have demonstrated that varicocele triggers ROS production, thereby affecting male reproductive potential, evidence remains limited to confirm a clear-cut relationship between obesity and varicocele.

Leukocytospermia is a medical condition associated with an elevated white blood cell count in semen and is often observed in obese men. It is usually seen in the process of warding off infection during the inflammatory response. Studies have linked sperm quality, sperm dysfunction and leukocytospermia to obesity; albeit, the evidence remains controversial [64–66]. Some have reported leukocytospermia to have an overall adverse effect on sperm function and quality, correlating to a decrease in sperm count, motility, morphology, hyperactivation and defective fertilization, while others show no effects [64–66]. Nevertheless, leukocytospermia can be regarded as a biological marker of systemic inflammation and potential sperm dysfunction.

### 26.3.1.2 Obesity and Oxidative Stress

An increase of ROS is triggered via high metabolic rates in order to maintain homeostasis in obese men. In localized areas near the testes, it can disturb spermatogenesis and result in a possible failure to discard the residual body into the Sertoli cell. Since testicular spermatozoa with proximal cytoplasmic retention lack adequate cytoplasmic reductive enzymes to control free radicals, a decline in antioxidant scavenging species would allow for a higher susceptibility to ROS impairment. The resulting imbalance of oxidant/antioxidant species (OS) is linked to suboptimal sperm function.
From the aforementioned evidence, it seems undoubtedly obvious to suggest that ROS-induced OS has a tremendous impact on male fertility, as well as on the detrimental obesity-implicated consequences. Since the absolute resting metabolic rates of obese individuals are higher than that of non-obese individuals (these differences disappear when resting metabolic rate is adjusted for differences in body composition), it is plausible to suggest that an increased level of stress in the testicular environment may be due to an accumulation of white adipose tissue. This collection of lipocytes would lead to an augmented ROS production and increase the temperature in the testes environment. A study by Hjollund et al. deduced that a reduction in sperm concentration was associated with moderately elevated physiological temperatures of the scrotal skin [67]. Both ROS generation and increase temperature in the testes may denature enzymes involved in spermatogenesis, providing further evidence for a link between obesity and male infertility.

### 26.3.2 Abnormal HPG Regulation

Although several mechanisms that parallel obesity to infertility have been proposed, many remain ambiguous and relatively undefined. Studies indicate that the central factor linking the mechanisms associated with obesity and infertility is an abnormal regulation of the HPG axis, as well as the previously discussed OS. The HPG axis responds to fluctuations in hormones causing a range of widespread and local effects on the body and aspects of reproduction. Excess fat accumulation can impair the feedback regulation of the HPG axis and be a contributing factor to abnormal semen quality. Since sex steroids and glucocorticoids control the interaction between the hypothalamic-pituitary-adrenal (HPA) and the HPG axes, any imbalance may in turn affect spermatogenesis and male reproductive function. The abnormal endocrine changes observed in obese, infertile men are not similar to men with either obesity or infertility alone. Therefore, simultaneous irregular hormonal profile and adipose-derived hormone levels, such as with aromatase, leptin, resistin, inhibin B, cytokines, as well as many genetic factors and physical manifestations may further explain the connection between the escalating frequency of global obesity and subfertility.

#### 26.3.2.1 Aromatase

White adipose tissue exhibits elevated aromatase activity and secretion of adipose-derived hormones in abdominal and visceral fat. Aromatase is an important cytochrome P450 enzyme involved in sexual development and is vital in the biosynthesis of estrogens from its precursor androgens, such as testosterone and dehydroepiandrosterone. Ironically, obese men show signs of elevated estrogen levels as well as low levels of testosterone and follicle-stimulating hormone (FSH) [10]. Depleted levels of free and total testosterone are interrelated to aromatase overactivity in both intra-abdominal and subcutaneous fat. This condition of hypotestosteronemia—low
levels of testosterone—and deregulated levels of sex hormones are related to a reduction in spermatogenesis and subsequent lowered sperm concentrations [68]. Therefore, both may potentially hinder additional aspects of male reproductive function causing suboptimal fertility in obese males.

In an in vitro study involving male mice, it was demonstrated that estrogen is required for fertility and that a mutation in the estrogen receptor gene leads to reduced mating frequency, lowered sperm numbers, and defective sperm function [69]. Nevertheless, since estrogen is more biologically active than testosterone, overproduction of estrogen from elevated expression levels of aromatase activity in obese men may elicit significant abnormal downstream effects in the testes. A report notes signs of both overexpressed levels and the absence of estrogen to elicit adverse effects on spermatogenesis, simultaneously affecting normal male reproductive potential [70].

The endocrine system, which is responsible for the regulation of metabolic activities, growth and development, as well as guiding reproduction, has estrogen receptors in the male hypothalamus involved in a negative feedback mechanism with gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and FSH from the anterior pituitary gland. As estrogen agonist levels are elevated, an inhibitory effect on androgen biosynthesis is observed, pointing to a regulatory role of the HPG axis to cause detrimental effects on spermatogenesis and, in turn, further increasing the likelihood of subfertility in obese men.

26.3.2.2  Leptin

Leptin is an adipose-derived peptide hormone secreted from white adipocytes vital in the regulation of energy intake and expenditure. Human leptin is a protein made up of 167 amino acids. The level of secreted and circulating leptin is directly proportional to the total amount of body fat. It acts on hypothalamic neurons responsible for the secretion of GnRH. This tropic hormone stimulates the synthesis and secretion of gonadotropins, FSH and LH from the anterior pituitary.

Normally, elevated leptin levels are associated with an increase in weight gain and respond through a feedback mechanism in the hypothalamus to reduce food intake and to increase both energy expenditure and sympathetic activity. On the other hand, leptin deficiency from mutations in the Ob(Lep) gene located on chromosome 7 has also indicated relations to obesity [1]. A majority of obese males presented elevated serum concentrations of leptin with no mutation in their leptin receptors. This indicates that the development of an insensitivity and resistance to the action of endogenous leptin is one of the fundamental mechanisms of obesity [71].

In addition, the aromatase overactivity expressed in obese men that causes a higher conversion of testosterone to estrogen will induce a negative feedback signal on the hypothalamus and anterior pituitary to inhibit GnRH, FSH and LH secretion. The combination of effects from both the insensitivity to endogenous leptin and stimulation of the negative feedback pathway may have profound effects on male reproductive function via abnormal hormonal regulation. Furthermore, an excess
secretion of leptin from adipose tissue in obese males illustrated deleterious effects on both spermatogenesis and the production of androgens from inhibitory receptors mediated by Leydig cells [72]. It has been speculated that the presence of leptin plasma membrane receptors in testicular tissue and semen samples may be the link between leptin and male reproductive function [73]. The findings reinforce a direct effect on sperm quality via abnormal HPG regulation and further suggest a plausible link between obesity and male infertility.

### 26.3.2.3 Resistin

Resistin is an endocrine secreted adipose-tissue specific factor. It is a cysteine-rich protein that serves in endocrine function and regulation. Resistin causes tissues, particularly the liver, to become insulin resistant. As a result, blood glucose levels rise from increased glycogenolysis and gluconeogenesis processes in the liver.

Glycogenolysis, glycolysis and the tricarboxylic acid cycle act to conserve energy as ATP from the catabolism of carbohydrates. If ATP supplies are sufficient, these pathways and cycles are allosterically inhibited. Although under conditions of excess ATP production, the liver will attempt to convert the excess mixture of molecules into glucose and/or glycogen. In general, during glycogenolysis, glycogen stored in the liver and muscle cells is converted to glucose-6-phosphate—the first byproduct of the glycolytic pathway.

In gluconeogenesis, glucose molecules are synthesized from non-carbohydrate sources, such as lactic acid, amino acids and glycerol. This process is constantly occurring in the liver in order to maintain glucose homeostasis. Gluconeogenesis proceeds in times of low acetyl CoA concentrations and high levels of ATP production.

Although both glycogenolysis and gluconeogenesis processes require ATP to take place, there is very little, if any, deficiency in ATP production reported that will hamper the motility of sperm. Although sperm motility is critical at the time of fertilization, as it allows the passage of sperm through the zona pellucida, a lack of ATP production from resistin and its subsequent impact on sperm motility cannot yet be confirmed as credible rationale for the increased incidence rate of male infertility.

Since resistin causes an increase in blood glucose levels from insensitivity to insulin, it is a primary factor associated with Non-Insulin-Dependent Diabetes Mellitus (NIDDM), or Type II diabetes. Over 80% of people with Type II diabetes suffer from obesity. Consequently, this resistance to insulin causes an increase in circulating insulin in the bloodstream—hyperinsulinemia—leading to an inhibitory effect on spermatogenesis and impacting male fertility potential. Interestingly, although diabetic men share normal semen parameters (concentration, morphology, and motility), the amount of impairment to nuclear and mitochondrial DNA was notably higher, again pointing to a reduction in reproductive capabilities and health.

Although resistin shows a strong association in humans with high levels of glucose, obesity and Type II diabetes, it is actually a major product of macrophages.
Macrophages are a type of white blood cells that ingest foreign material by means of phagocytosis. When the number of macrophages that reside in adipose tissue increases, this may result in elevated levels of ROS. Many studies have associated insulin resistance with elevated OS levels, inferring naturally produced ROS in obese males to maintain normal biological processes as a potential reason [74].

26.3.2.4 Inhibin B

Inhibin is a glycoprotein, growth-factor like hormone of gonadal origin. It is a dimer consisting of two covalently linked alpha and beta subunits. The beta subunit of inhibin exists in two forms, A and B. Although many studies have been conducted on inhibin, both in vivo and in vitro, they have failed to demonstrate and verify a systemic relationship between serum inhibin levels and spermatogenesis [75, 76].

The site of inhibin B production has been under much scrutiny as some studies indicate that germ cells and possibly Leydig cells can produce inhibin [77, 78]. However, the predominantly believed source of inhibin B originates from Sertoli cells, which play a supportive role in germ cell survival, in the testis into the seminal plasma [79, 80]. This hormone is involved in the HPG axis and displays a proportional decrease in obese males. The consequent decrease in germ cells demonstrates a decrease in sperm count and a reduced likelihood to fertilize.

The mechanistic pathway inhibin B follows to exert its biological effects remains unknown and is a subject of future study [81]. Normally, it acts to inhibit both FSH production and stimulation of testosterone release by Leydig cells. However, many studies have revealed that the expected compensatory increase in FSH levels in response to low levels of inhibin B were not observed in obese men. These low levels of inhibin B observed may have resulted from the suppressive effects of elevated estrogen levels from overly expressed aromatase in obese men.

Since inhibin B levels are directly related to sperm formation, low levels observed in obese males will result in abnormal spermatogenesis. As previously mentioned, the increased estrogen levels contribute to a negative feedback effect on the hypothalamus decreasing gonadoliberin and gonadotropin release, and subsequent lowered testosterone levels. As levels of testosterone fall, sperm function and quality become impaired, resulting in a reduction in male reproductive potential. Nevertheless, inhibin B seems to be an accurate biomarker of testicular damage and could become essential for future diagnosis of spermatogenic disorders in populations exposed to testicular toxicants.

Aside from both ROS and abnormal-induced HPG axis regulation, there continues to be a variety of other factors that have demonstrated evidence of recognized effects of obesity on male infertility. However, there still remain numerous cases of obese men with reproductive function and potential to fertilize. This present unexplained link in some instances may be credited to unfavorable inherited genotypes. Although it has been well documented that obese-infertile men show significantly lower testosterone levels than obese-fertile men, genetic mutations may exist to clarify this discrepancy [10].
26.3.2.5 Cytokines

As excess fat storage accumulates in tissues other than adipose tissue, such as in the liver or striated tissue of the skeletal muscle, local insulin resistance may ensue and cause inflammation. Inflammation is the response to tissue injury and is often characterized by an increase in blood flow to the tissue, consequently increasing temperature in the localized area, as well as redness, swelling and pain.

Changes in morphology and composition of adipose tissue from obesity can cause alterations in protein production and secretion. Many of the secreted proteins may be proinflammatory mediators produced by macrophages residing in the adipose tissue. Proinflammatory cytokines originating from adipose tissue display elevated signs of insulin resistance during inflammatory response. Cytokines have demonstrated to directly interfere with insulin signaling pathways by tumor necrosis factor-alpha (TNF-α), inhibiting tyrosine phosphorylation of insulin receptor substrate-1 \[82\]. Recent studies initiated and conducted by Hotamisligil have illustrated a positive correlation between an increase in adipose tissue accumulation and proinflammatory gene TNF-α expression \[82\]. It is indicated that the involvement of TNF-α and interleukin-6 cytokines results in a reduction in sperm motility during systemic inflammation response \[83\]. This decrease in motility may further result in the inability of the spermatozoa to progressively travel to the oocyte, thereby diminishing the likelihood of fertility.

Furthermore, an excess of white adipose tissue has shown to increase the secretion of adipocytokines, causing enhanced inflammation and a toxic effect on spermatozoa through the release of ROS \[84\]. This subsequent ROS release during periods of inflammation and its impact on sperm quality and function may be a causative aspect to male infertility. Therefore, it is reasonable to believe that excess fat buildup in obese men causing insulin resistance from elevated resistin levels, inflammation response, higher metabolic rates, release of ROS, and elevated temperatures may all be contributing factors to the previously noted nuclear and mitochondrial DNA damaged and, ultimately, decreased reproductive potential in Type II diabetic males.

26.3.3 Physical Manifestations

Obese males also encounter physical mechanisms that may enhance and, thus, further attribute to decreased fecundity and fertility. These problems include hypogonadotropic hypogonadism (HH), erectile dysfunction (ED) and sleeping disorders, such as sleep apnea.

26.3.3.1 Hypogonadotropic Hypogonadism

HH is a form of secondary hypogonadism in which a problem with the pituitary or hypothalamus gland causes the absence or a decreased function of the male testes.
This condition is elicited from a lack of gonadal stimulating hormones, including FSH and LH, which are essential in proper sexual function. Any disruption in the chain of events, from the hypothalamus in the brain secreting GnRH that stimulates the pituitary gland to release FSH and LH will cause a deficiency of sex hormones and prevent normal sexual maturation.

Many researchers have studied the relationship between obesity and HH, and their effects on male reproductive function. Strain et al. noted with significance that obese men had less than two-thirds the normal mean plasma levels of free testosterone, total testosterone and FSH; yet, 24-h LH levels appeared normal [85]. These findings represented a state of mild HH and appear to be characteristic of obese men [85]. It is speculated that the abnormality results from partial suppression of the pituitary by the elevated plasma estrogen levels [85, 86]. In addition, it has been noted that the subnormal levels of free and total testosterone and FSH are proportional to the degree of obesity [86].

Treatment with aromatase inhibitors or suppression of adrenocortical secretion of aromatase to stabilize estrogen levels in obese men has shown potential to normalize HH [86]. Additionally, the simple loss of weight has been shown to also normalize HH without any decrease in plasma estrogen levels [86]. It is suggested that weight loss in obese men results in diminished sensitivity of the GnRH-gonadotropin secretory mechanism to suppression by a given concentration of estrogen [86].

26.3.3.2 Erectile Dysfunction

ED is a medical condition in which a male is incapable to get or keep an erection firm enough for sexual intercourse. Although obesity itself does not seem to be the underlying factor, it still does impose a risk to vasculogenic impotence through the development of chronic vascular disease [87]. A recent study by Corona et al. revealed that after adjustment for comorbidities, obese males with ED presented low androgen levels [88]. Moreover, lowered androgen levels have been associated with reduced plasma testosterone levels [89]. A decrease in testosterone levels in obese males with ED may further contribute to suboptimal semen quality, as testosterone is essential for the onset of sexual characteristics and the production and maturation of sperm in males.

Despite the well-documented studies that indicate the association of ED to lowered fertility rates and being more prevalent in obese men, evidence and information of the pathophysiological link between obesity and ED remains limited. It has been hypothesized that visceral obesity increases proinflammatory factors and, in doing so, promotes an inflammatory response and contributes to ED [90]. Since an erection depends on hemodynamics and vascular health, any factor that causes endothelial dysfunction or impairs endothelial NO release and the integrity of the vascular bed will contribute to ED. Nevertheless, a report illustrated that changes only in one’s lifestyle improved sexual function in nearly one-third of obese men with ED [91].
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26.3.3.3 Sleep Apnea

Sleep apnea is a common disorder in which an individual has one or more pauses in breathing or shallow breaths while sleeping. The chronic condition affects 4% of middle-aged men, but usually goes undiagnosed. Interestingly, it has been reported that about two-thirds of middle-aged men with obstructive sleep apnea suffer from obesity, particularly central obesity [92].

Patients suffering from sleep apnea often have a fragmented sleep course due to repetitive episodes of upper airway obstructions and hypoxia followed by arousal [93]. Furthermore, these patients demonstrate a blunted nocturnal rise of testosterone needed for normal spermatogenesis [94]. This obstructive condition has been linked to lowered mean testosterone and LH values compared to both young and middle-aged controls [94], as well as reduced morning testosterone levels [95]. Weight loss in patients with obstructive sleep apnea has shown to increase testosterone levels [96]. Therefore, sleep apnea is associated with decreased pituitary-gonadal function and, thus, may contribute to hypogonadism and further explain male-factor infertility and abnormal seminal parameters [95].

26.4 Discussion

With the advances in technology that revolutionize everyday lifestyles and industrialization all around the world, obesity has become a modern-day global pandemic. Moreover, as obesity is predicted to reach record numbers in the near future and fertility rates continue to plummet, scientists have began to link the two together. They have revealed that as much as half of all fertility problems come from male-factor defects.

Many researchers have pointed to the increased adipocyte accumulation to generate ROS that propagate systemic and detrimental effects on male reproductive health, while others have attributed the abnormal hormonal profile as the central factor. It appears to be a complex composition of both and, in fact, the increase in adipose-derived hormones and adipokine levels may better explain the association of BMI, altered sperm parameters, and infertility. Recent studies have began to examine genetic biomarkers, an excess of adipose-derived hormones, adipokine release as well as OS. It is suggested that the consistent decrease in hormonal levels and specific proteomic sperm mutations observed in obese males may adversely impact spermatogenesis. Hence, these markers would in turn hinder normal sperm production, maturation and quality, accounting for some of the male-factor defects related to obesity.

The inconsistency in the results from studies demonstrates the necessity for further investigation when examining the effects of obesity on semen parameters. The numerous signs of decreased testosterone levels from excess fat accumulation pose attention for additional focus and study in understanding the overall mechanistic pathway in order to make a definitive link to male infertility.
Simple lifestyle changes have shown to benefit hormonal levels, yet effective treatments, proper lifestyle changes, and surgical options should be further explored. Since antioxidants have been shown to reduce ROS levels, thereby minimizing damage via OS, and have become a hot topic in possibly treating infertility, this natural remedy should be further explored as a potential treatment for obesity-related male infertility. Additionally, standard and accurate measurements to qualify an individual as obese should be established to confirm the links made to infertility and the health problems that accompany the condition. Nevertheless, the continuing rise and prevalence of both obesity and declining semen quality all over the world, both of which are associated to ROS, call for additional research and a greater awareness to obesity as a potential etiology of male infertility.

Acknowledgment The authors are grateful for the research support from the Center for Reproductive Medicine at Cleveland Clinic.

References

65. Tomlinson JM, Barratt CL, Cooke ID. Prospective study of leukocytes and leukocyte subpopulations in semen suggests they are not the cause of a male infertility. Fertil Steril. 1993; 60:1069–75.