Obesity

39

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Key Points

- Worldwide obesity pandemic may be a potential reason of the concurrent global decline in male fertility.
- Obesity may influence hypothalamic–pituitary–gonadal axis and increase in estrogen- and adipose tissue-derived hormones, such as leptin, along with reduction in testosterone and inhibin B.
- Obesity can cause sperm genetic and epigenetic changes, increased scrotal temperature, erectile dysfunctions, and other physical effects.
- Male obesity has deleterious impact on the outcomes of assisted reproductive techniques (ARTs).
- Lifestyle modifications may help to manage obesity-related disorders besides specific medications and surgical interventions.

39.1 Introduction

Men possess greater morbidity and mortality rates as compared to their female counterparts, with global men's health deteriorating gradually [1]. Male fertility is following a declining trend as well [2–4], with male factor infertility contributing to 40–50% of worldwide infertility [5]. Most of the male infertility cases are idiopathic, for which the exact cause remains unidentified [6]. Research suggests a potential role of modifiable and preventable lifestyle adoptions in the improvement of male fecundity [7]. As a result of improper lifestyle and dietary habits, the global prevalence of obesity is accelerating at a high pace, leading to a worldwide obesity pandemic. Obesity includes increased visceral (abdominal) adiposity and is clinically defined as a body mass index (BMI) that is equal to or greater than 30 kg/m^2 [8]. An increasing BMI correlates with higher morbidity and mortality. According to a 2016 WHO report, 39% of the world population of adults have a BMI of above the normal range (BMI between 18.5 and 24.9) [9]. The global decline in male fertility parameters and the concurrent increase in obesity prevalence have led to several research interventions to find the association between obesity and male infertility.

Obesity triggers an array of disorders and renders the body susceptible to various chronic diseases, including diabetes, cardiovascular disease, malignancies, early aging, and neurodegenerative diseases. Obesity-induced disorders are associated with comorbidities such as hyperleptinemia, hyperinsulinemia, hypertension, dyslipidemia, hyperglycemia, Th1 dominant chronic inflammation, as well as disrupted reproductive functions [10, 11]. The pathogenesis induced by obesity is mainly based upon the state of lipotoxicity that causes cellular injury and tissue dysfunctions [12].

A substantial percentage of infertile men are being assessed and treated for obesity [13]. Moreover, a well-defined J-shaped relationship showing increase in BMI with a decline in semen quality has been put forth [14]. Studies have also found increased rates of azoospermia and oligozoospermia in obese men compared to males with normal weight [15]. With every 3 kg/m^2 increase in BMI of the male partner, an estimated 12% reduction in achieving successful pregnancy is proposed [16]. Obesity reportedly affects sperm count, morphology, vitality, motility, and sperm DNA integrity, although further research in this direction is required for better understanding of their associations [13, 15]. Obesity may modulate the genetic and epigenetic constitution of spermatozoa or influence the endocrine regulation of the male reproductive system [13, 17–19]. This includes reduced levels of testosterone (total and free), progesterone, and sex hormone-binding globulin (SHBG), along with increased levels of estrogen, insulin, leptin, follicle-stimulating hormone

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S. J. Parekattil et al. (eds.), *Male Infertility*, https://doi.org/10.1007/978-3-030-32300-4_39

(FSH), luteinizing hormone (LH), and prolactin [20]. In addition, physical mechanisms in obesity-induced male reproductive dysfunction include erectile dysfunction and increased scrotal temperature [13].

Obesity in male partners of the couple undergoing assisted reproductive techniques (ARTs) reportedly increases the risk for decreased impregnation rates and live birth rates [21]. Paternal obesity has also been suggested to have an adverse impact upon the offspring's health, particularly affecting metabolic and reproductive functions. The effect of paternal obesity on the health of the offspring may be mediated via DNA damage and several epigenetic modifications borne by the sperm [22]. The present chapter emphasizes the possible mechanisms by which obesity in men affects male reproductive functions, influencing the complex endocrine regulations and surge of adipose tissue-derived substances, modulating the genetic or epigenetic constitution of sperm, or directly perturbing testicular functions. Besides providing a concise understanding of the link between obesity and male fecundity, the chapter also puts forth the management and treatment strategies to combat obesity-induced male infertility.

39.2 Obesity: Metabolic Syndrome and Male Infertility

Metabolic syndrome refers to disordered energy production, usage, and storage. It is diagnosed if any three out of the following five conditions co-occurs: hypertension, obesity, high serum triglycerides, low high-density cholesterol (HDL) levels, and high fasting level of blood glucose. Metabolic syndrome renders the body susceptible to develop cardiovascular disease, diabetes, as well as reproductive disorders. It has long been shown to have an association with male reproductive dysfunctions such as hypogonadism and erectile dysfunction (ED) [23]. Studies have presented an estimated prevalence of obesity alone in 35% of all adult population and almost 50% of the aging population in the USA [24]. The rudiments of this state are observed with regard to the detrimental effects of the syndrome on male fecundity [25]. Hyperglycemia and hyperinsulinemia are almost obvious occurrences in obese men that can be considered as the confounding factors of male obesity [26]. Metabolic syndrome and its detrimental bodily consequences impair sperm quantity and quality and, therefore, are potent contributors to the reduced fertility seen in obese men [26].

The physiological mechanisms that fine-tune metabolic energy balance with reproductive functions rely upon the cross talks among metabolic hormones, hypothalamic–pituitary–gonadal (HPG) axis, and neuronal control. The neural apparatus regulating metabolic rate and energy homeostasis is the body "metabolic sensor" that transforms hormonal signals into neuronal impulses, dictating the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator. Hypothalamic GnRH is the prime regulatory hormone that mediates the orchestration of pituitary gonadotropins and subsequent testicular sex hormones to control spermatogenesis and other reproductive functions [27]. Metabolic syndrome and the related array of bodily disorders have garnered focus owing to the established association among obesity, diabetes mellitus (DM), hyperleptinemia, and infertility. Metabolic indicator hormones, such as insulin-like growth factor-I (IGF-I), insulin, leptin, ghrelin, resistin, obestatin, and growth hormone (GH), have been reported to transmit signals of nutritional status to the hypothalamic centers. This may suggest a route by which they communicate and interfere with the HPG axis milieu in the regulation of male reproductive functions [27, 28].

39.3 Obesity and Semen Quality

Certain male factors are crucial in determining male fecundity, the most conventional ones being adequate sperm volume, distinct morphology, and robust sperm motility, among others. In men, seminal fluid characteristics are reliant upon their overall health as well as environmental cues. Semen parameters are susceptible to be jeopardized even at slightest deviation from homeostatic conditions. Conditions such as trauma, systemic illnesses, hectic lifestyle, poor nutritional status, environmental conditions, and obesity-related alterations can drastically affect semen parameters [15]. The counteractions among BMI, steroidogenesis, spermatogenesis, and male infertility have been elaborately studied but still lack complete understanding [13].

Obese men have three times more probability to possess a sperm count of less than 20 million/ml than do men with normal weight. This condition is referred to as oligozoospermia [29]. Chavarro et al. [30] had put forth that men with higher BMI (>25 kg/m^2) displayed poorer total sperm count than those with normal weight. The volume of ejaculate also declined with elevation in BMI. A broad-spectrum study including 1558 Danish military men also showed a negative correlation of increased BMI with total sperm count and concentration [31]. Obesity also impairs sperm motility and morphology, but the exact mechanism of this has not been established yet [25]. Nevertheless, numerous studies have corroborated these findings to strongly suggest the disrupting impact of obesity upon male fertility [32, 33].

Human semen quality has always been a reliable predictor of male fertility status, and it is showing a global declining trend [3, 34, 35]. An all-inclusive, evidence-based review showcased an overall 32.5% decrease in sperm concentration among European population in the past 50 years [3]. Obesity and overweight along with the related allostatic load have widely been reported to be closely associated with an ele-

vated occurrence of oligozoospermia and azoospermia [36]. Proper management and disciplined weight loss showed impressive improvement in testosterone levels and semen parameters [37].

39.4 Altered Spermatogenesis in Obese Men

The seminiferous tubules sustain a dynamic yet steady balance between cellular regeneration and their death [38]. To mediate this purpose, just after the first wave of spermatogenesis, there is a phase of germ cell differentiation under tight regulations of a distinctive hormonal microenvironment. If the production of cells in this phase exceeds the physiological need, they undergo apoptosis via the Bcl-xL and Bax systems [39, 40]. Spermatogonial apoptosis may be stimulated under specific physiological or pathological conditions and is monitored by various genes. The AI spermatozoa have been shown to undergo a significantly increased rate of apoptosis in conditions of obesity. According to recent research interventions, immoderate induction of apoptosis in spermatogenic cells contributes to a majority of male subfertility or infertility [41]. Spermatogonial apoptosis is mediated and controlled by the conventional Bax and Bcl-2 homeostasis. Obesity may induce apoptosis by disrupting the ratio of Bcl-2/Bax in the testis, with increased Bax and reduced Bcl-2 expressions, thereby activating the downstream signaling caspases, especially triggering caspase 3 [42]. Moreover, obesity incurs hyperlipidemia and lipid metabolic disorders elevating the stress upon the endoplasmic reticulum, which further leads to spermatogenic cell apoptosis through high GRP78 mRNA and protein expressions [43, 44].

39.5 Obesity and Sperm DNA Integrity

The association of BMI with male infertility in terms of impaired sperm quality has been highlighted in many studies [14, 30, 36, 45–48]. The effects of obesity on the functional aspects of sperm, especially in consideration of its DNA integrity, should be more extensively studied. Sperm DNA integrity represents the major nuclear component of spermatozoa that is vital for normal fertilization, implantation process, pregnancy sustenance, as well as fetal development [49]. Thus, besides conventional semen parameters, determination of sperm DNA fragmentation (SDF(can serve as an advanced sperm function test to assess the male fertility status. The American Center of Reproductive Medicine (ACRM) through an array of studies has put forth the relevant concepts regarding SDF and several potential laboratory methods to determine the clinical value for proper assessment of SDF in male infertility [17, 50–52]. The vitality of the SDF assay for assessment of male infertility had also been recognized by the American Urological Association (AUA) and European Association of Urology (EAU) guidelines [53].

Sperm DNA integrity is a major factor that is adversely affected in obese men. The possible mechanism by which obesity impairs sperm DNA integrity or causes SDF is by inducing oxidative stress. Although there aren't a significant number of studies that have assessed the influence of obesity on sperm DNA integrity, a few studies have shown a disparity in their findings that may be due to technical issues [30, 54]. However, it is essential to assess the potential impact of obesity on sperm DNA integrity, as much reduced pregnancy rates have been portrayed in correspondence to increased SDF [52, 55]. Kort et al. [46] showed an increase in SDF rates in obese men, as assessed through Sperm Chromatin Structure Assay (SCSA). This concept was also supported by the findings of Chavarro et al. [30] and Farriello et al. [56] who determined sperm DNA integrity by the single-cell gel electrophoresis assay method (comet assay). LaVignera et al. [57] also observed using the TUNEL assay with flow cytometry that obesity negatively affects sperm DNA integrity. Yet another extensive, 3-year multicenter study explored further the association of increased BMI with sperm DNA integrity and showed that obesity is indeed responsible for increased SDF [58]. In contrary, very few studies failed to find any significant relationship between BMI and sperm DNA integrity [45, 54].

39.6 Obesity and Hormones

39.6.1 Hypothalamic–Pituitary–Gonadal Axis (HPG) and Sex Hormones

The mechanisms justifying the association of obesity with male infertility are mostly ambiguous. The most acceptable mechanism may be the dysregulation of the HPG axis by obesity-related allostatic load. HPG axis is the prime endocrine regulator of male reproductive functions along with the pituitary gonadotropins, LH, and FSH, being regulated by pulsatile GnRH from hypothalamus. The LH and FSH regulate steroidogenesis via Leydig cells and spermatogenesis by acting upon the Sertoli cells, respectively. Obese couples have an increased number and size of adipocytes, which emanate abnormal levels of various hormones and regulatory molecules. These adipose tissue-derived substances interfere with the delicate orchestration of the HPG axis, and this may explain in part the mechanism by which obesity affects male fertility (Fig. 39.1). All the obesity-related parameters such as BMI, total body fat, subcutaneous fat, and intra-abdominal fat are associated with reduced levels of testosterone and higher estrogen levels [59]. This phenomenon can be justified by

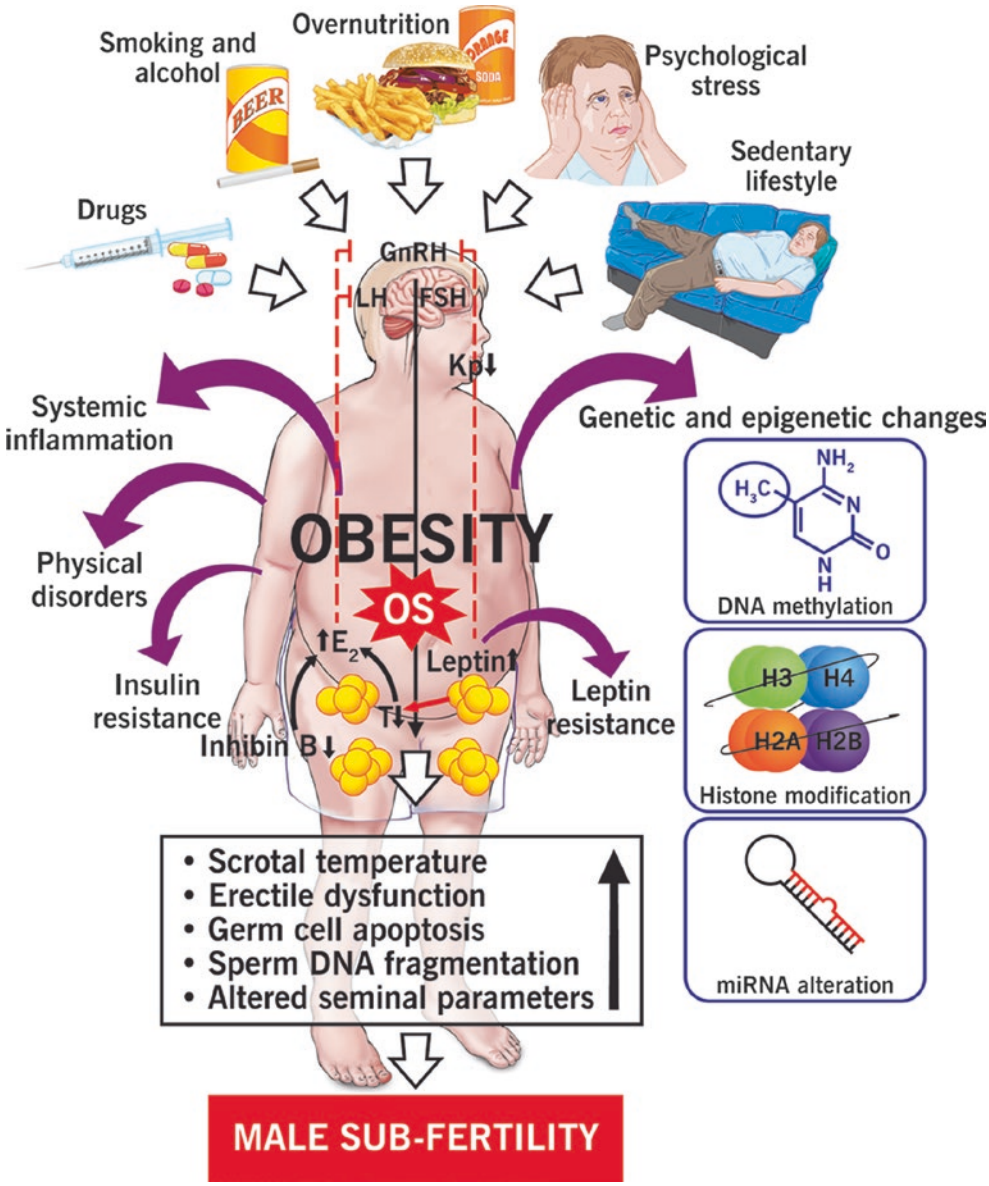

Fig. 39.1 Obesity-induced endocrine disruptions and its association with male infertility. *GnRH* gonadotropin-releasing hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *T* testosterone, E_2 estradiol, *Kp* kisspeptin, *OS* oxidative stress. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2019. All Rights Reserved)

overactivity of the aromatase cytochrome P450 enzyme, which is produced in excess in the white adipose tissue of obese men in addition to that produced by the Leydig cells. Thus the high estrogen level seen in obese men is due to elevated conversion of androgens to estrogens [60]. This impairment in sex hormone levels induces adverse alterations in spermatogenesis and other male reproductive functions. Estrogen is more biologically active as compared to testosterone. As such, even a very minute increase in its level may elicit substantial downstream impacts that could disrupt testicular functions [29]. On the other hand, complete reduction of estrogen level in the testes also affects normal steroidogenesis and spermatogenesis [61]. The presence of estrogen receptors in the male hypothalamus suggest that higher estrogen levels in obese men lead to low testosterone levels also via a negative feedback mechanism inhibiting the pulsatile GnRH release and subsequent release of LH and FSH [62]. This mechanism ultimately leads to insufficient gonadotropins for androgen production and spermatogenesis.

Inhibin B is a growth-like factor that is secreted by the Sertoli cells and mainly functions to inhibit FSH production. It also stimulates testosterone synthesis by the Leydig cells. Suppressed inhibin B production in obese men may be due to high estrogen level or any other mechanism indicating a direct disruptive effect of obesity on Sertoli cells [63].

Thus, infertile obese men exhibit hormonal alterations that differ from those demonstrated in men with either obesity or infertility alone.

39.6.2 Adipose Tissue and Metabolic Hormones

The working hypothesis used to explain the association of obesity with male reproductive dysfunctions is that white adipose depositions in obese men are responsible for elevated estrogen levels and the surge of adipose tissue hormones, which directly or indirectly affect steroidogenesis and spermatogenesis. The elevated estrogen level is due to increased aromatase enzyme activities that convert testosterone to estrogen. This is the result of excess aromatase cytochrome P450 enzyme production by the white adipose tissues in obese men in addition to that produced by the Leydig cells.

Obesity presents with complex disorders that greatly impairs hormonal regulation [64]. Obese men have a large deposition of adipose tissues, which, besides being a site of toxin depot, also emanate different hormones and inflammatory markers called adipokines. Obesity leads to alterations in adipose tissue hormonal levels in serum, such as that of ghrelin [65], leptin [66], orexin [67], adiponectin [68], obestatin [69], and other metabolic hormones [64]. Reportedly, leptin correlates positively with body fat mass [70, 71].

Leptin, a regulatory adipose tissue hormone, balances food intake and energy utilization through effects upon hypothalamic control. Leptin reportedly possesses both metabolic and neuroendocrine functions. Besides its well-known role in glucose metabolism, it can also modulate male sexual maturation and reproductive functions. Research has conveyed that the ob/ob mouse, devoid of a functional leptin gene, demonstrated reduced gonadotropin secretion which leads to infertility, while exogenous leptin treatment successfully restored fertility [72]. Moreover, chronic administration of anti-leptin antibody to rats proved detrimental to LH secretion and reproductive functions. Leptin also plays regulatory roles to mediate normal spermatogenesis as leptin-deficient mice showed disrupted spermatogenesis and elevated expressions of testicular pro-apoptotic genes, thus inducing germ cell apoptosis [73]. There are a few reports that contradict the ameliorating effects of leptin on male fertility, which shows that it also has inhibitory effects on testicular functions at levels exceeding the physiological limit [74]. Leptin induces reactive oxygen species (ROS) generation in human endothelial cells by increased mitochondrial fatty acid oxidation [70, 71]. Leptin may also stimulate the HPG axis by increasing the release of GnRH, FSH, and LH [75] (Fig. 39.1). It can impose its direct effect upon the gonads as its receptor isoforms are present in abundance in the gonadal tissue [75]. Serum adiponectin levels show an inverse relationship with both testosterone [76] and ROS levels [77].

Leptin may also regulate hypothalamic GnRH release through its influence on kisspeptin. The role of kisspeptin in regulation of reproduction is widely accepted. Located in the arcuate nucleus of hypothalamus, these peptides establish a metabolic and reproductive cross talk [78]. Kisspeptin have been reported to suppress lipogenesis and increase lipolysis [79]. In metabolic syndrome like obesity, there is reduced expression of kisspeptin mRNA, *KISS1* in hypothalamus as well as in the adipose tissues [78]. Since kisspeptin stimulates the pulsatile hypothalamic GnRH release, its deficiency in obesity may result in hypothalamic hypogonadism (Fig. 39.1) [78, 79].

Orexin (hypocretin) is another emerging adipose tissue hormone that reportedly stimulates testosterone production via inducing steroidogenic enzymes activities in Leydig cells [80]. Orexin also seems to attenuate oxidative cell damage [81].

The secretion of resistin, another adipose tissue factor, increases due to high adipocyte numbers in obese men. Resistin reportedly induces insulin resistance in obese men rendering them susceptible to type 2 diabetes [82, 83]. As per the regulations set by the Endocrine Society Clinical Practice Guidelines (2010), men with type 2 diabetes should be screened for low levels of testosterone [84]. This is justified as obese men with type 2 diabetes may possess secondary hypogonadism due to central or peripheral insulin resistance. This effect is aggravated by the deleterious actions of the associated pro-inflammatory cytokines (interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα)) upon the HPG axis [60]. Increased insulin levels in obese men lead to reduced SHBG levels, which may explain the decreased action of testosterone required to mediate normal spermatogenesis. However, compensation of low SHBG levels does not improve the low testosterone levels in conditions of insulin resistance in obesity, reflecting an autonomous direct impact of insulin resistance on the production of testosterone by the Leydig cells [13, 60].

Ghrelin, the "hunger hormone," is a neuropeptide produced by ghrelinergic cells in the gastrointestinal tract, whose association with altered serum testosterone levels has been suggested but is still contentious [85–87]. Ghrelin receptors are found in the testis, and it has a role in steroidogenesis. However, it has not yet been reported to have direct effects upon spermatogenesis [85]. Oxidative stress and ROS levels seem to positively correlate with levels of ghrelin, which trigger further obesity-related complications and in turn generate more ROS [88].

The complex network of such adipose tissue hormones, including adipokines, metabolic hormones, and classical hormones, comprising the HPG axis, mediate the pristine functioning of the male reproductive system. If any of these cross talks get jeopardized as in the case of obese men, reproductive functions are disrupted leading to male subfertility or infertility.

39.7 Obesity-Induced Genetic and Epigenetic Modifications

Obesity and male infertility can be linked through their root causes arising from genetic and epigenetic alterations. Few such common genetic mutations that find association of obesity with male infertility are conditions like Prader–Willi, Laurence–Moon–Bardet–Biedl, and Klinefelter syndromes [19, 89, 90]. Prader–Willi syndrome, characterized by abnormalities in chromosome 15, presents symptoms of both infertility and obesity. The human *ALMS1* gene mutation, causing Alström syndrome, presents metabolic and endocrinological modulations inducing childhood-onset obesity and infertility among other complications [91]. Moreover, an aromatase polymorphism has been reported to influence weight-mediated estradiol levels in obese men [92, 93]. This can be a potential reason why certain obese men have high estradiol levels followed by subfertility or infertility, while others face no such issues. Further interventions are required to find yet a wider genetic link between obesity and male infertility.

As discussed earlier, a wide range of environmental influences, including dietary and lifestyle factors, can cause obesity. These causatives can modify epigenetic arrangements which may elevate the risk of chronic systemic diseases not only in the affected individual but also his future generations.

In this context, a pioneering study by Ng et al. reported that high-fat diet in male rats results in β-cell dysfunction [94]. Early onset of disrupted insulin secretion as well as glucose tolerance was noted in the female offspring from these male rats. In another report by the same group, it was revealed that the transcriptome of retroperitoneal white adipose tissue of rat offspring was also concurrently affected [95]. Nevertheless, male germ cells were not analyzed for the same. Nonetheless, the developing germ cells in the male offspring may also carry several epigenetic changes, such as methylation, which are the essential cause of the transgenerational effects. The report from Fullston et al. revealed that diet-induced paternal obesity may affect molecular profiles of offspring spermatozoa. They have reported that mice fed with high-fat diet showed altered spermatozoa microRNA content and a 25% decline in sperm DNA methylation [96]. Palmer et al. reported that mice fed with high-fat diet presented a decrease in the level of sirtuin-6 (SIRT6), a histone deacetylase, in spermatozoa with increased DNA fragmentation [97].

Studies on the effects of obesity on human sperm epigenetics are scarce. To the best of our knowledge to date, no report has come out in human subjects revealing the function of RNA fragments in the transgeneration transmission of dietary intake. In 2014, Consales et al. examined the effect of lifestyle factors on human sperm DNA methylation in repetitive DNA sequences (LINE-1, Satα, and Alu). However, no significant correlation was found between BMI and sperm DNA methylation. Smoking, one of the causatives for obesity, showed a significant positive association with the LINE-1 methylation level [98]. There are very few studies that reported DNA methylation of individual gene or in genome of obese men. It has been reported that the DNA methylation percentages in obese men are significantly different from that of normal men [99]. Donkin et al. reported an interesting observation that loss of weight following bariatric surgery in morbidly obese men caused significant alterations in their sperm epigenetics [100].

Epigenetic modifications persevere for generations, with altered methylation patterns and molecular programming seen in the offsprings [101–103]. Children born to obese parents have been found to have altered sperm DNA methylation profiles compared to the children from non-obese parents [104]. Successively, another study has reported altered sperm DNA methylation at several differentially methylated regions, signifying that the male obesity status is perceptible from the spermatozoa epigenome [99].

39.8 Obesity-Related Disorders and Male Infertility

39.8.1 Increased Scrotal Temperature

Obesity may potentially affect sperm production/parameters by increasing gonadal heat as a result of high scrotal adiposity. Spermatogenesis is an extremely heat-sensitive process, with the human testes having an optimal temperature of 34–35 °C [60]. Testicular temperature may alter also due to several other conditions, such as varicoceles, sedentary lifestyle, using a laptop computer, sauna, warm baths, etc. [105]. In obese men, raised scrotal temperatures due to high scrotal adiposity and increased suprapubic and thigh fat also lead to sperm oxidative stress besides directly affecting spermatogenesis [13, 105]. This could damage sperm cells, reduce sperm motility, and increase SDF leading to subfertility or infertility [13].

39.8.2 Erectile Dysfunction

Infertility in obese men can also be related with decreased coital frequency. It is evident through various survey-based studies that obese men have almost one and a half times more chance of acquiring erectile dysfunction [106]. Erectile dysfunction positively correlates with male infertility [13, 107]. The mechanism by which obesity may be related to erectile dysfunction can be explained by a marked reduction in testosterone levels and the surge of potential pro-

inflammatory cytokines in obese men [108]. Such pro-inflammatory mediators are responsible for severe endothelial dysfunction that can directly lead to male erectile dysfunction acting via the nitric oxide pathway [109]. Obesity associates with several systemic pathogenesis, such as hypertension, diabetes, and dyslipidemia, which possess independent mechanisms in causing erectile dysfunction [110]. It would be beneficial if there are more research interventions to establish a consensus whether decreased coital frequency in obese men is the consequence of erectile dysfunction or if they relate to endocrine or psychological disorders [111].

39.8.3 Oxidative Stress

Reactive oxygen species are immensely reactive and unstable molecules that, when produced in excess exceeding the antioxidant defense of the tissues, lead to oxidative stress (OS). OS can induce severe cellular impairments throughout the body [112, 113]. Numerous reports have associated obesity and its related complications with increased OS [13, 33, 58, 64, 66]. Obesity marks an increase in serum free fatty acids as well as unsaturated fatty acids. These fatty acids are vulnerable to oxidative attack by ROS and subsequently undergo peroxidation, reduction in antioxidant enzyme levels, and malondialdehyde (MDA) accumulation, reflected by a state of OS in obese men [114]. As discussed above, adipocytes emanate a surge of adipokines such as IL-6, TNFα, plasminogen activator inhibitor-1 (PAI-1), and tissue factors [60, 68]. Increased levels of these adipokines owing to high white adipose tissue deposition in obese men lead to inflammatory conditions that impose toxic effects on sperm. These effects are mediated via induction of excess ROS and reactive nitrogen species (RNS) generation in testis [115]. The increased metabolic rates to sustain normal biological processes in obese men as well as high levels of stress in the immediate testicular environment trigger yet more ROS production. The local influences of pro-inflammatory mediator molecules contributed by activated leukocytes in response to inflammatory signals in obesity also aggravate the damage to the sperm and inhibit spermatogenesis. ROS is an independent causative and an emerging marker of male infertility that evidently incurs an array of disruptions in sperm production, morphology, and functions and may also curb hormonal regulations of male reproductive functions [17, 51, 107, 112, 113].

39.8.4 Sleep Apnea

Sleep apnea (SA) refers to a particular sleep disorder in which breathing pauses frequently or there is shallow or infrequent breathing during sleep. This pause in breathing leads to hypoxemia, which is very common in obese people. There is scarcity of evidence to come to a rigid conclusion that sleep apnea in obese men causes infertility, but the association cannot be ruled out. Sleep apnea affects the HPG axis and may also decrease gonadal function [13, 107]. Moreover, it is reported that sleep apnea in obese men decreases morning testosterone concentrations [116]. This can be explained by the hypothesis that fragmented sleep resulting from sleep apnea may be responsible for disruption of the nocturnal testosterone rhythm. Moreover, it is being put forth that reduction in total testosterone levels in obese men is proportional to the severity of sleep apnea, thus also disrupting spermatogenesis and inciting other sexual dysfunctions. The combination of these deleterious effects of sleep apnea associated with obesity may have a compounding effect on male fertility [60].

39.9 Consequences of Male Obesity on ART Outcomes

An increasing body of evidence claims that the non-genetic impact of a prolonged health issue of paternal origin can be transmitted to the offspring via the male gamete [96, 104]. Among the factors that can influence sperm health, obesity is of immense importance. In light of the ever-growing prevalence of obesity, it is essential to intensify the understanding of the clinical consequences of the male partner being obese. Influence of male factors upon ARTs or sperm viability needs extensive research.

39.9.1 Obesity and Pregnancy Onset from ART

There are only few studies focusing upon the impact of male obesity on achieving clinical pregnancy for the couple undergoing ART (in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)). The assessment of clinical pregnancy following ART was done by either of the following methods: fetal heartbeat detection per embryo transfer (ET) [21], intrauterine gestational sac on transvaginal sonogram per cycle [117], ultrasound confirmation (giving no further details) per embryo transfer cycle [118], and heartbeat detected per ICSI cycle [119, 120]. Reports suggest that there is a decline in clinical pregnancy rates in couples undergoing ART with the male partner being obese.

39.9.2 Obesity and Pregnancy Outcome After ART

Significant decrease in live birth rate from ART has been reported for obese men compared to men with normal weight. Live birth rate following pregnancy through ART has

been reported by various studies through embryo transfer cycle [118], oocyte retrieval [21], treatment cycle [121], cycles of ICSI [119], and IVF cycle [120].

39.9.3 Paternal Obesity and Infant Development Following ART

Paternal obesity has also been found to affect offspring development in terms of alterations in the infant BMI growth curves from birth till the age of 3.5 years as compared with normal weight fathers [122].

With obese men being more susceptible to acquire subfertlity or infertility, the ART outcomes of couples with an obese male partner display poorer impregnation rate and live birth rate as well as compromised health of the infant. This may be explained by disruption of normal sperm morphology, increased SDF, and low mitochondrial membrane potential (MMP) in obese men.

39.10 Management of Obesity-Induced Male Infertility

39.10.1 Lifestyle Modifications

Lifestyle modifications to trigger weight loss include alterations in dietary habits such as reduction in meal portions and restricting certain high calorie food, along with adequate exercise, so as to restore a normal energy balance. It is evident that natural weight loss via strict diet and/or proper exercise improves the levels of androgen, SHBG, and inhibin B while reducing the levels of insulin and leptin. This in turn ameliorates semen parameters in obese men [30, 89]. Moreover, weight loss leads to substantial reduction in the adipose tissue mass, thus decreasing the concentrations of inflammatory mediators such as TNFα, IL-6, and other cytokines that are associated with infertility [123]. A sensible diet plan and conscious effort to exercise lead to a gradual weight loss which should be maintained for a long time. This can be stimulated through self-determination, tenacity to exercise, cognitive behavior therapy, and association with supportive groups. These lifestyle adoptions form the primary healthcare in the treatment of obesity-induced infertility [18, 124].

39.10.2 Prescription Medicine

Obesity-induced male infertility can be clinically dealt via two ways, either by providing medications for weight loss or directly addressing the male reproductive dysfunction. There are a couple of anti-obesity medications that can be used for a long period as per approval by the Food and Drug Administration (FDA). Orlistat (Xenical) is used to decrease intestinal fat absorption hindering pancreatic lipase activity. Another drug is sibutramine (Meridia) that works by inhibiting neurotransmitter deactivation, namely, norepinephrine, dopamine, and serotonin. This leads to decreased appetite and hence a modest weight loss [18, 125]. Short-term medications include a broad arena of treatment options including noradrenergic receptor activation, gastrointestinal lipase inhibition, serotonin receptor activation, and combination therapies [125].

Obese men with secondary infertility may be treated via GnRH pump or injection of human chorionic gonadotropin (hCG) that mediates the action of LH on the Leydig cells to stimulate testosterone secretion. This is effective in restoring normal spermatogenesis in obese men to some extent [126]. Aromatase inhibitors (testolactone or anastrozole) are also a potent medication option that works by inhibiting the conversion of testosterone to estrogen. These are shown to improve testosterone levels and in turn male fecundity in obese subjects [126–129]. The new era treatment approach for obesity-induced male infertility attempts to directly mitigate two simultaneous concerns: one being testosterone insufficiency and the other being excess adipose tissue-derived factors. These are attempted via testosterone replacement therapy along with regulation strategies to inhibit adipose tissue hormones, especially leptin. Reduction in leptin level in obese men may be beneficial to improve reproductive functions because leptin indirectly influences GnRH, LH, and FSH and also impose direct testicular effects [130, 131]. Modulation of some prime metabolic hormones associated with obesity such as ghrelin may lead to further insights in the development of new medications in obesity-induced health disorders as well as in male infertility [13, 17, 18].

39.10.3 Surgical Interventions

Obese men with infertility may conveniently opt for IVF. Although there are reported cases of unfavorable outcomes in IVF/ICSI cycles among the morbidly obese [132], male partner obesity does not appear to affect the results of their female healthy partners in IVF or ET [13, 18].

Subject-specific surgical interventions for obese men with heavy fat accumulation around the scrotum can be scrotal lipectomy. In such obese men, the accumulated fat results in increased scrotal temperature or toxin buildup. This procedure evidently leads to restoration of the male fertility status as it is claimed that one-fifth of obese men undergoing scrotal lipectomy were able to successfully impregnate their partners [133]. Severely obese men (BMI > 40) should go through rigorous dietary and behavioral modifications, together with surgery to decrease or bypass parts of their stomach or small intestine called the bariatric surgery ("weight loss surgery") [133]. Studies report that these sur-

geries lead to significant decline in the estrogen/testosterone ratio and aid in the restoration of other hormones and adipokines. However, bariatric surgery should be avoided if the severity of obesity-linked male infertility is lesser, until it is confirmed to have no deleterious long-term effects.

39.11 Conclusion

Obesity, characterized by BMI value that is equal to or greater than 30 kg/m^2, is a metabolic syndrome that renders the body susceptible to various pathological conditions. The simultaneous global decline in male fertility, and increase in obesity prevalence, supports an association of obesity with male infertility.

Obese men have substantial deposition of adipose tissues, which, besides being a site of toxin depot, also are sources of hormones (ghrelin, leptin, orexin, adiponectin, obestatin, etc.) and *adipokines*. Leptin acts both at HPG regulatory axis and directly on testicular cells to modulate male reproductive functions. It may trigger excess ROS to induce OS in testicular tissue, while orexin has been reported to attenuate oxidative damage. Orexin also serves to stimulate testosterone production in Leydig cells. Resistin is another important adipose tissue hormone that induces insulin resistance in obese men. In addition, obese men possess higher estrogen than testosterone owing to increased aromatase activities or by negative feedback mechanism of estrogen to inhibit the pulsatile GnRH release and subsequent release of LH and FSH. Obesity leads to reduced inhibin B production, which may also attribute to high estrogen level.

Besides indirect effects of obesity on male reproduction via hormonal cross talks, the chapter also has highlighted the direct effects of obesity on gonadal functions. Obesity may disrupt spermatogenesis by immoderate induction of germ cell apoptosis. It impairs semen quality through various mechanisms such as elevated scrotal temperature, ROS production, and increased sperm DNA fragmentation. The chapter has put forth the possible link between obesity in male partner of couple undergoing ART and its undesirable outcomes. However, there are promising strategies to prevent as well as manage obesity and its related disorders. The concise concept of obesity and its association with male infertility presented in this chapter will aid better understanding of the subject and encourage researchers to explore new therapeutic interventions.

39.12 Review Criteria

An extensive literature search has been performed to find the relationship between obesity and male infertility using search engines such as Science Direct, OVID, Google Scholar, PubMed, and MEDLINE. The overall strategy for study identification and data extraction was based on the following keywords "obesity," "metabolic syndrome," "infertile men," "infertility," "semen parameters," and "assisted reproduction" and the names of specific obesity and male infertility markers. Articles published in languages other than English were also considered. Data that were solely published in conference or meeting proceedings, websites, or books were not included. Websites and book chapter citations provide conceptual content only.

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