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REVIEW

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Obesity and male infertility: multifaceted reproductive disruption

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Abstract

Background: The global prevalence of obesity has soared to a concerning height in the past few decades. Interestingly, the global decline in semen quality is a parallel occurrence that urges researchers to evaluate if obesity is among the most essential causatives of male infertility or subfertility.

Main body: Obesity may alter the synchronized working of the reproductive-endocrine milieu, mainly the hypothalamic-pituitary-gonadal (HPG) axis along with its crosstalks with other reproductive hormones. Obesity-mediated impairment in semen parameters may include several intermediate factors, which include physical factors, essentially increased scrotal temperature due to heavy adipose tissue deposits, and systemic inflammation and oxidative stress (OS) initiated by various adipose tissue-derived pro-inflammatory mediators. Obesity, via its multifaceted mechanisms, may modulate sperm genetic and epigenetic conformation, which severely disrupt sperm functions. Paternal obesity reportedly has significant adverse effects upon the outcome of assisted reproductive techniques (ARTs) and the overall health of offspring. Given the complexity of the underlying mechanisms and rapid emergence of new evidence-based hypotheses, the concept of obesity-mediated male infertility needs timely updates and pristine understanding.

Conclusions: The present review comprehensively explains the possible obesity-mediated mechanisms, especially via physical factors, OS induction, endocrine modulation, immune alterations, and genetic and epigenetic changes, which may culminate in perturbed spermatogenesis, disrupted sperm DNA integrity, compromised sperm functions, and diminished semen quality, leading to impaired male reproductive functions.

Keywords: Male infertility, Hormones, Obesity, Inflammation, Oxidative stress

Background

Infertility seems to be one of the genuine reproductive health hazards with the development of age. This threat counts for infertility prevalence of 15% amongst the couples where 50% is solely male infertility [1]. Many spermatic dysfunctions due to hormonal and metabolic disorders, stressful lifestyle, diet, sleep apnea, or other pathologic conditions may account for infertility [2, 3] where decline in semen quality is a potent feature [4–9]. Obesity has been termed as "enemy of male fertility" by El Salam in 2018 [10] which affects 400 million adult population worldwide [11]. Several studies put forward to present different views regarding this distress [12–14], but correlation between obesity and male infertility needs to be further unveiled. It has been reported that the obesity can make changes in semen parameters that lead to reduce testicular volume, decline in semen quality, and impaired spermatogenesis [4, 15]. So, obesity is a biomarker of infertility for its epidemic features [16, 17]. Prevalence of obesity depends on conditions like geographical locations, food habit, socioeconomic status, etc., and it has also been found as example that high socioeconomic status may lead to sedentary lifestyle with high consumption of energy (food) and is a major reason for obesity as compared to lower socioeconomic

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status [18]. The present article aims to review the correlations between obesity and different infertility parameters which may have some impact in male infertility.

Main text

Obesity-induced genetic and epigenetic modifications and male infertility

Male obesity and infertility can be associated with genetic and epigenetic changes by their root causes. Prader-Willi, Alström, Laurence-Moon-Bardet-Biedel, and Klinefelter syndromes are among few disorders which can be triggered by genetic defects and have been linked to obesity-related male infertility [19–23]. Prader-Willi syndrome, exhibiting symptoms of both obesity and infertility, is characterized by abnormalities in chromosome 15 [24]. Alström syndrome, which is caused by human *ALMS1* gene mutation, presents metabolic and endocrinological modulations that cause childhood obesity and related infertility [20]. In some obese males, an aromatase polymorphism has been reported to increase weight-mediated estradiol levels followed by subfertility or infertility [25].

Few studies have reported the difference of DNA methylation in normal and obese men. The percentage of DNA methylation in obese men has been reported to be considerably different from that of normal men [12]. As epigenetic changes remain for decades, the evolving patterns of methylation and molecular programming can also be observed in offsprings [12, 26]. Children born to obese parents have been shown to have altered profiles of sperm DNA methylation relative to those born to non-obese parents [26]. Studies on the effect of obesity on the epigenetics of human sperm are however scanty. A broad range of environmental influences such as dietary and lifestyle factors not only impact obesity but also alter epigenetic arrangements that impact not only that individual but also his generations to come. The report from Fullston et al. revealed that diet-induced paternal obesity can affect molecular sperm profiles of the offspring. They have reported that the sperm DNA methylation has decreased by 25%, and the quality of sperm MicroRNA has changed in mouse fed with high-fat diets [27]. Palmer et al. showed that mice fed with high-fat diet had decreased the level of histone deacetylase Sirtuin-6 (SIRT6) in spermatozoa with an increase in DNA fragmentation [28]. In 2014, Consales et al. investigated the effect of lifestyle factors in repetitive DNA sequences on human sperm DNA methylation (LINE-1, Sat-α, and Alu) [29]. However, between sperm DNA and BMI, no meaningful association was found. One cause of obesity, smoking, demonstrated a considerable positive correlation to methylation level LINE-1 [30]. Donkin et al. reported a significant remark that weight loss after bariatric operation induces substantial modification of sperm epigenetics in morbidly obese males [31].

Disruption of endocrine crosstalk

Abnormal sex hormone levels are commonly observed in obese males. As a stressor, obesity alters the homeostasis for intracellular endocrine communication. Body temperature is strongly associated with obesity markers in men [32], and this may cause a heat stress which decreases the activity of antioxidant enzymes and increases NADPH oxidase activity leading to disruption of mitochondrial homeostasis like in Sertoli cells which cause reduced formation of testosterone [33].

Secondary hypogonadism is often detected in individuals with moderate to severely obese male with a reported prevalence of about 45% [34] and also with higher prevalence rate than type-2 diabetes mellitus (T2DM) in obese males [35, 36]. Secondary hypogonadism is associated with sexual dysfunction, depression, fatigue, decreased lean body mass, reduced mineral bone density, etc. [37]. Hormonal imbalance during secondary hypogonadism is associated with the decrease in both testosterone (free and total plasma concentration) and sex hormone-binding globulin (SHBG) and conversely increased plasma estrogen level within the obese male individuals [38]. Multiple studies have been revealed the inverse relationship between BMI and plasma testosterone concentration among the obese subjects besides the appearance of low testosterone and high estrogen level among the subjects with metabolic syndrome [39, 40]. Waist circumference also shows an inverse relationship with plasma concentration of testosterone. An increased waist circumference is supposed to be the expression of large amount of visceral adipocytes leading to increased intra-adipocyte aromatase activity [41] which is established to increase the conversion of circulating testosterone to the 17β-estradiol in obese male and resulting to the development of secondary hypogonadism. The continuous conversion of circulating testosterone to the 17β-estradiol contributes to the higher body weight and excessive accumulation of abdominal fat [42]. Physiologically, testosterone is responsible for several metabolic impacts by acting through the androgen receptors present on adipocytes; especially, it improves the insulin sensitivity and prevents the visceral fat accumulation. Thus, it plays a protective role on pancreatic β-cells by enhancing the activity of antioxidant enzymes which helps to prevent the β-cells from apoptosis during glucotoxicity [43]. Thus, increased intra-adipocyte aromatase activity reduces the plasma concentration of testosterone which again cause the genesis of insulin resistance and T2DM as found not

only in obese male with secondary hypogonadism but also for men receiving treatment for androgen suppression suffering from prostate cancer and age-related hypogonadism [44]. Interestingly, skeletal muscle mediates the effect of testosterone on adipocytes as the testosterone is now crucial for the energy homeostasis mechanisms. Thus, it was shown that testosterone may enhance the myogenic commitment of pluripotent mesenchymal stem cells and inhibit the adipogenic differentiation by interacting with its androgen receptors [45, 46]. Multiple studies have predicted the low testosterone level for the development of T2DM besides its negative correlations with dyslipidemia followed by blood pressure [47, 48]. Conversely, high testosterone level causes reduced risk in T2DM [49]. Release of several pro-inflammatory cytokines from visceral adipocytes and macrophages seems to be a cause of obesity, as they disrupt the insulin response during the process of metabolism. Several studies have been explained the correlation between insulin resistance, T2DM, and hypogonadism in obese male individuals [44, 50]. Pasquali et al. explained the effect of hyperinsulinemia to decrease testosterone level in which insulin was seen to exert its effect both centrally and peripherally [51, 52]; centrally, it was responsible for impaired activity of GnRH neurons in hypothalamus, and peripherally, it suppressed SHBG synthesis, physiological action of LH followed by modulation of Leydig cell physiology [53, 54]. Low-circulating testosterone is another important clinical feature among patients with obstructive sleep apnea, but testosterone replacement was shown worsening clinical symptoms in these patients [55].

Aldosterone is best known as a mineralocorticoid hormone, produced from adrenal glands in response to angiotensin II. It may exert its effects through mineralocorticoid receptor (MR). Na^+ transport is the well-described classical action of aldosterone which is mediated by MR present in epithelial cells [56]. This MR has also been shown to be present on other cell types including adipocytes [57]. Primary hyperaldosteronism or Conn syndrome can be described as continuous or excess autonomous production of aldosterone by an adrenal adenoma or bilateral adrenal zona glomerulosa hyperplasia providing a relevant model for systemic aldosterone excess on adipose tissue [58]. Activation of MR causes the differentiation of preadipocytes to mature adipocytes. Thus, testosterone may exert its positive role for the modulation of the renin-angiotensin-aldosterone pathway by reducing the expression followed by action of angiotensin-II type-1 receptor (AGTR1) [59, 60]. In obesity, the low-circulating testosterone may cause the elevated release of aldosterone which in turn activates the proliferation and maturation of adipose tissue; thus, MR mRNA expression was shown to be positively correlated with increasing BMI in humans and in obese db/db mice [61].

It was previously established that prolonged stress causes the release of glucocorticoid which reduces the serum testosterone levels [62] directly by suppressing Leydig cell steroidogenesis and by decreasing gonadotropin stimulation of cAMP production as well as the activity of 17α-hydroxylase [63]. Thus, in obese male, reduced testosterone level may promote the action of glucocorticoid which in turn impacts on adipose tissue development, metabolism, and their secretion; besides, those, synergistically with insulin, glucocorticoids promote differentiation of preadipocytes to mature adipocytes [64]. Depending on physiological context, nutrition, and other hormonal *milieu*, the glucocorticoids affect the lipid synthesis and lipolysis possibly by exerting lipogenic effects on visceral adipose tissue (VAT) and lipolytic effects on subcutaneous adipose tissue (SAT) [65]. Cortisol synergistically may stimulate adipocyte expansion during energy surplus and insulin supply, such as what would occur in Cushing syndrome. During catabolic states, cortisol production increases as a part of the stress response. It has large lipolytic role and mobilizes vital energy stores. This paradigm may partially explain that hypercortisolism is associated with increased adiposity in Cushing syndrome and paradoxically with decreased adiposity in states of undernutrition, such as anorexia and acute illness. Hypothalamic-pituitary-adrenal (HPA) axis dysfunction, as well as local metabolism of glucocorticoids in adipose tissue, can cause alterations of circulating cortisol dynamics, which have been linked to obesity and the metabolic syndrome [66]. Obese individuals show markedly higher ACTH, and cortisol may respond to vasopressin (AVP) and corticotropin-releasing hormone (CRH) [67, 68], whereas dose-response ACTH stimulation test may interfere to elevated cortisol level [69].

More to the point, Kisspeptin is a hypothalamic peptide which plays an important role in HPG axis during pubertal development [70], and it controls the release of LH and FSH via GnRH and also maintains the spermatogenesis by FSH, SHBG, and inhibin-B release [71]. Kisspeptin neurons transmit the signals regarding the steroid feedback mechanism to the GnRH neurons [72] which is an important regulator of the pulsatile release of GnRH [73, 74]. Recently, it has been postulated that kisspeptin may convey the facts regarding the body's metabolic status to the HPG axis [72] especially to the GnRH neurons [75]. It is reported that inactivation of Kisspeptin receptor genes leads to obesity in mice [76] as well as in human through a signal transduction pathway involving the hypothalamic modulatory circuits and thereby maintains the reproductive homeostasis [77]. It also has been

observed that maturation of kisspeptin receptor genes is associated with decreased sex steroid levels along with LH and FSH levels (hypogonadotropic hypogonadism) [78]. It is compulsive that energy balance also plays a vital role in maintenance of fertility [79], so that, undernourished or obese, both the conditions may cause alterations in fertilization capacity [79, 80]. Adiposity and T2DM were also observed to be associated with decreased circulating level testosterone and reduced frequency of LH pulse in male [81].

Sertoli cells, another crucial regulator of testicular functions, provide a structural and hormonal support, and its numbers represent the functional status of the testis [82, 83]. Obesity leads to suppression of all gonadal hormones, and as a result of it, Sertoli cells release less inhibin that leads to compromised spermatogenesis [82].

Leptin and ghrelin, two significant polypeptides, are required for the maintenance of body weight via the changes in eating behavior [84]. Leptin works directly on HPG axis and decreases testicular androgen production [85], which causes alterations in sperm morphology, sperm concentration, and sperm motility, as observed in obese individuals [86]. It was also found that leptin level positively correlates with total body fat, and it induces the generation of reactive oxygen species (ROS) in human endothelial cells which causes increased fatty acid oxidation in mitochondria [87]. Leptin may also exert its direct effect on gonadal cells due to the presence of its receptor isoforms [88]. Moreover, leptin has been hypothesized to have negative effect on testicular steroidogenesis by diminishing the pulse amplitude of luteinizing hormone-releasing hormone (LHRH) or LH or through the activation of its receptor present on Leydig cells [89]. In addition, stress-related pro-inflammatory cytokines produced by inflamed adipose tissue (such as IL-6 and TNF-α) and elevated serum leptin may together additionally suppress reproductive functions.

The other polypeptide ghrelin is chiefly secreted from fundus of the stomach and works through hypothalamic GnRH release [90, 91]. Under the control of LH, the presence of ghrelin was demonstrated in Leydig cells, and a positive correlation was demonstrated between ghrelin and testosterone level by Pagotto et al. [92] as the ghrelin receptors are present in testis, but do not affect spermatogenesis directly [93]. An increased ghrelin secretion may also result in increased ROS production, as observed in obese males [94].

Beside those two metabolic peptides, obesity may also alter the serum profiling of other metabolic peptides like adiponectin, obestatin, and orexins [95]. Negative correlations were reported for adiponectin to ROS and testosterone, respectively [96, 97]. Obestatin is released from specialized epithelium of the stomach and intestine and has also been detected in semen [98]. Very few works demonstrated the role of obestatin on testicular functions. It was described that intraperitoneal obestatin administration causes the increase in testosterone level significantly, besides an increase in primary and secondary spermatocytes along with Leydig cell population [99].

Visfatin is another metabolic peptide, secreted by various tissues, visceral adipocytes, and the testis [100, 101]. It mimics the insulin action by acting through insulin receptor, thus helping to lower blood glucose level and related to reduce body weight as well as testicular weight [102]. It has been found that visfatin and serum testosterone concentrations are positively correlated to each other which are supposed to enrich the male reproductive quality. Several studies explained that less expression of testicular visfatin was observed in male with T2DM [103, 104] which also supports the association of poor reproductive health in male with T2DM.

Resistin is another adipocyte-derived protein and supposed to have its multiple effects on insulin sensitivity and adipocyte differentiation [100, 101]. Resistin is expressed in Leydig cells and Sertoli cells under the regulation of gonadotropins [105]. It exerts negative effect on male reproductive functions, especially the sperm quality with higher concentrations, as seen in smokers, subjects with leukocytospermia, etc. [105, 106].

Orexins are best known as an arousal neuropeptide; it reduces ROS-induced cell damage [107, 108] and stimulates several steroidogenic enzymes in Leydig cells, thus increasing the testosterone production [109, 110] (Fig. 1).

Obesity, increased scrotal temperature, and male infertility

Spermatogenesis is known as an extremely heat-sensitive process in reproductive physiology, and 32–35 °C is considered as optimal temperature for this physiological process in human testes [111]. Production of extragonadal heat has also become a major problem among the obese individuals resulting from increased scrotal adiposity and sometimes increased suprapubic as well as increased thigh fat, etc. [64, 112]. Sedentary lifestyle, using a laptop based on the thigh, sauna, spontaneous habit of warm baths, and varicoceles may also lead to increased testicular temperature [113]. In obese men, any such conditions may lead to direct effect on spermatogenesis, occurrence of OS, or event of direct sperm cell damage besides the reduction in sperm motility [114]. These changes ultimately cause increased sperm DNA fragmentation (SDF) leading to subfertility or infertility [115, 116].

Obesity and spermatogenesis

The testis has two major functions: spermatogenesis and steroidogenesis. Spermatogenesis is a multistep process of sperm production from the primordial germ cells. It

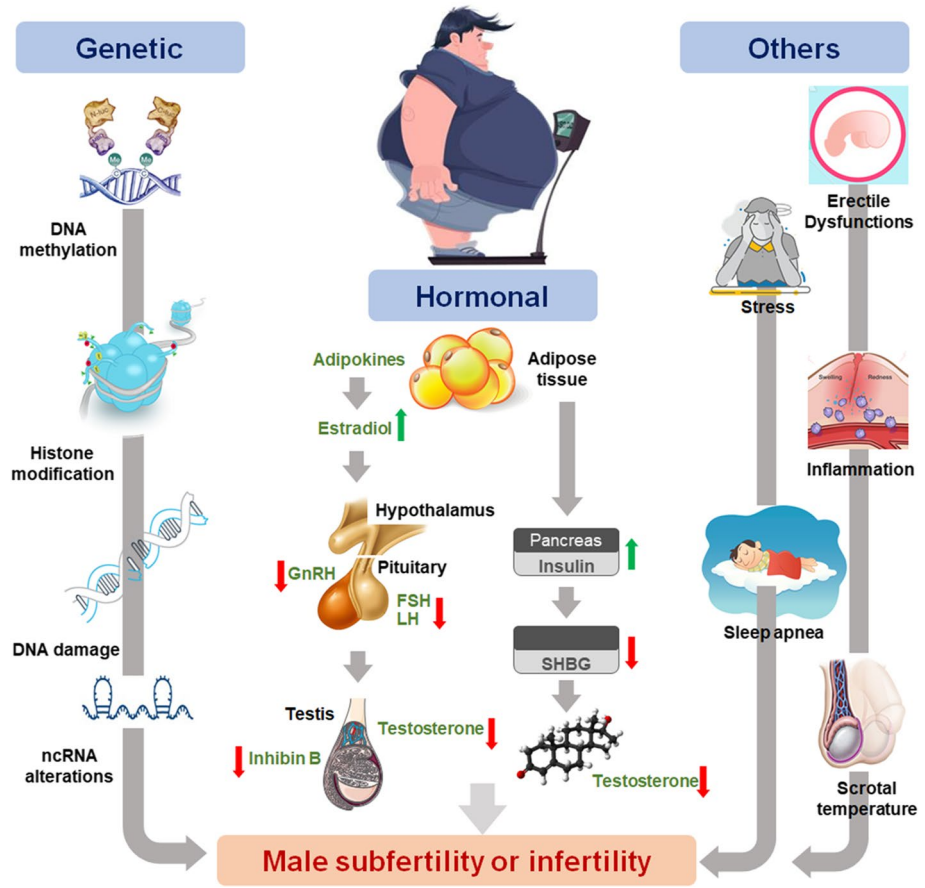

Fig. 1 Key mechanisms linking obesity and male infertility

occurs in the seminiferous tubules that contain two distinct cell populations: (a) primordial germ cells, from which spermatozoa are derived, and (b) Sertoli cells whose main function is to nourish the developing spermatozoa during spermatogenesis. Steroidogenesis is another multistep process occurs in the interstitial cells of Leydig for biosynthesis of steroid hormones from cholesterol. Sertoli cells are activated by the FSH, and Leydig cells are stimulated by LH produced by anterior pituitary. The seminiferous tubules maintain a dynamic yet steady balance between cell death and regeneration [117]. To mediate this purpose, a distinct hormonal microenvironment tightly regulates the phase of germ cell differentiation, just after the first wave of spermatogenesis. If the production of spermatogenic cells in this phase goes beyond the physiological need, they undergo apoptosis, mediated and controlled by the conventional Bcl-xL and Bax systems [118, 119]. Specific physiological or pathological conditions may stimulate spermatogonial apoptosis and are regulated by various genes. Recent research interventions found that the A1 spermatogonia undergo a significantly increased rate of apoptosis in conditions of obesity. Immoderate induction of apoptosis in spermatogenic cells can contribute to a majority of male subfertility or infertility [120]. Obesity induces spermatogonial apoptosis by increasing Bax and by decreasing Bcl-2 expressions in the testis, thereby triggering the downstream signaling caspases, especially caspase-3 [121]. Moreover, obesity incurs hyperlipidemia and lipid metabolic disorders, which elevates the stress upon endoplasmic reticulum, which further leads to spermatogenic cell apoptosis through elevated expressions of GRP78 mRNA and protein [122, 123].

Obesity and oxidative stress

Oxidative stress (OS) in obese persons may play a key role for male infertility [33]. Reactive oxygen species (ROS) can be generated due to varieties of factors like heat stress, exposure to environmental toxicants

like heavy metal or pesticides, psychological stress, chronic strenuous physical activity, alcohol consumption, smoking, high-fat and high-protein food, intake of anabolic steroids, drug-induced stress (like Marijuana), stress due to reproductive tract infections, aging, and obesity [124–128]. In spermatozoa, most abundant ROS is $O_2^{\bullet-}$ which used to produce by oxidative phosphorylation by the addition of a single electron to intracellular oxygen also been created through electron transport chain in between complex I and III located in mitochondria present in midpiece of the sperm [129]. Besides that, H_2O_2 is a well-known uncharged biochemical molecule found in the intracellular areas in the body; they can easily cross the plasma membrane and lead to initiate the peroxidative damage of membranes of germ cells. Generally, with the presence of some transitional or heavy metals (irrespective to essential or relatively harmless or toxic) such as iron (Fe^{3+}), the production of reduced ferrous iron (Fe^{2+}) will take place through the Haber-Weiss reaction by the formation of highly reactive $OH^{\bullet}$ from the $O_2^{\bullet-}$ and H_2O_2. Subsequently, through the Fenton reaction, again the Fe^{2+} is oxidized by H_2O_2 to ferric iron (Fe^{3+}) by which the OH^- and $OH^{\bullet}$ are formed. Moreover, the $O_2^{\bullet-}$ interacts with nitric oxide (NO) and produce peroxynitrite ($ONOO^-$) which subsequently triggers either apoptotic or necrotic cell death [114, 129]. During the subsequent OS, a Ca^{2+}-dependent NADPH oxidase, known as NOX5 which is found in midpiece and acrosome of human sperm, is the major producer of reactive oxygen species [129] and also leads to DNA fragmentation of sperm. The vulnerability of DNA damage is much higher in Y chromosome because of its genetic arrangements, atypical recombination events between the X and Y chromosomes or itself within the Y chromosome due to exchange of sister chromatid with unbalanced manner [130].

Obesity and semen parameters

Obesity is associated with altered semen quality in terms of concentration, motility, and morphology [131, 132] due to abnormal hormonal levels of gonads. Studies have established a dose-response relation between body mass index (BMI) and infertility, plateauing over BMI > 32–35 kg/m^2 [133]. Elevated estrogen levels in obese person can cause spermatogenic disruptions [134], and as a result of it, these hormones show an adverse effect on spermatogenesis by its feedback mechanisms [4, 11, 135]. BMI has been found to be a critical parameter for infertility (BMI $\geq$ 30 kg/m^2) [136]. In another study, BMI levels have been shown to be highest in azoospermic subjects compared to others [14]. In addition, these epidemiologic studies support the negative correlation between BMI and fertility. It includes changes in total sperm count, sperm concentration, sperm morphology, and motility having same negative correlations [16, 137]. Another study focusing on the effect of obesity on sperm parameters in men has found that as BMI increases, so does the prevalence of men with low motile sperm count (normal body weight, 4.52%; overweight, 8.93%; and obese, 13.28%). Similarly, incidence of oligozoospermia has been determined to increase with BMI (normal body weight, 5.32%; overweight, 9.52%; and obese, 15.62%) [134]. Studies have also found a negative correlation between total motile sperm count and body weight, waist, and hip circumference [2, 134].

Obesity and sperm DNA fragmentation

The association of BMI with male infertility in terms of impaired sperm quality has been described in many studies [17, 133, 138–142]. But, the effects of obesity on sperm DNA integrity need more extensive studies. Sperm DNA integrity represents the major nuclear component of spermatozoa. It is essential for normal fertilization, implantation process, pregnancy maintenance, and fetal development [143]. Besides regular semen parameters, determination of sperm DNA fragmentation (SDF) can serve as an advanced sperm function test (SFT) to assess the condition of male fertility. An array of studies have put forth the relevant concepts about SDF and several potential laboratory methods to determine the clinical value for assessing SDF in male infertility [144–147]. The American Urological Association (AUA) and European Association of Urology (EAU) have also recognized the vitality of the SDF assay for assessment of male infertility [148].

Obesity adversely affects sperm DNA integrity or causes SDF possibly by inducing OS. A reduced pregnancy rates have been portrayed in correspondence to increased SDF [146, 149]. Although there is dearth of studies, a few studies have assessed the influence of obesity on sperm DNA integrity. Kort et al. [139] showed an increase in SDF rates in obese men assessed through sperm chromatin structure assay (SCSA). Chavarro et al. [17] and Farriello et al. [150] also supported this concept. They determined sperm DNA integrity by the single-cell gel electrophoresis assay or comet assay method. LaVignera et al. [151] used TUNEL assay with flow cytometry and found that obesity negatively affects sperm DNA integrity. An another 3-year multicenter study explored the relation of increased BMI with sperm DNA integrity and showed that obesity is undeniably responsible for increased SDF [90]. In contrary, very few studies failed to find any significant relation between BMI and sperm DNA integrity [138, 152].

Altered testicular immune defense and male infertility

Excessive body weight and obesity in humans constitute an unconventional, unremitting, and low-grade inflammatory state [64, 153]. It is frequently accompanied with chronic inflammation over the whole body and is always associated with symptoms that arise from metabolic and vascular alterations [154]. The increase of adipose tissue causes enhanced secretion of pro-inflammatory hormones and cytokines into the circulation (adipokines), originating from adipocytes and from macrophages that are recruited and infiltrate the expanding adipose tissue [155, 156]. These pro-inflammatory adipokines activate the acute phase reaction and progressively impose a generalized chronic inflammatory stress on the body [100, 157]. Importantly, two of the main pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are secreted in significant quantities by the enlarging adipose tissue, especially in visceral obesity. In addition to their immunomodulating effects, TNF-α and IL-6 directly stimulate the HPA axis, central stimulation of cortisol secretion, suppression of thyroid stimulating hormone (TSH), and testosterone secretion, which in turn favors visceral fat accumulation and dysfunction of the HPG axis [158–163]. Increases in pro-inflammatory cytokine levels can impair male fertility via inducing germ cell apoptosis, disrupting Sertoli cell junctions, directly impairing spermatogenesis, and compromising testicular blood-testis barrier (BTB) integrity [154]. Such effects eventually adversely impair the biological functions of mature gametes.

Obesity can induce testicular inflammation through activating several different signaling pathways. Increased secretion of leptin (pro-inflammatory properties) and decreased secretion of adiponectin (anti-inflammatory properties), an adipose tissue-derived hormones, can enhance the imposed inflammatory load in obesity [164–168]. A prolonged high-fat diet could lead to increases in NLRP3 inflammasome and pro-inflammatory cytokine expression level such as IL-6 and TNF-α in the testis, epididymal caput, epididymal cauda, prostate, and seminal vesicle [154]. In order to verify the correlation between being overweight or obese and sperm parameters as well as pro-inflammatory cytokine levels in semen plasma, researchers collected semen samples from 272 donors, including 82 normal weight, 150 overweight, and 40 obese individuals, respectively. They found that both overweight and obese males were associated with low sperm counts and decline in sperm motility. Moreover, the concentrations of IL-6 and TNF-α significantly increased in the semen plasma of obese or overweight males than normal body weight individuals [166]. These observations demonstrated that obesity or overweight can indeed upregulate cytokine concentrations in the male genital tract and impair sperm quality.

Recently, a mechanism of escape of spermatozoa antigen toward the lumen of the spermatic tubuli during spermiation has been described, which participates in the preservation of local immunity [169]. For completion of spermatozoa maturation process, pre-leptotene and leptotene spermatocytes residing in seminiferous epithelium need to pass through the blood-testis barrier at stage-VIII of spermatogenesis [170].

Inflammation of the testis causes infiltration of leukocytes which subsequently releases ROS. The resulting oxidative imbalance is responsible for peroxidation of the spermatozoa's membrane, affecting the fertilizing potential [114, 171]. Literature suggests that redox imbalance has a role in inducing defective spermatogenesis in varicocele cases [25]. Even in varicocele cases with a normal spermiogram, seminal plasma shows excessive OS. Varicocelectomy, a therapeutic manipulation, reduces OS in seminal plasma, thus ameliorating DNA damage [172].

Obesity and erectile dysfunction

Erectile dysfunction (ED) is an inability to develop a sufficient penile erection that leads to reduced frequency of satisfactory sexual intercourse. Its pathophysiology involves a complex crosstalk of psychological, neuromuscular, endocrinological, and vascular factors along with their correlations with several lifestyle habits like cigarette smoking and alcohol consumption and sometime due to some drug side effects. It is well known to all that the increase in penile length and diameter during the sexual arousal is due to production of NO with the help of nitric oxide synthase (NOS) via the non-adrenergic non-cholinergic (NANC) activity. This NO induces the smooth muscle relaxation and vasodilation followed by penile erection [173]. Thus, for the sufficient erection, both NOS and NO both necessary, and for NOS activity, NANC must be active. However, a recent study reported weak cholinergic response and altered autonomic activity in obese rat with peripheral insulin resistance [174, 175]. Importantly, male infertility due to ED shows a positive correlation with increased BMI and waist circumference [176]. In addition to age, ED is associated with obesity and metabolic syndrome by considering it as a risk factor for cardiovascular disease, type-II diabetes mellitus (T2DM), hyperinsulinemia, and hyperleptinemia [159, 177]. OS is also associated with ED-related infertility in male [114] which is common in obesity. In comparison with normal BMI group, obese male (BMI > 28.7 Kg/m^2) shows a 30% higher risk of ED [178], and thus, obesity was also appeared as an potent inhibitor of the major enzyme phosphodiesterase-5 which is used as well-known agent for the treatment of ED [179]. Probably due to formation

of ROS in endothelial cells during clinical obesity or disorders like metabolic syndrome, it mediates TNF-α activity which causes lesser production of NOS followed by NO resulting vasoconstriction in penile structure [180]. Thus, any cause related to endothelial dysfunction will be the common cause for the erectile dysfunction and which also includes arteriolosclerosis and fibrous tissue resulting in altered to and from blood flow in the penis as they affect the vasculature of the penis [113, 181].

Conclusions

Obese men possess heavy adipose tissues depot, which home several toxins, adipokines, and other hormones (adiponectin, leptin, ghrelin, orexin, obestatin, etc.). High adipose tissue accumulation also leads to increased scrotal temperature, sleep apnea, systemic inflammation, and OS. Obesity-mediated systemic disbalance in metabolism and metabolic hormones affects the HPG regulatory axis and may also directly affect the testicular cells, thereby disrupting the normal functions of the testes. It has also been discussed that obesity can potentially influence the genetic and epigenetic processes in the spermatozoa; even children born to obese parents can possess altered sperm epigenetics compared to those born to nonobese parents. Moreover, male obesity has great influences over the assisted reproductive techniques (ARTs) outcome, and this area needs more research attention to bring to surface newer technology mainly for sperm retrieval and selection from obese men. Thus, the complex mechanism and updated evidence-based hypotheses of obesity-mediated male infertility or subfertility will benefit the reader for better understanding the concepts and will encourage further in-depth research interventions in this field.

Abbreviations

AGTR-1: Angiotensin type-1 receptor; ART: Assisted reproductive technology; BMI: Body mass index; BTB: Blood-testis barrier; ED: Erectile dysfunction; FSH: Follicle stimulating hormone; HPA: Hypothalamopituitary adrenal axis; HPG: Hypothalamopituitary gonadal axis; IL: Interleukin; LH: Luteinizing hormone; MR: Mineralocorticoid receptor; NANC: Non-adrenergic non-cholinergic; NAFLD: Nonalcoholic fatty liver disease; NLRP3: NLR family pyrin domain containing 3; NOS: Nitric oxide synthase; OS: Oxidative stress; PCOS: Polycystic ovarian syndrome; ROS: Reactive oxygen species; SAT: Subcutaneous adipose tissue; SDF: Sperm DNA fragmentation; SFT: Sperm function test; SHBG: Steroid hormone-binding globulin; T2DM: Type 2 diabetes mellitus; TGF: Transforming growth factor; TLR: Toll-like receptor; TNF: Tumor necrosis factor; TSH: Thyroid-stimulating hormone; VAT: Visceral adipose tissue; WHO: World Health Organization.

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Authors' contributions

PS, SD, and KB designed and planned the research. GRC, AD, SBK, KB, SD, PS, and AKS wrote the article and made the final revisions. The last corrections and adjustments have been made by PS and SD. All authors have read and approved the manuscript.

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