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REVIEW

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Metabolic–endocrine and epigenetic mechanisms linking obesity to male infertility: a narrative review

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Abstract

Obesity is a globally prevalent chronic condition and a well-recognized metabolic disorder associated with systemic metabolic dysregulation and various diseases. In recent years, growing evidence suggests that obesity also plays a significant role in male reproductive dysfunction. This narrative review was based on a targeted literature search primarily conducted in PubMed using combinations of keywords. Priority was given to recent high-quality clinical and experimental studies, and seminal earlier studies and additional relevant references from key articles were also included. Current evidence indicates that obesity impairs male reproductive health through multiple interconnected mechanisms, including adipokine dysregulation, chronic inflammation, insulin resistance, endocrine imbalance, impaired spermatogenesis, and sperm epigenetic remodeling. However, findings regarding paternal obesity and assisted reproductive technology (ART) outcomes remain inconsistent, although some studies suggest potential associations with adverse offspring outcomes. Lifestyle modification and pharmacological interventions can partially improve obesity-associated reproductive impairment, underscoring male obesity as a modifiable risk factor. In summary, by integrating metabolic, endocrine, and epigenetic perspectives, this review provides a mechanistic framework to better understand obesity-related male infertility and to inform future clinical and translational research.

Keywords

Obesity; Male fertility; Sperm epigenetics; Endocrine dysfunction

1. Introduction

Obesity is a globally prevalent chronic metabolic disorder and has escalated into a major public health concern over recent decades. According to the World Health Organization (WHO), the prevalence of obesity continues to rise globally, which contributes significantly to the burden of cardiovascular diseases, type 2 diabetes mellitus (T2DM), and various cancers [1]. Since 1975, the global prevalence of obesity has nearly tripled, and it is expected to reach 1.02 billion adults (18% of the population) by 2030 [2].

In parallel, a notable global decline in male fertility has been documented, with studies reporting reduced sperm counts and impaired semen quality [3], and increased dependence on assisted reproductive technologies (ART) [4]. This downward trend has prompted increasing attention to modifiable risk factors, such as obesity. Mechanistically, obesity-induced hormonal imbalance [5–7], inflammation, and oxidative stress may jointly disrupt the hypothalamic–pituitary–testicular (HPT) axis and impair spermatogenesis [8, 9].

Beyond these direct effects, recent studies have highlighted the potential for transgenerational consequences of paternal obesity via epigenetic modifications in sperm [8, 10–12]. At the molecular level, paternal obesity has been shown to reduce chromatin accessibility and alter the histone landscape in sperm, potentially affecting offspring metabolic and reproductive outcomes [11, 12]. While some studies have examined the association between paternal obesity and ART success, the relationship remains inconclusive, likely due to heterogeneous methodologies and inconsistent definitions of obesity [13, 14].

Despite these advances, existing research remains fragmented. Most studies focus on isolated mechanisms or clinical endpoints without integrating molecular, clinical, and intergenerational perspectives. Additionally, there is no consensus on how to assess obesity effectively in reproductive studies, many rely solely on body mass index (BMI), which may not fully capture central adiposity or metabolic dysfunction. Moreover, while animal studies support the role of epigenetic inheritance, human data remain sparse and largely observational.

In this narrative review, we conducted a targeted literature search to synthesize recent experimental and clinical evidence on the multifaceted effects of obesity on male reproductive function. Unlike previous reviews that focus on isolated clinical or metabolic outcomes, this review integrates endocrine dysregulation, sperm epigenetic remodeling, and potential in-

tergenerational effects to provide a comprehensive mechanistic framework linking obesity to male infertility.

2. Literature search strategy

This narrative review was based on a targeted literature search primarily conducted in PubMed. The search focused on studies related to obesity and male reproductive dysfunction using combinations of keywords derived from the core topics of this review, including "obesity", "male infertility", "sperm epigenetics", and "endocrine dysfunction".

Priority was given to recent high-quality studies published in peer-reviewed journals, including clinical studies, experimental studies, and influential review articles. Seminal earlier studies were also included when relevant. Additional references were identified by screening the reference lists of key publications to ensure comprehensive coverage of important studies in this field.

3. Definitions and diagnoses of obesity

Obesity is the excessive accumulation of fat in various parts of the body or organs [15]. According to WHO, obesity is defined as a BMI $\geq$30 kg/m^2 (http://www.who.int). However, it is important to consider that BMI is only useful as a screening tool because it is not a direct measure of adiposity. Therefore, as a complementary criterion to BMI, assessment of Waist Circumference (WC) is helpful for evaluating cardiometabolic disease risk [16].

WHtR (Waist-to-Height Ratio) and WHT-5R (WC divided by height$^{0.5}$) are two anthropometric predictors of fat distribution. WHtR has been shown to be a better surrogate measure of body adiposity compared with other anthropometric indexes in adults, adolescents, and children [17]. For WHT-5R, it has been proposed as a suitable index for screening for metabolic disease [18].

Advanced imaging methods, such as dual X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI), can accurately assess fat mass and distribution [19, 20], but high costs of advanced imaging methods limit routine use [21]. In contrast, bioelectrical impedance analysis (BIA) and digital anthropometry provide quick, noninvasive, and affordable alternatives [22], while three-dimensional (3D) optical and two-dimensional (2D) photographic systems offer precise digital assessments of body composition [23].

In summary, although BMI is still widely used as an easy, quick, low-cost, and reproducible method, BMI alone is insufficient to evaluate obesity and body composition. Therefore, clinical practice recommends combining WC, WHtR, and more precise body composition analysis methods to improve the accuracy and effectiveness of obesity diagnosis and management.

4. Global burden of high BMI

High BMI has increasingly become a significant public health risk factor, contributing to a growing burden of disease worldwide. It accounts for 129 million Disability-Adjusted Life Years (DALYs) and is responsible for 3.7 million deaths globally, ranking as the seventh leading risk factor for attributable DALYs [24]. Apart from increasing the incidence of various chronic diseases, high BMI also imposes a substantial burden on healthcare systems, underscoring the urgent need for effective prevention and management strategies at a global level.

The burden of diseases linked to high BMI is primarily driven by non-communicable diseases (NCDs), notably diabetes, nephrological, and cardiovascular diseases [24]. Although a direct relationship between high BMI and male reproductive health is not well established, these metabolic comorbidities are strongly associated with impaired reproductive function [25–27].

From 2010 to 2021, DALYs related to high BMI increased by 44.6%, and its ranking raised from eighth in 2010 to seventh in 2021, reflecting the growing severity of overweight and obesity issues worldwide [28]. Interestingly, DALYs caused by high BMI are slightly higher in men than in women [29]. Given the growing global burden, understanding how obesity impacts male reproductive health is increasingly important.

5. Consequences of obesity on male reproductive health

5.1 Obesity as a metabolic disorder: pathophysiological insights

Metabolic homeostasis plays a crucial role in reproductive health, yet obesity undermines this equilibrium through multiple mechanisms [30]. Obesity disrupts metabolic homeostasis through adipokine dysregulation, chronic inflammation, and insulin resistance, which may directly impair sperm function and the testicular microenvironment [4, 31].

Adiponectin is negatively associated with body fat mass and positively associated with total sperm count, sperm concentration, as well as the percentage of spermatozoa with normal morphology [32, 33]. In addition, adiponectin can enhance insulin sensitivity, regulate food intake, and exert anti-inflammatory effects [34]. Individuals with obesity have increased leptin levels and leptin resistance, which in turn affects sperm motility and sperm morphology [35]. Resistin and irisin are negatively correlated with BMI and are suggested to exert anti-inflammatory effects [32, 36].

Chemerin has emerged as a metabolically relevant adipokine that may contribute to obesity-related male reproductive dysfunction [37, 38]. An observational study (n = 4101) demonstrated that circulating chemerin levels were positively associated with BMI, WC, and WHtR [39]. Chemerin is mainly secreted by the liver and is found to reduce sperm count and motility *in vitro* in roosters [40]. In clinical studies of obese men, altered circulating or seminal levels of chemerin/adipokine profiles have been associated with poorer reproductive hormone balance and/or semen quality [41].

Obesity-induced chronic inflammation directly impairs male reproductive function. Obesity-induced inflammation is an important pathogenic mediator of many metabolic diseases, including insulin resistance, T2DM, and cardiovascular diseases [42–44]. Clinical evidence indicates that obese men exhibit increased tumor necrosis factor alpha (TNF-

α) and Interleukin-6 (IL-6) levels in seminal plasma, and these cytokines are positively correlated with BMI, but inversely correlated with sperm concentration and motility [45]. Experimental studies further show that obesity-induced inflammation disrupts Sertoli-cell function, increasing reactive oxygen species (ROS) production, and promoting blood-testis barrier injury, thereby impairing spermatogenesis [46]. In addition, obesity-associated activation of the proprotein convertase subtilisin/kexin type 9–NLR family pyrin domain containing 3 (PCSK9–NLRP3) inflammasome in Leydig cells has been shown to reduce testosterone production and disrupt spermatogenesis in high-fat-diet mice [47].

Additionally, insulin resistance may directly impair male reproductive function. In a rat model, diet-induced hyperinsulinemia and insulin resistance were accompanied by reduced sperm motility, and decreased testosterone levels [48]. In obese men, increased serum and seminal insulin concentrations have been reported together with reduced sperm concentration, lower sperm vitality, and increased sperm DNA fragmentation [49]. Moreover, homeostatic model assessment of insulin resistance (HOMA-IR) has been negatively correlated with serum testosterone, semen volume, and the percentage of progressively motile sperm. These findings support a direct association of obesity-related insulin resistance with impaired sperm quality and a less favorable testicular endocrine environment for spermatogenesis.

Together, these findings indicate that adipokine imbalance, chronic inflammation, and insulin resistance are direct metabolic mechanisms linking obesity to impaired spermatogenesis, sperm dysfunction, and testicular microenvironmental injury.

5.2 Obesity and HPT axis

The HPT axis regulates the spermatogenesis in the testis and synthesis of testosterone in humans and animals [50, 51]. Concerning gonadotropin-releasing hormone (GnRH) secretion, KNDy (kisspeptin/neurokinin B/dynorphin A) is considered as a crucial regulator and is co-secreted by neurons of the hypothalamus [52]. GnRH in turn stimulates pituitary secretion of gonadotropins, including follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [52, 53]. FSH and LH act on specific gonadal cells to stimulate the secretion of testosterone, estrogen, and gametogenesis. Testosterone is an important anabolic hormone, circulating as albumin-bound or sex hormone-binding globulin-bound (SHBG), while only a minor fraction is free and bioactive [54].

FSH primarily acts to stimulate testicular Sertoli cell function. These cells promote spermatogenesis, as each cell is able to support the maturation of 2–4 germ cells on average [55]. Testosterone has a synergistic effect with the FSH to support spermatogenesis [56]. FSH supports germ cells until the stage of spermatocyte, while it synergistically supports spermatids to differentiate into spermatozoa together with intratubular testosterone [57]. LH triggers the testosterone synthesis in Leydig cells, and the proliferation of Leydig cells depends on FSH [58, 59]. LH beta-null male mice are reported to be infertile, combined with defects in Leydig cells and suppression of testosterone level [60]. Circulating sex hormone concentrations, metabolic disorders, and environmental factors directly or indirectly regulate the HPT axis.

Regarding the effects of increased body weight on serum steroid hormone levels, a recent systematic review concludes that obesity is negatively correlated with total testosterone and SHBG levels, while positively correlated with estrogen levels [61]. These hormonal changes are partly attributable to the excessive conversion of testosterone into 17 beta-estradiol by adipocytes [62]. Elevated 17β-estradiol may further modulate the expression of the kisspeptin gene, which regulates pulsatile GnRH secretion to inhibit the HPT axis [63, 64].

Beyond this aromatase-dependent mechanism, obesity-related metabolic disturbances likely act upstream of endocrine dysfunction, rather than representing an independent parallel pathway. Hyperleptinemia accompanied by leptin resistance may impair hypothalamic kisspeptin/GnRH signaling [65, 66], whereas insulin resistance is closely linked to suppression of the HPT axis and low-testosterone states [67, 68]. In addition, chronic low-grade inflammation may impair Leydig-cell steroidogenesis through pro-inflammatory cytokines [69]. Adipokine imbalance may further contribute to this process: beyond leptin excess, experimental studies suggest that adiponectin signaling can modulate hypothalamic GnRH/KiSS-1 metastasis suppressor (KISS1) activity and pituitary LH release [70–72].

5.3 Obesity and testicular dysfunction

Due to the excess aromatase activity in many men with obesity, obese males often present with functional hypogonadism [62]. It is characterized by inappropriately normal levels of gonadotropins despite low testosterone levels [73]. Combined with the inhibition of SHBG on testosterone function, the lower level and lower activity of circulating testosterone facilitate the accumulation of body fat. Thus, a vicious circle of obesity, low testosterone levels, and hypogonadism is formed. Due to its inhibitory effect on testicular function, aromatase inhibitors have been used in hypogonadism treatment.

A recent observational study investigating the relationship between BMI and erectile dysfunction (ED) risk found that obese individuals had a 1.3-fold greater risk of ED than normal-weight individuals [74]. This association suggests that metabolic abnormalities accompanying obesity, such as insulin resistance and hyperglycemia, may play a pivotal role in the pathophysiology of erectile dysfunction.

Hyperglycemia triggers a cascade of cellular events that increases the production of ROS and oxygen-derived free radicals, contributing to increased oxidative stress. Additionally, hyperglycemia can lead to the glycation of penile cavernosal tissue, compromising collagen production and potentially contributing to ED [75]. Hyperglycemia, along with obesity interfering steroidogenesis in Leydig cells by proinflammatory cytokines, like IL-1β, IL-6 and TNF-α, can lead to ED [76]. Testosterone supplementations are encouraged by European Society of Endocrinology to improve erectile function [77].

It is noted that the prevalence of obesity has coincided with a steady decline in sperm quality worldwide, particularly in sperm counts over the past 50 years [3, 78, 79]. Obesity is also associated with a pro-inflammatory environment derived from

adipose tissue that is likely detrimental to sperm function and spermatogenesis [80, 81]. Obesity-associated co-morbidities, such as metabolic syndrome and increased scrotal temperature in case of increased abdominal adiposity, are amongst other causal mechanisms impacting the male reproductive axis and semen parameters [82–85].

5.4 Obesity and sperm epigenetics

Beyond hormonal mechanisms, obesity can exert heritable effects via sperm epigenetic reprogramming. Animal studies have shown that paternal obesity impaired the structure of testicular seminiferous tubules and reduced the number of epididymal sperm in offspring [86, 87]. These findings highlight the importance of further investigating the underlying mechanisms.

Insulin resistance and inflammation should be considered an upstream metabolic disturbance linked to sperm epigenetic remodeling. Sperm from obese men with abnormal glucose metabolism exhibit altered small non-coding RNA expression and DNA methylation patterns, and these methylation signatures can be dynamically remodeled after substantial weight loss [88]. Experimental studies further show that paternal high-fat diet induces impaired glucose tolerance and insulin tolerance, together with altered sperm tsRNA profiles [89]. Moreover, paternal obesity has been associated with changes in sperm histone H3 lysine 4 trimethylation (H3K4me3) enrichment at loci related to metabolic and developmental regulation [9]. In parallel, inflammation appears to be one of the mediating pathways, as paternal inflammation has been shown to alter sperm 5′-tsRNAs, whereas anti-inflammatory treatment in high-fat-fed sires reduces specific sperm tsRNAs and partially improves offspring metabolic phenotypes [90, 91].

There is mounting evidence that obesity in males is associated with altered sperm DNA methylation and may contribute to offspring phenotypes [92, 93]. A human study in Germany collected sperm from 294 participants at the Fertility Center Wiesbaden, fetal cord blood samples were successfully obtained from 103 pregnancies resulting in live births after ART [94]. In this study, maternally expressed gene 3-intergenic (*MEG3*-IG) differentially methylated region (DMR), sperm DNA methylation, and *MEG3*-IG DMR cord blood DNA methylation in male offspring showed a positive correlation with male BMI [94]. Hypoxia inducible factor 3 subunit alpha (*HIF3A*) cord blood DNA methylation in male offspring showed a positive correlation with the paternal BMI, while insulin-like growth factor 2 (*IGF2*) DMR0 in female offspring showed a negative correlation with the paternal BMI [94]. Another study investigated 67 men and found that overweight/obese individuals had differences in mature spermatozoa DNA methylation profiles. They identified 3264 cytosine-phosphate-guanine (*CpG*) sites in human sperm that correlated significantly with BMI [95].

As a subtype of sncRNA, tRNA-derived small RNAs (tsRNAs) are known to be abundant in mammalian sperm, including humans [96]. Human sperm are acutely sensitive to nutrient flux, both in respect of sperm motility and changes in sperm tsRNA (primarily from mitochondrial origin: mt-tRNAs), and a 1-week sugar-rich dietary intervention was shown to increase mitochondrial tsRNAs while reducing sperm motility [97]. In mice, acute paternal HFD-feeding leads to impaired glucose homeostasis in male offspring via mt-tRNAs [98]. Mechanistically, increased accumulation of mt-tRNAs is transcribed and fragmented in mature spermatozoa, which can be transferred to the oocyte at fertilization and results in early altered transcription of genes important for oxidative metabolism, shown to predispose to adult-onset glucose intolerance [98].

Regarding the sperm proteome, a recent study identified 2034 proteins by analyzing sperm samples from healthy (BMI $\leq$25 kg/m^2, n = 5) and obese men (BMI $\geq$30 kg/m^2, n = 5) using liquid chromatography-tandem mass spectrometry (LC-MS/MS) [99]. They found significantly altered abundances in 27 of those proteins, which are involved in a variety of biological processes, including oxidative stress (glutathione synthetase, GSS; NADH:ubiquinone oxidoreductase core subunit S2, NDUFS2; jagunal homolog 1, JAGN1), inflammation (suppressor of G2 allele of skp1 homolog 1, SUGT1; leukotriene A4 hydrolase, LTA4H), translation (eukaryotic translation initiation factor 3 subunit F, EIF3F; eukaryotic translation initiation factor 4A2, EIF4A2; casein kinase 1 gamma 1, CSNK1G1), DNA damage repair (ubiquitin protein ligase E3A 4, UBEA4), and sperm function (N-ethylmaleimide-sensitive factor attachment protein alpha, NAPA; arginyl aminopeptidase, RNPEP; barrier-to-autointegration factor 2, BANF2) [99]. In addition, a prospective study performed seminal plasma proteomic analysis in eutrophic (BMI 18.5–24.9 kg/m^2, n = 20) and obese men (BMI $\geq$30 kg/m^2, n = 27), and identified 69 differentially expressed proteins between the two groups [100]. Importantly, these proteomic alterations were accompanied by impaired sperm morphology, reduced acrosome integrity, decreased mitochondrial activity, and increased sperm DNA fragmentation in the obese group [100]. It has been demonstrated that sperm telomere length (STL) is significantly shorter in obese individuals (n = 32) compared to normal-weight controls [101]. And this telomere shortening turns out to be correlated negatively with age, BMI, DNA fragmentation index (DFI), the percentage of sperm with immature chromatin, and intracellular reactive ROS levels [101].

In summary, the impact of paternal obesity is not limited to the individuals themselves, but may also be transmitted to offspring through epigenetic modifications in sperm. Therefore, further elucidation of the sperm epigenetic mechanisms involved in the transgenerational inheritance of obesity is of great significance for understanding hereditary risks associated with obesity and guiding clinical preventive strategies.

5.5 Clinical implications and interventions

Given the adverse effects of obesity on sperm parameters and testicular function, increasing attention has been paid to its potential impact on ART outcomes. A largely retrospective cohort study in China (n = 11,191) assessed the effect of female and male overweight/obesity on In Vitro Fertilization (IVF) outcomes individually and in combination. Although

the combined overweight/obesity was associated with fewer available and high-quality embryos, as well as lower fertilization and normal fertilization rates, no significant association was observed between male overweight/obesity alone and clinical pregnancy rate (CPR), live birth rate (LBR), or abortion rate [102]. Similar results are reported in a more recent retrospective cohort study of 2075 oligozoospermia and/or asthenospermia males in which obesity was not associated with fertilization, *in vitro* embryonic development, and pregnancy outcomes [103]. However, they show that paternal BMI is positively correlated with macrosomia, large for gestational age (LGA), and very LGA [103].

However, the reported effects of paternal obesity on ART outcomes remain inconsistent. In a recent observational study, infertile individuals (n = 296) were categorized into three groups by WC [104]. They found that males with a WC larger than 100.5 cm had a 33.5% lower total sperm count than males with a WC of 90 cm [104]. Additionally, WC is negatively correlated with the probabilities of implantation, clinical pregnancy, and live birth rate during ART treatment [104]. However, when using BIA and BMI as adiposity measurement metrics, paternal obesity shows no meaningful impact on embryologic or clinical results on IVF (including blastocyst formation rates, miscarriage rates, sustained implantation rates, and live birth rates) [105]. These conflicting findings may partly reflect methodological heterogeneity across studies, particularly differences in obesity assessment, sample size, patient selection, and study design [13, 103, 106].

A prior systematic review and meta-analysis of 30 studies and 115,158 participants has indicated that obese men are more likely to experience infertility than their nonobese counterparts [107]. A major challenge of obesity treatment is weight regain after weight loss. This has prompted increasing interest in whether effective weight-loss interventions can also improve male reproductive outcomes.

Recently, a randomized, head-to-head, placebo-controlled trial was designed and enrolled obese adults whose BMI was 32–43 (did not have diabetes) [108]. These adults (n = 195) underwent an 8-week low-calorie diet and had a mean decrease of 13.1 kg in body weight [108]. After that, participants were randomly assigned for 1 year to one of four strategies: placebo plus habitual activity (placebo), exercise training plus placebo (exercise), the Glucagon Like Peptide 1 (GLP-1) analogue liraglutide plus usual activity (liraglutide), exercise training plus liraglutide (combination) [108]. In the first year, all the active-treatment strategies led to a decreased body weight and body-fat percentage, and additional health benefits, such as improvements in the insulin sensitivity, glycated hemoglobin level, cardiorespiratory fitness, emotional well-being, and physical functioning were found in combination group [108]. Further research in semen parameters indicates that adult men who delivered semen samples (n = 56, aged 18–65) lost on average 16.5 kg body weight during the 8-week low-calorie diet, which increased sperm concentration 1.49-fold and sperm count 1.41-fold [20]. Moreover, these improvements in men who maintained the weight loss were maintained for 1 year, but not in men who regained weight [20].

Although clinical management of obesity remains challenging, exercise combined with weight-loss medications may be an effective treatment for weight loss and has potential benefits for obesity-related reproductive disorders. To visually summarize the multifactorial mechanisms linked to obesity in male infertility and highlight potential intervention targets, an integrated mechanistic framework is presented in Fig. 1.

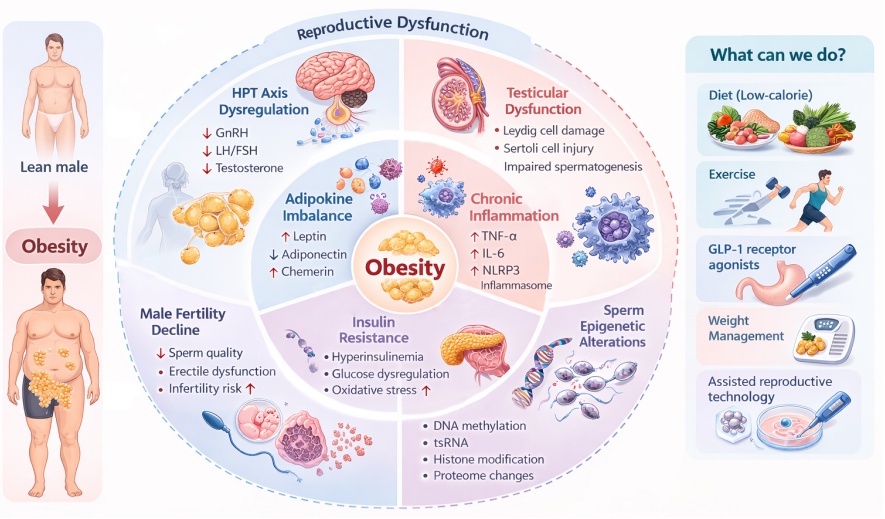

FIGURE 1. Integrated metabolic-endocrine-epigenetic framework linking obesity and male infertility and potential interventions. Obesity induces interconnected metabolic disturbances including adipokine dysregulation, chronic inflammation, and insulin resistance (inner circle). These upstream mechanisms disrupt the hypothalamic–pituitary–testicular axis, impair testicular function, and induce sperm epigenetic alterations, ultimately contributing to male infertility (outer circle). Lifestyle interventions, pharmacological treatments, and assisted reproductive technologies may partially mitigate these effects. GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; GLP-1: Glucagon Like Peptide 1; TNF-α: tumor necrosis factor alpha; IL-6: Interleukin-6; NLRP3: NLR family pyrin domain containing 3.

6. Strengths and limitations

This review provides a comprehensive overview of the multifaceted impact of obesity on male reproductive health, encompassing key mechanisms, such as endocrine disruption, inflammatory responses, adipokine regulation, and epigenetic alterations. It highlights both the direct and transgenerational effects of obesity on fertility. Moreover, the review emphasizes the clinical relevance of body composition assessment tools beyond BMI, as well as the value of lifestyle interventions, offering theoretical support for future research and clinical strategies.

The included studies vary considerably in design, population characteristics, and methods of obesity assessment, which limits the comparability and generalizability of the conclusions. In addition, much of the mechanistic evidence is derived from animal or *in vitro* studies, and clinical validation remains insufficient. Research on ART outcomes and long-term offspring health in the context of male obesity is still limited. As a narrative review, there is also an inherent risk of selection bias in the literature included.

7. Conclusions

Obesity is increasingly recognized as a multifactorial metabolic disorder that negatively impacts male reproductive health. Current evidence suggests that obesity impairs the HPT axis, disrupts steroid hormone balance, and interferes with spermatogenesis and sperm function through interconnected mechanisms involving adipokine dysregulation, chronic inflammation, insulin resistance. In addition, obesity may exert potential transgenerational effects through sperm epigenetic alterations, including changes in DNA methylation, small non-coding RNAs, and chromatin-related markers.

Although the association between male obesity and ART outcomes remains inconsistent, obesity should still be regarded as an important and modifiable risk factor in reproductive medicine. Future studies should adopt more comprehensive measures of adiposity beyond BMI and further clarify the integrated metabolic, endocrine, inflammatory, and epigenetic pathways linking obesity to male infertility. In clinical management, attention should be paid not only to weight reduction and metabolic improvement, but also to the potential reproductive and transgenerational consequences of obesity. A better understanding of these mechanisms may help refine prevention strategies and improve reproductive outcomes for affected individuals and future generations.

ABBREVIATIONS

2D, two-dimensional; 3D, three-dimensional; ART, assisted reproductive technology; BANF2, BANF family member 2; BIA, Bioelectrical Impedance Analysis; BMI, Body Mass Index; CpG, cytosine-phosphate-guanine; CPR, Clinical Pregnancy Rate; CSNK1G1, casein kinase 1 gamma 1; CT, computed tomography; DALYs, Disability-Adjusted Life Years; DFI, DNA Fragmentation Index; DMR, differentially methylated region; DXA, Dual X-ray Absorptiometry; ED, Erectile Dysfunction; EIF3F, eukaryotic translation initiation factor 3 subunit F; EIF4A2, eukaryotic translation initiation factor 4A2; FSH, Follicle-Stimulating Hormone; GLP-1, Glucagon Like Peptide 1; GnRH, Gonadotropin-Releasing Hormone; GSS, glutathione synthetase; H3K4me3, histone H3 lysine 4 trimethylation; HIF3A, hypoxia inducible factor 3 subunit alpha; HOMA-IR, homeostatic model assessment of insulin resistance; HPT axis, Hypothalamic–Pituitary–Testicular Axis; IGF2, insulin-like growth factor 2; IL-6, Interleukin-6; IVF, In Vitro Fertilization; JAGN1, jagunal homolog 1; KISS1, KiSS-1 metastasis suppressor; KNDy, kisspeptin/neurokinin B/dynorphin; LBR, live birth rate; LC-MS/MS, liquid chromatography–tandem mass spectrometry; LGA, large for gestational age; LH, Luteinizing Hormone; LTA4H, leukotriene A4 hydrolase; MEG3-IG, MEG3 intergenic differentially methylated region; MRI, Magnetic Resonance Imaging; NAPA, NSF attachment protein alpha; NCDs, non-communicable diseases; NDUFS2, NADH, ubiquinone oxidoreductase core subunit S2; PCSK9–NLRP3, proprotein convertase subtilisin/kexin type 9–NLR family pyrin domain containing 3; ROS, reactive oxygen species; RNPEP, arginyl aminopeptidase; SHBG, Sex Hormone-Binding Globulin; STL, Sperm Telomere Length; SUGT1, SGT1 assembly cochaperone of MIS12 kinetochore complex; T2DM, Type 2 Diabetes Mellitus; TNF-α, tumor necrosis factor alpha; tsRNA, tRNA-derived Small RNA; UBEA4, ubiquitination factor E4A; WC, Waist Circumference; WHO, World Health Organization; WHtR, Waist-to-Height Ratio.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

GQZ—drafted and revised the manuscript. MH—communicated with the journal and editorial office during the submission process. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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