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Review

Advances in Understanding the Mechanisms of Oxidative Stress in Infertile Obese Men

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Abstract

Obesity-related male infertility has emerged as a significant global health concern, impacting both reproductive ability and overall well-being in men. A critical factor in the pathogenesis of infertility among obese men is oxidative stress, which not only affects reproductive hormone levels, sperm quality, and the function of reproductive organs but also potentially worsens infertility through mechanisms such as inducing inflammatory responses and promoting cell apoptosis. Although there has been some progress in understanding how oxidative stress contributes to obesity-related male infertility, further investigations into its specific biological mechanisms and potential intervention strategies are needed. The aim of this review was to synthesize recent research advances on oxidative stress in the context of obesity-related male infertility, thereby providing a foundation for the development of new therapeutic approaches.

Keywords: oxidative stress; obesity; male infertility; hormones; semen analysis

1. Introduction

The global prevalence of obesity among both men and women is increasing, significantly impacting chronic health and medical comorbidities. Obesity has emerged as a major public health concern worldwide, with the incidence of obesity among adult men increasing from 4.8% in 1990 to 14% in 2022 [1]. Additionally, awareness of the effects of obesity on reproductive health has increased. Obesity is linked to diminished male fertility through a complex and multifaceted etiology. In addition to its associations with metabolic and cardiovascular diseases, sleep apnea syndrome, and various other chronic conditions [2], as well as thromboembolic events and cancer [3,4], obesity adversely affects semen quality and reproductive hormone levels [5,6], resulting in compromised male reproductive function. Studies estimate that the risk of infertility in obese men has tripled [7,8], which has significant implications for male fertility (Table 1, Ref. [5,6,7,8,9,10]).

Oxidative stress is an imbalance between oxidants and antioxidants in the body, resulting in elevated levels of reactive oxygen species (ROS) that can damage cells and tissues. Oxidative stress plays a crucial role in various physiological and pathological processes, including the regulation of reproductive function [11]. In the male reproductive system, oxidative stress adversely affects sperm production, maturation, and function and can also damage sperm DNA, thereby impacting fertility [12]. Research indicates that oxidative stress levels are typically increased in obese men, and this relationship is closely correlated with the inflammatory response and metabolic disorders in adipose tissue [13]. Thus, understanding the specific mechanisms through which oxidative stress contributes to infertility in obese men is essential for developing effective prevention and treatment strategies.

A comprehensive literature search was conducted across the PubMed, Embase, Cochrane Library, and Web of Science databases from January 2000 to October 2025. The search employed a combination of keywords and MeSH terms, including: ("obesity" OR "adiposity" OR "body mass index") AND ("male infertility" OR "spermatogenesis") AND ("oxidative stress" OR "reactive oxygen species" OR "antioxidants") AND ("sperm DNA fragmentation" OR "sperm DNA damage" OR "semen quality") AND ("inflammation" OR "adipokines" OR "testosterone" OR "estradiol"). The inclusion criteria prioritized original research articles, meta-analyses, and systematic reviews focusing on human studies or mechanistic preclinical models relevant to male fertility. The exclusion criteria eliminated non-English articles, studies focused solely on female infertility, and articles that did not primarily address the mechanistic link between obesity, oxidative stress, and male reproductive dysfunction.

The aim of this review was to investigate the mechanisms of oxidative stress in obesity-related male infertility and their impact on reproductive function. In examining the relevant literature, we concentrated on the effects of obesity-induced oxidative stress on sperm function, endocrine hormone levels, and other aspects of reproductive health. Additionally, we explored potential interventions, such as antioxidant use and lifestyle modifications, to assist obese men in restoring their fertility [14]. Through comprehensive research into these mechanisms, we hope to provide new insights and directions for the treatment of obesity-related male infertility.

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Table 1. Mechanisms linking obesity to male infertility.

Study	Mechanism	Key findings
Cannarella et al. (2024) [5]	Oxidative stress, chronic inflammation, hormonal dysregulation (testosterone reduction, estradiol elevation)	Obesity-induced adipokine dysregulation (leptin, adiponectin) promotes testicular oxidative stress and inflammation, impairing spermatogenesis.
Eisenberg et al. (2023) [6]	Oxidative stress, insulin resistance, impaired hypothalamic-pituitary-gonadal (HPG) axis function	Obesity is a major modifiable risk factor for male infertility, with oxidative stress as a central mediating pathway.
Du Plessis et al. (2010) [7]	Testicular hyperthermia, oxidative stress, reduced testosterone	Obese men have higher scrotal temperature, increased reactive oxygen species (ROS), and lower testosterone, all associated with reduced sperm quality.
Service et al. (2023) [8]	Metabolic dysfunction (insulin resistance, dyslipidemia), chronic inflammation	Metabolically unhealthy obesity strongly correlates with reduced sperm count, motility, and increased DNA fragmentation
Dutta et al. (2021) [9]	Testicular inflammatory pathways (NF-κB, TNF-α), oxidative stress	High-fat diet-induced obesity increases testicular inflammation and ROS, leading to impaired spermatogenesis and reduced fertility.
Rotimi et al. (2024) [10]	Oxidative stress-induced hormonal disruption (testosterone reduction, LH/FSH imbalance)	Obese infertile men have elevated malondialdehyde (MDA)/8-OHdG (oxidative stress markers) and lower testosterone, which correlate with poor sperm parameters.

2. Oxidative Stress and Male Reproductive Health

2.1 Basic Concepts of Oxidative Stress

2.1.1 Definition and Mechanisms of Oxidative Stress

ROS are highly reactive oxidizing free radical agents, which include superoxide anions (O_2•), hydrogen peroxide (H_2O_2), peroxyl (ROO•), and hydroxyl (OH•) radicals. The primary sources of ROS in sperm are activated leukocytes in the seminal plasma and mitochondria within the spermatozoa. A substantial body of evidence indicates that ROS-mediated damage to spermatozoa significantly contributes to the pathology of infertility in 30–80% of infertile men. Additionally, ROS plays a crucial role in the physiological processes of sperm development, capacitation, and function.

Oxidative stress is characterized by an overwhelmed cellular antioxidant scavenging system due to the excessive production of ROS. This situation results in an oxygen paradox, where free radicals are essential for cellular processes but can also disrupt vital metabolic functions at increased concentrations. Oxidative stress is a primary contributor to cellular dysfunction, leading to damage to the structural and functional integrity of sperm, which is a significant factor in male infertility. Under normal physiological conditions, cells generate a certain amount of ROS that play crucial roles in processes such as cell signaling and immune responses. However, when ROS production surpasses the clearance capacity of the antioxidant system, oxidative stress ensues, resulting in damage to cell membranes, proteins, and DNA, which ultimately impacts cell function and survival [15]. Oxidative stress is closely linked to the development of various diseases, including cancer, cardiovascular diseases, diabetes, and neurodegenerative disorders [16,17,18]. Furthermore, the occurrence of oxidative stress is significantly influenced by environmental factors, lifestyle choices, and genetic predispositions [19]. Research has demonstrated that improving the antioxidant status can effectively mitigate the damage caused by oxidative stress, underscoring the importance of continuing research in this area in the prevention and treatment of related diseases [20,21].

Table 2. Oxidative stress biomarkers in obesity and male infertility.

Biomarker	Detection method	Study association	Reference(s)
Reactive Oxygen Species (ROS)	Flow cytometry, chemiluminescence	Increased in obese men; positively correlated with sperm DNA damage and reduced motility	[6,7,9,25]
Malondialdehyde (MDA)	Thiobarbituric acid reactive substances (TBARS) assay	Elevated in obese infertile men; associated with lower testosterone and sperm count	[10,24]
Superoxide Dismutase (SOD)	Spectrophotometry	Decreased in obese men; inverse correlation with sperm DNA fragmentation	[9,22]
Glutathione Peroxidase (GPx)	RT-qPCR, Western blot	Decreased mitochondrial membrane potential (MMP) and ATP production, leading to lower sperm motility	[9,23]
8-Hydroxydeoxyguanosine (8-OHdG)	ELISA	Increased in obese men; strong association with sperm DNA damage	[10,25]

2.1.2 Biomarkers of OS

Biomarkers of oxidative stress are specific molecules produced in the body that serve as indicators of the presence of oxidative stress (Table 2, Ref. [6,7,9,10,22,23,24,25]). Common biomarkers include malondialdehyde (MDA), ROS, and 8-hydroxydeoxyguanosine (8-OHdG). The levels of these biomarkers reflect the degree of oxidative stress in the body and are closely associated with the development and progression of various diseases [26]. For example, MDA, a product of lipid peroxidation, is often linked to the onset of chronic diseases such as cardiovascular disease and diabetes [27]. Furthermore, 8-OHdG, a marker of DNA oxidative damage, is significantly correlated with the occurrence of conditions such as cancer and neurodegenerative diseases [28,29]. Monitoring these biomarkers can provide crucial diagnostic and prognostic information in clinical settings, assisting healthcare providers in assessing disease severity and treatment effectiveness [30]. Therefore, further exploration of the clinical applications of oxidative stress biomarkers is essential for improving early diagnosis and intervention capabilities for related diseases.

2.2 Obesity and Oxidative Stress

2.2.1 Impact of Obesity on Oxidative Stress

Obesity is recognized as a significant contributor to oxidative stress damage. Research indicates that the level of oxidative stress in obese individuals is markedly greater than that of individuals with normal weight, a phenomenon closely associated with increased adipose tissue, inflammatory responses, and metabolic disorders. The enlargement and proliferation of fat cells result in the secretion of various proinflammatory factors, including tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), by adipose tissue. The release of these factors facilitates the onset of oxidative stress. Moreover, obesity can lead to a reduction in antioxidant substances, further intensifying oxidative stress. For example, studies have demonstrated that oxidative stress markers in the red blood cell membranes of obese patients are significantly increased, potentially due to metabolic dysfunction-associated steatotic liver disease (MASLD) [31]. Additionally, obesity may induce dysfunction of the salivary glands and disrupt the balance of antioxidant components, resulting in increased oxidative damage in saliva [32]. These alterations not only compromise the metabolic health of individuals but also may adversely affect other systems, such as the cardiovascular and nervous systems. Consequently, managing body weight and improving metabolic status are essential for mitigating oxidative stress levels.

2.2.2 Obesity and Health Risks

Research data on the relationship between obesity and oxidative stress indicate that oxidative stress levels are generally greater in obese individuals and are associated with multiple health risk factors. For example, a study investigated the correlation between visceral fat mass, oxidative stress, and proinflammatory cytokine levels in individuals of varying weights and revealed a positive association between increased visceral fat mass and increased oxidative stress levels [33]. Furthermore, studies on exercise interventions in overweight and obese populations have demonstrated that moderate physical activity can significantly reduce oxidative stress and inflammation markers, thereby increasing overall health [34]. Additionally, another study revealed that obesity is closely linked to increased oxidative stress levels and their impact on cognitive function in elderly individuals, suggesting that obesity may be a potential risk factor for Alzheimer's disease [35,36]. In summary, there is a clear association between obesity and oxidative stress. Interventions targeting obesity not only aid in weight management but also effectively reduce oxidative stress levels, thereby improving associated health risks.

2.2.3 The Differences in Oxidative Stress Levels Between Fertile and Infertile Obese Individuals

In obese men, excessive adiposity and metabolic dysfunction drive ROS generation through pathways such as mitochondrial dysfunction, NADPH oxidase activation, and lipid peroxidation [9,37]. Notably, emerging evidence distinguishes fertile from infertile obese men by their ability to regulate oxidative stress. Obese infertile males have been reported to show higher levels of MDA and worse sperm parameters than both non-obese fertile males and non-obese infertile males [13]. For example, Han et al. [12] utilized an obese mouse model to demonstrate that obesity reduces the expression of NRF2, SOD, and GPx, leading to elevated levels of MDA and excessive accumulation of oxidative stress in testicular tissue. Concurrently, obesity significantly downregulates the expression of GLUT8 and LDH-A, impairing the energy supply necessary for normal spermatogenesis and ultimately diminishing male fertility. In contrast, infertile obese mice displayed severe oxidative damage, increased germ cell apoptosis (elevated caspase-3 activity), and impaired sperm production—phenotypes directly linked to reduced fertility. These findings suggest that the capacity to balance ROS and antioxidants is a pivotal determinant of reproductive success in obese men. In infertile obese men, chronic oxidative stress accumulates, damaging sperm DNA (e.g., increased 8-hydroxydeoxyguanosine [8-OHdG] levels), disrupting chromatin structure, and impairing motility—all of which reduce fertilization capacity [9,37].

2.3 Oxidative Stress and Reproductive Hormones

Oxidative stress refers to the disruption of the equilibrium between the body's antioxidant defense system and ROS, resulting in the excessive accumulation of ROS and subsequent cellular damage and functional impairment. In the reproductive system, oxidative stress significantly influences the synthesis and regulation of reproductive hormones. Recent studies have demonstrated that oxidative stress can decrease testosterone synthesis by damaging testicular tissue and interfering with the activity of steroidogenic enzymes [37,38]. Furthermore, oxidative stress can impact the hypothalamic–pituitary–gonadal (HPG) axis, leading to a decrease in the secretion of gonadotropins such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [9], thereby affecting reproductive hormone levels and potentially resulting in reproductive dysfunction [10]. Consequently, understanding the impact of oxidative stress on reproductive hormones is essential for maintaining reproductive health.

2.3.1 Impact of Oxidative Stress on Testosterone Levels

Testosterone is the primary sex hormone in males and plays a crucial role in maintaining reproductive function and sexual characteristics. Oxidative stress negatively impacts testosterone levels by increasing the production of ROS and inhibiting the activity of antioxidant enzymes, leading to damage to Leydig cells, the interstitial cells of the testes, which affects testosterone synthesis. Research indicates that testosterone levels are significantly reduced in individuals with diabetes and obesity, conditions closely associated with increased oxidative stress in the body [22]. Additionally, chronic stress conditions inhibit the activity of enzymes involved in testosterone synthesis, further decreasing testosterone secretion [39]. Oxidative stress can decrease testosterone levels by suppressing the Nrf2/HO-1 signaling pathway and the function of antioxidant enzymes [40]. Consequently, antioxidant therapy may represent a potential strategy for increasing testosterone levels and promoting reproductive health.

2.3.2 Impact of Oxidative Stress on Other Reproductive Hormones (Such as LH, FSH, and Estrogen)

Total antioxidant capacity is influenced by the levels of systemic hormones, including FSH, LH, testosterone, estradiol (E2), and prolactin (PRL). Antioxidant hormones such as testosterone and melatonin play a protective role against harmful ROS in sperm and other testicular cells [10]. Oxidative stress not only impacts testosterone levels but also significantly affects other reproductive hormones, including LH, FSH, and E2. LH and FSH are secreted by the pituitary gland and are essential for regulating the functions of the testes and ovaries. The presence of oxidative stress disrupts the HPG axis, resulting in abnormal secretion patterns of LH and FSH. Evidence indicates that ROS may adversely affect LH signaling by modifying oxidant-sensitive mitogen-activated protein kinase (MAPK) pathways and impeding cholesterol transport within mitochondria [41]. In murine Leydig cancer cells (MLTC-1), Zaidi et al. [42] demonstrated that oxidative stress-induced activation of the p38 MAPK protein negatively affects the gene transcription of the StAR protein, leading to impaired mitochondrial cholesterol transport and a subsequent decrease in androgen production. Serum levels of testosterone, E2, and free thyroxine are inversely related to sperm DNA damage [43]. Furthermore, the levels of triiodothyronine, thyroxine, and noradrenaline (a neurotransmitter) and sperm DNA damage may all be influenced by antioxidant inhibition [43]. The prolonged use of antioxidants may alter the levels of FSH, testosterone, and inhibin B (INHB). Notably, testosterone has been reported to induce DNA damage in Sertoli and germ cells through the activation of caspase activity in Sertoli cells [44]. Studies indicate that during oxidative stress, the levels of LH and FSH may either increase or decrease, depending on various physiological and pathological conditions [45]. In females, oxidative stress may also adversely affect ovarian function, leading to a reduction in estrogen synthesis, which subsequently impacts the menstrual cycle and reproductive capacity [46]. Therefore, the effects of oxidative stress on these hormones are likely to play crucial roles in reproductive health and fertility.

2.3.3 Impact of Oxidative Stress on Anti-Müllerian Hormone (AMH)

AMH is a crucial indicator of the ovarian reserve, and the influence of oxidative stress on AMH levels has garnered considerable attention. Research indicates that oxidative stress can diminish AMH secretion by damaging follicular cells, thereby impacting ovarian function and fertility [47]. In addition to being a key indicator of ovarian reserve function in females, AMH in males is predominantly secreted by Sertoli cells in the testes and is essential for the development and function of the male reproductive system. Recent studies suggest that oxidative stress may decrease AMH secretion by damaging Sertoli cells, thereby affecting spermatogenesis and male fertility. Additionally, oxidative stress may initiate inflammatory responses and apoptosis in testicular tissue, further contributing to the reduction in AMH levels [48,49]. Antioxidant therapy has been proposed as a potential intervention strategy to mitigate oxidative stress-induced damage to the testes, preserve AMH levels, and increase male fertility.

2.3.4 Relationship Between Oxidative Stress and INHB

INHB is a hormone secreted by the ovaries and testes and is involved primarily in the feedback regulation of FSH secretion. The influence of oxidative stress on INHB has garnered increasing attention from researchers. Oxidative stress may impact INHB secretion by impairing gonadal function. Some studies indicate that INHB levels can significantly decrease under conditions of oxidative stress, potentially due to damage to and dysfunction of gonadal cells [50]. Furthermore, oxidative stress may inhibit the synthesis and secretion of INHB by affecting intracellular signaling pathways [51]. Consequently, investigating the effects of oxidative stress on INHB is crucial for understanding the regulatory mechanisms of reproductive endocrinology.

2.4 Impact of Oxidative Stress on Semen Analysis

Oxidative stress is an imbalance between ROS and the body's antioxidant system, wherein excessive ROS can damage reproductive cells. Both intrinsic and extrinsic factors play crucial roles in regulating oxidative stress, which must be maintained at moderate levels to ensure optimal sperm function, cellular homeostasis, and the integrity of redox-sensitive signal transduction pathways. Studies have demonstrated that the effects of oxidative stress on sperm quality primarily involve parameters such as sperm concentration [52], motility, morphology, sperm DNA fragmentation index [53,54], and mitochondrial membrane potential [23,55]. A decrease in sperm concentration is closely linked to oxidative stress, particularly in male patients with infertility, where an increase in the ROS level in semen often correlates with a reduction in sperm concentration [23,56]. Furthermore, oxidative stress can lead to diminished sperm motility, adversely affecting swimming ability and, consequently, fertility [57,58] (Fig. 1).

2.4.1 Impact of Oxidative Stress on Sperm Concentration

Studies have demonstrated that oxidative stress significantly reduces sperm concentration. The excessive production of ROS can damage testicular cells, thereby impacting sperm generation and maturation. In men exposed to environmental pollutants, such as polycyclic aromatic hydrocarbons, increased oxidative stress levels in the body are correlated with a notable decrease in sperm concentration [59]. Additionally, increased ROS generation in seminal plasma has been associated with various lifestyle factors, including alcohol and tobacco use, exposure to toxicants, obesity, varicocele, stress, and aging [10]. Mori et al. [60] reported that DNA aptamer raised against AGEs (AGE-Apt) may increase sperm concentration, motility, and viability by mitigating AGE-RAGE-induced oxidative stress and inflammation in the testes of diabetic mice. Moreover, obesity and metabolic syndrome are recognized as contributing factors to oxidative stress that can further diminish the sperm concentration by altering the microenvironment of the testes [61]. Therefore, managing oxidative stress may represent a crucial strategy for improving sperm concentration.

2.4.2 Impact of Oxidative Stress on Sperm Motility and Morphology

Oxidative stress not only affects sperm concentration but also negatively impacts sperm motility and morphology. Research has demonstrated that increased ROS can lead to oxidative damage in sperm membranes, thereby compromising both the motility and structural integrity of sperm [62]. In various experiments, the administration of antioxidants significantly improved sperm motility, underscoring the critical role of oxidative stress in sperm dysfunction [63]. Excessive ROS may serve as a primary factor contributing to impaired sperm motility, likely due to damage caused by mitochondrial energy production. Under oxidative stress conditions, autophagy is markedly activated in sperm, as evidenced by the upregulation of p62, increased conversion of LC3, and upregulation of several autophagy-related proteins, including charged multivesicular body protein 2a, the mitochondrial import receptor subunit TOM22 homolog, and WD repeat domain phosphoinositide-interacting protein 2 [64]. Furthermore, sperm morphological abnormalities, such as head deformities and tail defects, are closely associated with oxidative stress. These morphological changes can directly affect the fertilization capacity of sperm [56].

2.4.3 Impact of Oxidative Stress on the Sperm DNA Fragmentation Index

Oxidative stress and compromised antioxidant defense mechanisms are critical factors in the etiology of male infertility. Alterations in the production of ROS and disturbances in calcium (Ca^{2+}) homeostasis contribute to mitochondrial dysfunction in spermatozoa, primarily through

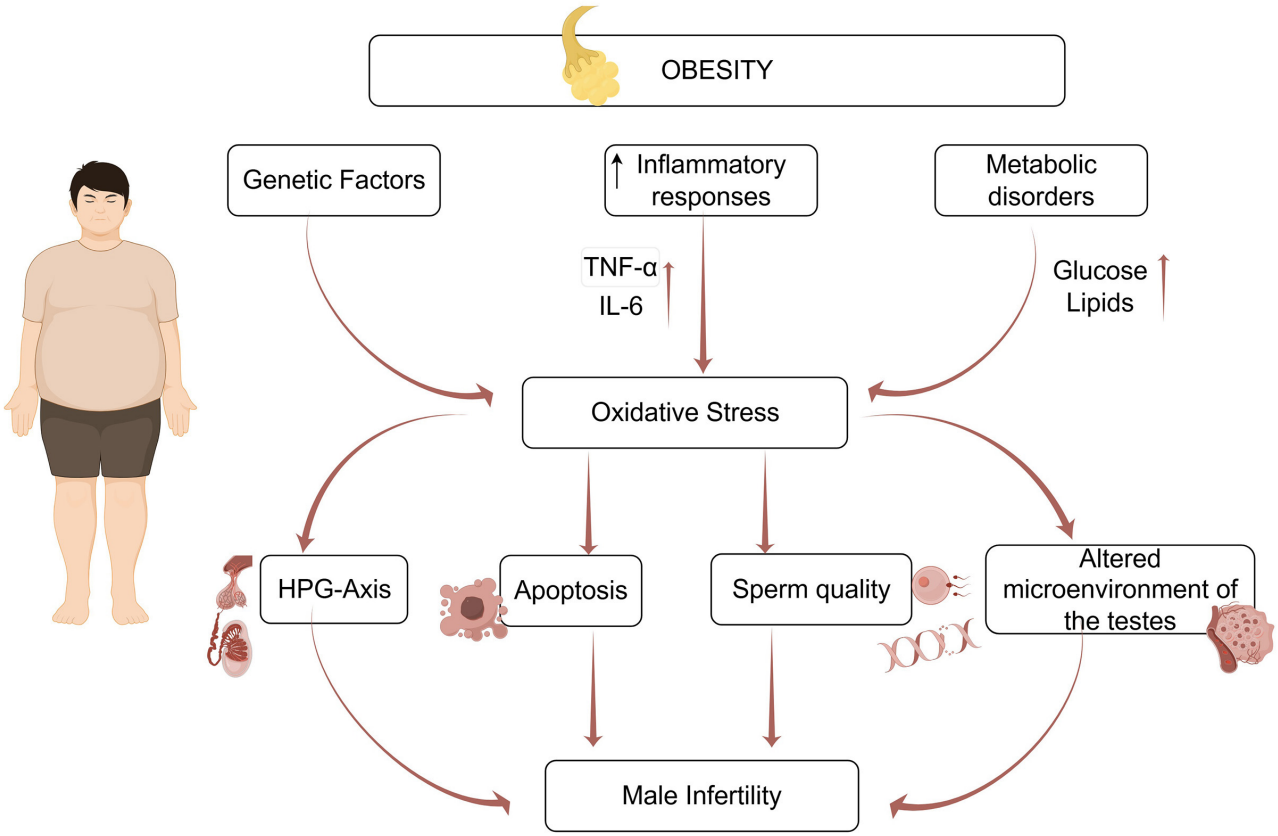

Fig. 1. Obesity induces alterations in oxidative stress levels through various pathways, including genetic factors, inflammatory responses, and metabolic disorders. These changes result in abnormalities in the hypothalamic-pituitary-gonadal (HPG) axis, increased cell apoptosis, deterioration in semen quality, and dysfunction of the testicular microenvironment, ultimately leading to infertility. This figure was created with Figdraw.

the activation of the mitochondrial permeability transition pore (mPTP) [65]. Research has demonstrated that ROS can directly damage sperm DNA, leading to fragmentation and decreasing the integrity of genetic material [66,67,68]. This damage reduces the mitochondrial membrane potential and ATP production [23], ultimately decreasing sperm quality. In patients with male infertility, the extent of sperm DNA fragmentation is positively correlated with oxidative stress levels, suggesting that this damage may be closely associated with reproductive failure [69,70,71]. Varicocele can diminish male fertility potential through several mechanisms linked to oxidative stress. Repairing a varicocele may mitigate oxidative stress levels, resulting in reduced sperm DNA damage and improved male fertility [72]. The use of antioxidants is thought to alleviate DNA damage induced by oxidative stress, thereby increasing sperm quality and fertility [72,73,74]. Consequently, monitoring and managing oxidative stress levels are highly important for improving male fertility.

2.5 Intervention Measures and Future Research Directions

Interventions targeting oxidative stress have emerged as promising strategies for addressing male infertility, particularly in obese or metabolically challenged individuals. These interventions include antioxidant therapies, probiotics, lifestyle modifications, GLP-1 receptor agonists, and others (Table 3, Ref. [24,75,76,77,78,79]).

2.5.1 Application of Antioxidants and Their Effects

The use of antioxidants is gaining increasing attention in medical research, particularly for the prevention and treatment of diseases related to oxidative stress. Oxidative stress is regarded as a significant mediator of various chronic conditions, including cardiovascular diseases, cancer, and neurodegenerative disorders. Research has demonstrated that antioxidants such as vitamin C, vitamin E, selenium, and carotenoids can effectively neutralize free radicals, thereby mitigating cellular damage. For example, one study indicated that vitamin E supplementation significantly enhances cognitive function in elderly patients, highlighting the potential role of antioxidants in neuroprotection [80]. Furthermore, plant-derived antioxidants, including polyphenols and isoflavones, have exhibited substantial antioxidant effects and have shown positive effects on improving cardiovascular health [81]. The administration of *Blautia wexlerae* has been found to improve

Table 3. Interventions targeting oxidative stress and male infertility: efficacy and outcomes.

Intervention type	Investigators	Design	Main outcomes
Antioxidants (vitamin C/E, zinc, selenium)	Steiner et al. (2020) [75]	RCT	Improved sperm motility and reduced ROS vs. placebo; no effect on pregnancy rate.
N-acetyl-cysteine (NAC)	Jannatifar et al. (2019) [24]	RCT	Increased sperm count, motility, and reduced DNA fragmentation vs. placebo.
FamiLact (probiotic + prebiotic)	Abbasi et al. (2021) [79]	RCT	Elevated sperm concentration, total motility and the proportion of morphologically normal sperm, reduces sperm DNA fragmentation vs. placebo.
Lifestyle modification (diet + exercise)	Park et al. (2024) [77]	Systematic review/meta-analysis	Reduced body weight and improved sperm count in men with metabolic syndrome.
Combined antioxidants	Mele et al. (2023) [76]	Observational	Antioxidant supplementation correlated with improved circRNA expression (linked to sperm quality) and reduced ROS.
GLP-1 RAs	Gregorič et al. (2025) [78]	RCT	Semaglutide markedly improved sperm morphology, total testosterone levels and symptoms of hypogonadism.

Table 4. Summary of key human studies on obesity, oxidative stress, and male infertility.

Investigators	Year	Design	Main findings
Cannarella et al. (2024) [5]	2024	Narrative review	Obesity induces oxidative stress, inflammation, and hormonal dysregulation, all contributing to male infertility.
Eisenberg et al. (2023) [6]	2023	Disease primer	Obesity is a leading modifiable risk factor for male infertility, mediated by oxidative stress and impaired spermatogenesis.
Service et al. (2023) [8]	2023	Systematic review	Metabolically unhealthy obesity is strongly associated with reduced sperm quality
Steiner et al. (2020) [75]	2020	RCT	Antioxidant supplementation improves sperm motility and reduces oxidative stress in infertile men.
Jannatifar et al. (2019) [24]	2019	RCT	NAC improves sperm count, motility, and reduces DNA fragmentation.
Gill et al. (2024) [25]	2024	Cross-sectional	Low sperm motility is associated with increased oxidative stress (MDA, 8-OHdG) and sperm DNA damage.

obesity-associated male infertility while regulating oxidative stress and nod-like receptor protein 3 (NLRP3) inflammasome activity [82]. Male infertility can also be addressed by phytotherapeutics that suppress lipogenesis; increase the levels of testosterone, 3β-HSD, and 17β-HSD; and increase sperm parameters while attenuating testicular dyslipidemia, oxidative stress, inflammation, and germ-cell apoptosis [83]. Antioxidant therapy has been shown to alleviate the adverse effects of oxidative stress on reproductive hormones, thereby increasing male fertility [75,84,85]. Antioxidants positively influence the functional axis of obesity-dependent circular RNAs (circRNAs) and improve sperm quality [76]. Additionally, probiotic supplementation in infertile men has led to significant increases in sperm concentration and motility, along with notable reductions in oxidative stress and inflammatory marker levels. Thus, oral intake of probiotics may represent a promising strategy for alleviating oxidative damage to sperm [79]. Additionally, oral supplementation with N-acetyl-cysteine may improve sperm parameters and the oxidant/antioxidant status in infertile males [24]. Appropriate antioxidant therapy has the potential to reduce the sperm DNA fragmentation index and lower seminal oxidative stress levels in patients diagnosed with asthenozoospermia [25]. However, despite the considerable potential of antioxidant applications, further research is necessary to clarify the optimal dosage, timing of administration, and combinatory effects with other treatments to develop more effective intervention strategies.

2.5.2 Potential Impact of Lifestyle Interventions

Lifestyle interventions play crucial roles in enhancing health status and preventing chronic diseases. Lifestyle modification, the most effective intervention for obese men, profoundly impacts weight loss, metabolic health, and reproductive outcomes by modulating reactive oxygen species (ROS), hormone balance, and semen quality. A systematic review demonstrated that comprehensive lifestyle interventions can effectively improve health indicators, including weight, blood glucose levels, and lipid levels, in patients with metabolic syndrome [77]. Weight loss through dietary restriction or exercise reduces adiposity, thereby decreasing adipose-derived pro-inflammatory cytokines (e.g., TNF-α, IL-6) that drive testicular oxidative stress [12,66]. This reduction in ROS correlates with improved sperm DNA integrity [61,67] and decreased sperm apoptosis, while normalizing aromatase-driven estrogen excess and restoring testosterone levels critical for spermatogenesis [66]. Antioxidant-rich diets or supplements (e.g., N-acetyl-cysteine) further mitigate seminal oxidative stress, enhancing sperm motility and chromatin integrity [24], while low-glycemic diets improve insulin sensitivity and reduce metabolic endotoxemia, linking to lower sperm DNA fragmentation [61]. One study revealed that irisin supplementation in mice activates the AMPKα signaling pathway, which protects against high-fat diet (HFD)-induced spermatogenesis dysfunction and increases testosterone levels. Furthermore, irisin treatment significantly alleviated HFD-induced oxidative stress, endoplasmic reticulum (ER) stress, and testicular apoptosis [86]. Additionally, lifestyle interventions have shown promising results in fostering the development and maintenance of healthy behaviors [87,88,89]. However, the implementation of lifestyle interventions continues to face numerous challenges, including individual differences, cultural backgrounds, and socioeconomic factors. Therefore, future research should prioritize the optimization of lifestyle intervention strategies to increase their adaptability and effectiveness across diverse populations.

2.5.3 Impact of GLP-1 RAs on ROS, Hormones, and Semen Quality

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), primarily utilized for the management of type 2 diabetes and obesity, have emerged as promising interventions for enhancing male reproductive health through several pathways: managing reactive oxygen species (ROS), balancing hormones, and enhancing semen quality. These agents mitigate ROS, a significant contributor to sperm dysfunction in obesity, through dual mechanisms: indirect metabolic enhancement and direct cellular effects. By promoting weight loss and improving insulin sensitivity, GLP-1 RAs decrease adipose tissue-derived pro-oxidants (e.g., adipokines) and augment systemic antioxidant capacity [90,91]. GLP-1 RAs enhances the action on gonadotropin-releasing hormone and Kiss neurons, remodels testicular architecture, reduces oxidative stress, and improves testosterone and gonadotropin levels [92]. Preclinical studies indicate that GLP-1RAs enhance spermatogenesis, gonadal hormone profiles, and sperm function in obese and diabetic rodent models through the cAMP/PKA and PI3K/Akt signaling pathways. Exenatide, a GLP-1RA, has been shown to improve sperm count and motility and attenuate testicular inflammation in obese mice, with improvements in sperm mitochondrial membrane potential and DNA integrity [93,94,95]. GLP-1 RAs restore hormonal dysregulation commonly observed in obesity, particularly imbalances in the HPG axis. Dulaglutide therapy might bring obese men additional benefits by recovering testicular dysfunction induced by obesity [96]. Medical weight loss achieved through GLP-1 RAs also normalizes the estrogen/testosterone ratio, thereby reducing testicular oxidative stress and enhancing spermatogenic microenvironments [91]. The cumulative effects of reduced ROS and hormonal normalization result in significant improvements in semen parameters. A study enrolled 25 obese male patients with type 2 diabetes, who were administered semaglutide at a dosage of 1 mg per week or intramuscular testosterone undecanoate at a dosage of 1000 mg every 10 to 12 weeks over a period of 24 weeks. In the SEMA group, there was a significant increase in the proportion of morphologically normal sperm from baseline to the end of the study (2% [2; 3.5] vs. 4% [2; 5.5]; $p = 0.012$), which also exhibited significantly higher counts of morphologically normal sperm, sperm concentration, and total sperm number [78]. These improvements are correlated with restored mitochondrial function in spermatozoa and decreased oxidative damage to chromatin, highlighting the multifactorial benefits of GLP-1 RAs for male reproductive health [65,92]. GLP-1 RAs represent a promising therapeutic approach for obese men experiencing infertility, addressing both upstream metabolic dysfunction and downstream reproductive impairments. Although current evidence primarily stems from observational studies and small trials, ongoing randomized controlled trials are expected to elucidate the long-term safety and efficacy of these agents in reproductive contexts. Clinicians should consider incorporating GLP-1 RAs into comprehensive lifestyle interventions—including dietary modifications and exercise—to optimize semen quality in obese males [77,91].

2.5.4 Recommendations and Prospects for Future Research

Future research should emphasize the integrated application of antioxidants and lifestyle interventions, specifically investigating their synergistic effects in the prevention and treatment of various diseases. First, it is advisable to conduct large-scale randomized controlled trials to assess the effectiveness of combining antioxidants with lifestyle interventions in improving health outcomes [97]. Second,

research should focus on developing personalized intervention plans that consider the influence of genetic background, lifestyle habits, and environmental factors, thereby aligning with the objectives of precision medicine. Furthermore, advancements in technology present new opportunities for lifestyle interventions, such as the implementation of digital health technologies, including mobile health applications, to monitor and encourage changes in healthy behaviors [98]. Finally, researchers should promote interdisciplinary collaboration by integrating knowledge from fields such as nutrition, psychology, and public health to enhance the scientific rigor and feasibility of intervention strategies.

3. Conclusions

The importance of oxidative stress in male infertility related to obesity is increasingly being acknowledged. Recent studies indicate that obesity not only adversely affects male reproductive function but also increases the production of ROS within the body, resulting in diminished sperm quality, hormonal imbalances, and dysfunction of reproductive organs. Cellular damage and inflammatory responses induced by oxidative stress may be critical factors contributing to male infertility among obese individuals. Current research has established a connection between oxidative stress and infertility in obese men, indicating that oxidative stress-induced damage may impair male fertility and lead to infertility (Table 4, Ref. [5,6,8,24,25,75]). Some studies highlight the beneficial effects of lifestyle interventions, such as dietary modifications and exercise, in reducing oxidative stress levels and increasing fertility. Conversely, other studies propose that lifestyle changes alone may not be adequate to improve reproductive health comprehensively. Consequently, future research should strive to balance diverse intervention methods with individual differences, integrate clinical practice to assess the efficacy of various strategies and provide a scientific foundation for managing male infertility in obese individuals. In conclusion, the role of oxidative stress in male infertility associated with obesity is intricate and extensive. Through multidisciplinary collaboration and thorough investigation, we aim to develop more effective solutions to this increasingly pressing health issue in the future, thereby improving male reproductive health and enhancing quality of life.

Abbreviations

ROS, reactive oxygen species; MDA, malondialdehyde; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; 8-OHdG, 8-hydroxydeoxyguanosine; HPG, hypothalamic–pituitary–gonadal; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MAPK, mitogen-activated protein kinase; PCOS, polycystic ovary syndrome; mPTP, mitochondrial permeability transition pore; HFD, high-fat diet; ER, endoplasmic reticulum; GLP-1 RAs, Glucagon-like peptide-1 receptor agonists.

Author Contributions

Conceptualization, HM, JX; Methodology, JX; Software, YZ; Validation, JX, HM and YZ; Formal Analysis, JX; Investigation, JX; Resources, PS; Data Curation, JX; Writing – Original Draft Preparation, JX; Writing – Review & Editing, JX, HM, PS, YZ; Visualization, JX, YZ, PS, HM; Supervision, HM; Project Administration, JX; Funding Acquisition, JX. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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