Potential Effects of Liraglutide on Male Reproductive Dysfunction Associated with Obesity

Mohamed Abdel Raouf ElGhannam, Reham Hassan Ibrahim, Nada Abdel Maksoud Mohamed Salah Eldeen, Lamiaa Goda Mohammad

Department of Physiology, Faculty of Medicine, Zagazig University

Corresponding Author: Nada Abdel Maksoud Mohamed Salah Eldeen

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Abstract

Background: Obesity is increasingly recognized as an important contributor to male reproductive dysfunction through hormonal imbalance, insulin resistance, chronic inflammation, oxidative stress, impaired hypothalamic-pituitary-gonadal axis activity, and direct damage to testicular tissue. These alterations may reduce testosterone production, impair spermatogenesis, decrease sperm quality, and increase the risk of hypogonadism and infertility. Liraglutide, a glucagon-like peptide-1 receptor agonist, is widely used for glycemic control and weight management and may exert additional reproductive benefits through metabolic, anti-inflammatory, antioxidant, and endocrine mechanisms. This review evaluates the potential effects of liraglutide on obesity-associated male reproductive dysfunction.

Conclusion: Available evidence suggests that liraglutide may improve male reproductive function by promoting weight loss, enhancing insulin sensitivity, reducing oxidative stress and inflammation, restoring hormonal balance, and supporting testicular steroidogenesis and spermatogenesis. However, most current evidence is derived from experimental studies, and further well-designed clinical trials are required to confirm its reproductive efficacy, optimal dosage, long-term safety, and therapeutic relevance in obese men.

Keywords: Liraglutide, Male Reproductive Dysfunction, Obesity

Introduction

Obesity is a complex, multifactorial, and chronic disease characterized by abnormal or excessive fat accumulation that poses a health risk. It results from the interaction of genetic, metabolic, social, behavioral, and cultural factors. Obesity significantly impacts the health, psychosocial well-being, longevity, and quality of life of affected individuals [1].

Obesity is increasingly recognized as a neurohormonal and immunometabolic disorder involving complex interactions between adipose tissue, the central nervous system and systemic metabolic pathways [2].

One of the most significant consequences of obesity is a condition known as functional hypogonadism which is characterized by low testosterone levels despite normal or low levels of luteinizing hormone (LH). This results in reduced libido, erectile dysfunction and impaired spermatogenesis. Furthermore, increased aromatase activity in adipose tissue leads to the conversion of testosterone to estradiol with suppressing the HPG axis through negative feedback mechanisms [3].

Beyond hormonal imbalance, obesity is also associated with structural and functional alterations in the testes, including damage to Sertoli and Leydig cells, reduced seminiferous tubule diameter and disruption of the blood-testis barrier. These changes contribute to poor sperm quality, reduced sperm count, and decreased motility [4].

Importantly, recent studies have indicated that GLP-1 receptor agonists may also exert beneficial effects on reproductive function through improvement of insulin resistance, reduction of obesity-associated oxidative stress, and modulation of hypothalamic–pituitary–gonadal axis activity, although this area remains under investigation [5,6].

These findings underscore the importance of addressing obesity not only as a metabolic disorder but also as a contributor to male infertility. Understanding these physiological pathways is crucial for developing targeted interventions, such as the use of GLP-1 receptor agonists, which may help reverse these effects [7].

Glucagon-Like Peptide-1 and GLP-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by L-cells of the distal small intestine and colon in response to nutrient intake, particularly carbohydrates and fats. It acts in an endocrine, paracrine, and neuroendocrine manner to help regulate postprandial glucose levels by stimulating insulin secretion, inhibiting glucagon release, slowing gastric emptying and promoting satiety [8].

Native GLP-1 has a very short plasma half-life (<2 minutes) due to rapid enzymatic degradation by dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidases (NEP), which limits its therapeutic application [9]. To overcome this limitation, GLP-1 receptor agonists (GLP-1 RAs) have been developed. These synthetic analogs resist enzymatic degradation, have longer half-lives and mimic the physiological actions of endogenous GLP-1, making them effective for glycemic control and weight management [10].

GLP-1RAs can be broadly classified based on their duration of action into short-acting and long-acting agents. The currently available GLP-1RAs include:
Exenatide, Lixisenatide, Liraglutide, Dulaglutide, Semaglutide, Albiglutide [11].

These agents differ in their pharmacokinetic profiles, dosing frequency, and structural modifications that confer resistance to degradation by dipeptidyl peptidase-4 (DPP-4). Long-acting GLP-1RAs, such as liraglutide, semaglutide, and dulaglutide, provide more sustained receptor activation and have demonstrated superior efficacy in glycemic control and weight reduction compared to short-acting agents [12].

Recently, dual incretin receptor agonists such as tirzepatide have been developed, targeting both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, offering enhanced metabolic effects [13].

Liraglutide: Structure and Pharmacokinetics

Liraglutide is a long-acting GLP-1 RA, sharing 97% amino acid sequence homology with native GLP-1. Its pharmacokinetic profile is enhanced by two structural modifications: substitution of lysine with arginine at position 34 and attachment of a C16 fatty acid (palmitic acid) to lysine at position 26 via a glutamic acid spacer, which prolongs its plasma half-life [14]. Liraglutide is produced using recombinant DNA technology in Saccharomyces cerevisiae (baker's yeast). After expression, the peptide precursor is chemically modified by attaching the fatty acid chain, which is crucial for its prolonged action in vivo [14].

These modifications significantly enhance the drug's pharmacokinetic profile by enabling strong albumin binding (≈98%), which protects it from enzymatic degradation and reduces renal clearance, thereby extending its half-life to approximately 13 hours. As a result, liraglutide can be administered once daily by subcutaneous injection, making it more convenient than earlier GLP-1 receptor agonists like exenatide, which required twice-daily dosing [15].

Upon subcutaneous administration, peak plasma concentrations are reached at approximately 11 hours, and the absolute bioavailability is about 55%. The drug has a large volume of distribution, consistent with extensive tissue distribution and protein binding. It is not significantly metabolized by the cytochrome P450 system, and elimination occurs via slow proteolytic degradation into small peptides, which are subsequently cleared by the liver and kidneys [16].

Action of Liraglutide

Liraglutide acts as a GLP-1 receptor agonist, activating the receptor expressed on pancreatic β-cells, α-cells, hypothalamic neurons and peripheral tissues [17].

1-Pancreatic β-Cells: Liraglutide stimulates glucose-dependent insulin secretion through increased cyclic adenosine monophosphate (cAMP) production, activating protein kinase A (PKA) and exchange proteins activated by cAMP (EPAC), enhancing insulin exocytosis and β-cell survival [18].

2-Pancreatic α-Cells: It suppresses glucagon secretion via cAMP-PKA mediated pathways and promotes α-cell apoptosis partly through modulation of microRNA-375, reducing hepatic glucose output [19].

3-Central Nervous System: Acting on hypothalamic and brainstem GLP-1 receptors, liraglutide reduces appetite and promotes satiety. So, contributing to weight loss [20].

4-Gastrointestinal Tract: It delays gastric emptying.so, attenuating postprandial glucose excursions [21].

5-Peripheral Tissues: Liraglutide activates hormone-sensitive lipase (HSL) through AC3/cAMP/PKA signaling in adipose tissue, promoting lipolysis and enhancing insulin sensitivity [22].

Liraglutide exhibits potent antioxidative activity by reducing reactive oxygen species (ROS) production and enhancing endogenous antioxidant defense systems, including superoxide dismutase (SOD) and glutathione peroxidase (GPx). These effects are mediated through activation of the AMP-activated protein kinase (AMPK) pathway and inhibition of oxidative stress–related signaling cascades, thereby protecting cellular structures from oxidative damage [23].

Furthermore, liraglutide reduces systemic and tissue-specific inflammation by downregulating pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), mainly via suppression of nuclear factor kappa B (NF-κB) signaling. This anti-inflammatory action contributes to improved endothelial function and metabolic homeostasis [24].

Obesity and Male Reproductive Health

One of the most significant consequences of obesity is a condition known as functional hypogonadism which is characterized by low testosterone levels despite normal or low levels of luteinizing hormone (LH). This results in reduced libido, erectile dysfunction and impaired spermatogenesis. Furthermore, increased aromatase activity in adipose tissue leads to the conversion of testosterone to estradiol with suppressing the HPG axis through negative feedback mechanisms [25].

Beyond hormonal imbalance, obesity is also associated with structural and functional alterations in the testes, including damage to Sertoli and Leydig cells, reduced seminiferous tubule diameter and disruption of the blood-testis barrier. These changes contribute to poor sperm quality, reduced sperm count, and decreased motility [26].

The hypothalamic-pituitary-gonadal (HPG) axis is the central endocrine system regulating male reproductive function. It orchestrates the production and release of key hormones necessary for spermatogenesis and testosterone synthesis. The axis begins with the hypothalamic secretion of gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH acts on Leydig cells to promote testosterone production, while FSH targets Sertoli cells to support sperm development [27].

Obesity disrupts the normal functioning of the HPG axis at multiple levels. Expansion of adipose tissue promotes upregulation of adipocyte aromatase, thereby enhancing the peripheral conversion of androgens to estrogens, particularly the conversion of testosterone to 17β-estradiol. This estrogenic microenvironment exerts negative feedback on the HPT axis, suppressing GnRH pulsatility and consequently reducing the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion [28]. The suppressed gonadotropin release leads to impaired Leydig cell function and compromised spermatogenesis [26].

Kisspeptin, Insulin Resistance, and Male Infertility

Kisspeptin gene expression, which plays a regulatory role in the HPG axis and spermatogenesis, may be downregulated in obesity, contributing to suppressed reproductive hormone secretion and reduced testicular function [29].

Kisspeptin, a peptide encoded by the Kiss1 gene, has emerged as a critical regulator of the HPG axis. It

acts primarily through stimulation of gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus, thereby influencing the secretion of LH and FSH from the pituitary and subsequently testosterone production in the testes [30].

Kisspeptin is not only active centrally but is also expressed peripherally, including in the testicular tissue, indicating a possible direct role in local testicular function [30].

Kiss1 mRNA and its receptor GPR54 (Kiss1R) are identified in testicular cells, such as Leydig cells, Sertoli cells and even germ cells [30]. The exact role of testicular kisspeptin remains under investigation, but current hypotheses include:

- Regulation of steroidogenesis (testosterone synthesis).
- Involvement in spermatogenesis and germ cell maturation.
- Interaction with local paracrine signaling within the testes [30].

Obesity has been associated with a downregulation of Kiss1 expression, both centrally and peripherally. This downregulation contributes to the suppression of the HPG axis and may be a key mechanism linking metabolic disorders to male infertility [31]. In testicular tissue, decreased kisspeptin expression may impair local testosterone production and reduce spermatogenic efficiency. Oxidative stress and altered insulin signaling both common in obesity may contribute to this dysregulation [29].

Insulin resistance represents a key contributor to the link between obesity, male hypogonadism and infertility. It is characterized by reduced cellular responsiveness to insulin, even in the presence of normal or elevated glucose levels [32]. To compensate, the pancreas increases insulin secretion, resulting in hyperinsulinemia. Over time, this condition can progress to hyperglycemia, glucose intolerance and ultimately type 2 diabetes mellitus (T2DM) [32].

Insulin resistance may impair GnRH secretion, disrupt gonadotropin release and ultimately lower testosterone production [33]. Moreover, hyperinsulinemia reduces hepatic synthesis of sex hormone-binding globulin (SHBG), increasing biologically active estrogen and further disturbing hormonal homeostasis in obese males [33].

Insulin resistance also negatively impacts spermatogenesis, increasing both nuclear and mitochondrial sperm DNA damage. Notably, this relationship is bidirectional—testosterone deficiency can worsen insulin sensitivity, stimulate adipose tissue expansion and accelerate fat accumulation [33].

Obesity, Inflammation, Oxidative Stress and Testicular Function

Obesity promotes a state of chronic low-grade systemic inflammation that profoundly impacts male reproductive health. High-fat diet (HFD)-induced obesity activates the NOD-Like Receptor family, Pyrin domain-containing 3) NLRP3(inflammasome in testicular tissue, leading to pyroptotic cell death and disrupted spermatogenesis [26]. This pro-inflammatory milieu is maintained through elevated cytokine production and infiltration of immune cells particularly neutrophils and macrophages into the epididymis, resulting in epithelial cell apoptosis and impaired sperm maturation [26].

A key mechanism involves the generation of reactive oxygen species (ROS), which drive inflammasome activation and increase the release of interleukin-1β (IL-1β) from testicular support cells. This cascade interferes with testosterone biosynthesis, compromises blood–testis barrier (BTB) integrity via occludin degradation and disrupts spermatogenesis [26]. Furthermore, obesity alters the immune landscape of the seminal plasma, reducing levels of TGF-β1, IL-10 and TNF, alongside a marked decline in regulatory T cell subsets diminishing the semen's immunomodulatory capacity [26].

Additionally, pro-inflammatory adipokines such as IL-6 and TNF-α stimulate the hypothalamic–pituitary–adrenal (HPA) axis, elevating cortisol and suppressing both thyrotropin and testosterone, thereby exacerbating visceral adiposity and impairing the HPG axis [33]. Obesity-related inflammation also interferes with hypothalamic neuronal integrity, leading to decreased gonadotropin and testosterone levels, further compromising fertility. These endocrine and immunological disruptions collectively impair sperm development, function and male reproductive potential [33].

Oxidative stress is a critical pathophysiological mechanism implicated in male reproductive dysfunction, particularly in the context of obesity. It results from an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates through antioxidant

defense mechanisms [34]. While low levels of ROS play physiological roles in processes such as spermatogenesis and sperm capacitation, excessive ROS can lead to cellular damage, apoptosis and impaired testicular function [34].

In obese individuals, the accumulation of adipose tissue promotes chronic low-grade inflammation and increased oxidative stress [33]. This heightened oxidative environment affects testicular function in several ways:

• Lipid peroxidation of sperm membranes compromises membrane integrity, fluidity and motility.
• DNA fragmentation in spermatozoa leads to reduced fertilization potential and increased risk of miscarriage.
• Damage to Sertoli and Leydig cells interferes with spermatogenic support and testosterone synthesis [34].

One of the most commonly used biomarkers of oxidative stress is malondialdehyde (MDA), a byproduct of lipid peroxidation. Elevated levels of MDA have been consistently observed in the testes and semen of obese males, both in clinical and experimental settings [34]. In contrast, the activities of key antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), are often reduced, indicating an overwhelmed antioxidant defense system [34].

Understanding the contribution of oxidative stress to obesity-induced reproductive dysfunction is essential for interpreting the outcomes of interventions targeting metabolic pathways and for identifying novel therapeutic strategies aimed at preserving male fertility [34].

Molecular and Direct Testicular Effects of Obesity

Obesity has been found to alter gene expression profiles involved in reproductive regulation [12]. One obesity locus identified by genome wide association studies is situated within or near the AC3 gene. The AC3 gene encodes the membrane associated enzyme Adenylyl Cyclase 3, which catalyzes the synthesis of cyclic AMP (cAMP) from adenosine triphosphate (ATP). Numerous studies show that cAMP and its downstream effector, Protein Kinase A (PKA), are essential for sperm formation (spermatogenesis), sperm motility and capacitation [34]. Recent evidence suggests that obesity can downregulate the expression of the Adenylyl Cyclase 3 (AC3) gene, particularly in reproductive tissues such as the testis [34].

Spermatogenesis is widely recognized as a process highly sensitive to temperature variations within reproductive physiology, requiring an optimal thermal range of 32–35 °C for proper function in the human testis [28]. Obesity has been associated with increased body temperature, particularly in the scrotal region. Furthermore, extragonadal heat production has emerged as a significant concern in obese individuals, primarily due to increased scrotal adiposity as well as augmented fat deposits in the suprapubic and thigh regions [28]. In obese conditions, the accumulation of scrotal fat correlates with elevated levels of ROS [28]. This disruption in thermal regulation adversely affects testicular physiology, thereby impairing spermatogenic efficiency and reproductive capacity [28].

The BTB is a crucial testicular structure that separates developing germ cells from the immune system, thereby protecting these cells from autoimmune attack and maintaining an immune-privileged environment essential for spermatogenesis [26]. Disruption of the BTB compromises sperm production and can lead to infertility [26].This barrier is composed of several types of intercellular junctions, including tight junctions, gap junctions, basal ectoplasmic specializations characterized by proteins such as beta-catenin and N-cadherin and desmosomes [26].Among these, tight junction proteins like Claudin, Occludin and Zonula Occludens-1 (ZO-1) are particularly critical in maintaining BTB function and are potential molecular targets for factors inducing barrier disruption [26].

Studies indicate that a high-fat diet leads to increased circulating leptin levels which can directly impair BTB integrity by downregulating tight junction proteins and altering the expression of adhesion molecules [33]. Elevated leptin has been implicated in the deterioration of BTB structure, resulting in increased permeability of the barrier, germ cell apoptosis and a subsequent decline in sperm quality. These findings highlight leptin's role as a key mediator linking metabolic imbalance and testicular dysfunction, complementing evidence of hormonal disruptions observed in obese males [26].

Conclusion

Obesity contributes to male reproductive dysfunction through hormonal disruption, insulin resistance, inflammation, oxidative stress, altered kisspeptin signaling, impaired blood-testis barrier integrity and direct testicular damage. Liraglutide may improve reproductive function by reducing body weight, enhancing insulin sensitivity, restoring hormonal balance and limiting inflammatory and oxidative injury. However, further clinical studies are required to confirm its efficacy and long-term safety in obese men with reproductive dysfunction.

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