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Review

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Male hypogonadism in overweight and obesity

Eleni Armeni

2nd Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Aretaieio Hospital, Athens GR-11528, Greece.

Correspondence to: Dr. Eleni Armeni, 2nd Department of Obstetrics of Gynecology, National and Kapodistrian University of Athens, 76 Vas Sofias Street, Athens GR-11528, Greece. E-mail: elenaarmeni@hotmail.com

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Abstract

Obesity-related gonadal dysfunction in males has been defined recently as male obesity secondary hypogonadism (MOSH). Affected individuals present with signs and symptoms related to the sex hormone imbalance but also with a burden of metabolic risk factors and occasionally compromised fertility. In pathophysiological terms, excess body fat is associated with leptin and insulin resistance. Accelerated synthesis of leptin and hyperinsulinemia downregulate the expression of kisspeptin receptors and, consequently, the action of kisspeptin. This critical neuropeptide is known to control gonadotropin secretion. In obese males, enhanced activity of the aromatase enzyme is associated with an increase in the conversion of circulating testosterone to estrogen, further promoting a state of hypogonadism. In addition, high fat and low fiber intake alter the intestinal microbiome and the dysfunction of the gut-brain axis. Weight loss appears to be the key to readjusting the function of the hypothalamus-pituitary-gonadal axis. It can be achieved with lifestyle measures in combination with weight loss medications or bariatric surgery. The degree of weight loss appears to resolve the symptoms related to hypogonadism and improve fertility chances. However, the role of hormone replacement is also important, as testosterone replacement has been shown to reduce fat mass and increase the amount of lean body mass while also contributing to weight loss and the regulation of body mass index and waist circumference. This narrative review analyzes the evidence on developing obesity-related endocrinopathies and the available management options. Further research is required to estimate the cut-off of body mass index associated with a higher risk for hypogonadism.

Keywords: Obesity-related endocrinopathies, metabolic obesity secondary hypogonadism, weight loss, bariatric surgery

INTRODUCTION

Undoubtedly, obesity is the new pandemic for which global attention is needed. The latest World Health Assembly in May 2022 predicted that by 2030 at least 1 in 5 women and 1 in 7 men would be living with excess body weight[1]. The problem of weight excess is complex, driven by multiple factors and important causes, such as learned behaviors, genetics, cultural eating habits, or societal beliefs[2]. Public awareness campaigns that target body positivity can help perpetuate myths around obesity and clarify the true public health impact of this chronic disease[3,4].

Following the "obesity paradox, "according to which the patients with extreme obesity present with lower cardiovascular risk, researchers tried to define the subgroups of patients with the most significant risk for adverse health outcomes. In this context, the obesity phenotypes stratified overweight and obese patients according to their cardiometabolic burden[5]. Consequently, obese patients can be classified into metabolic unhealthy obesity (MUO) and metabolic healthy obesity (MHO). In contrast, normal or overweight patients with features of metabolic syndrome can be classified as metabolic unhealthy normal weight (MUHNW). This category corresponds to a different stage of cardiometabolic risk[5,6].

The most common obesity-related endocrinopathy is expressed as a transient gonadal dysfunction, likely to be ameliorated with successful management of weight excess[4]. Obesity-related gonadal dysfunction in males has been recently defined as MOSH (male obesity secondary hypogonadism). Besides signs and symptoms directly related to the sex hormone imbalance, individuals with obesity-induced gonadal dysfunction also express challenges when seeking fertility[7].

Treatment for obesity-related gonadal dysfunction consists of simple measures such as lifestyle and diet and medical or surgical interventions to promote weight loss and restore levels of sex hormones[8]. This narrative review aimed to provide an update on the latest evidence addressing the link between hypogonadism in overweight or obese male individuals.

METHODOLOGY

For this narrative review, the following search terms were used: "obesity" or "overweight" or "adiposity" or "obesity-related endocrinopathies" or "male obesity secondary hypogonadism," or "MOSH" or "hypogonadism" or "prevalence" or "clinical implications" or "pathogenesis" or "medical treatment" or "surgical treatment" or "bariatric surgery."

THE MALE STORY: MALE OBESITY SECONDARY HYPOGONADISM

MOSH is defined in obese men (body mass index, BMI of at least 30 kg/m^2) who have been found to have low testosterone levels with either standard or low levels of gonadotrophins and present clinical signs of hypogonadism[6].

Prevalence

The prevalence of hypogonadism in obese male patients has been estimated as approximately 32.3% to 64%[4,7]. A recent study described that secondary hypogonadism was present in 56% of men with obesity class II (BMI 35-39.9 kg/m^2) and 61% of men with obesity class III (BMI > 40 kg/m^2)[9]. An earlier study showed that obese patients have a 2.86 times higher risk of developing secondary hypogonadism than patients who are either overweight or of average weight. Similarly, abdominal adiposity is associated with a gradient increase in the risk for MOSH, estimated as 2.64 times higher for men with a WC > 102 cm *vs.* average[8,10]. Finally, the Massachusetts Male Ageing Study (1987 to 1997) showed that obesity is a substantial risk factor predicting the development of testosterone deficiency (OR 2.67, 95%CI: 2.0-3.57),

P-value < 0.0001), and vice versa. Interestingly, the European Male Ageing Study survey explored 3369 community-dwelling men aged 40-79 years, who were retrieved from 8 different European centers to analyze the possible role of predictors of hypogonadism in older men[11]. This study reported that a body mass index of at least 30 kg/m^2 was significantly associated with secondary hypogonadism (Relative risk ratio of 8.74, $P < 0.001$), with primary hypogonadism (RRR 2.37, 95%CI: 1.01 to 5.58) and compensated hypogonadism (RRR 0.73, 95%CI: 0.50-1.07). (for details on more studies, see Table 1).

Pathophysiology

The temporal relationship between testosterone deficiency (TD) and obesity is complex, not well-defined, and remains, at best, poorly understood[26-28]. Overall, the relationship between obesity and hypogonadism is complex and bi-directional. Excessive body fat is linked with lower testosterone production and vice versa; hypogonadal men are more prone to body fat accumulation[28].

The role of obesity in gonadal function

The obesigenic environment is characterized by visceral fat accumulation and decreased fat-free mass. The changes in fat distribution contribute to the following pathophysiological alterations: (1) A profound increase in the level of inflammatory mediators (e.g., TNF-a, interleukin 6, and interleukin 1)[29]. (2) Muscle inflammation that leads to increased myokine levels and insulin resistance[8,30]. Both of the alterations mentioned above are known to affect the hypothalamus-pituitary-gonadal axis (HPG) function negatively. The pituitary corresponds via reduced production of gonadotrophins[10]. In addition, the HPG function is further downregulated by the degree of hypothalamic inflammation[8,31].

Adipose tissue and leptin

White adipose tissue produces leptin, a hormonal mediator of testicular function and metabolic regulation. The concentrations of leptin are proportional to the size of the adipose tissue and the number of adipocytes[32,33]. Leptin is a well-documented regulator of the hypothalamic production of gonadotrophin-releasing hormone (GnRH). The effect of leptin molecules on the GnRH neurons is mediated by forebrain kisspeptin-producing neurons[34]. Moreover, elevated leptin levels act on Leydig cells and reduce their responsiveness to pituitary gonadotrophins and the subsequent steroidogenic capacity[35-37]. On the other hand, hyperleptinemia results in saturation of leptin transport to the brain, with a consequent decrease in the expression of leptin receptors. The ensuing leptin resistance contributes to HPT dysregulation, decreased testosterone production, increased energy accumulation, food intake, and increased appetite[28,38]. In addition, lower testosterone levels favor lipid accumulation in the adipose tissue[28].

Adipose tissue and aromatase activity

Visceral adiposity and increased adipocyte mass lead to increased expression of the aromatase enzyme[39]. The latter can mediate the conversion rate of free testosterone to 17βestradiol[40,41]. In a vicious cycle, the increased oestradiol levels contribute to the hypofunction of the HPG axis. However, the raised oestradiol levels also interact with serotoninergic respiratory pathways, contributing to obstructive sleep apnea and disrupted sleep[35]. On the contrary, recent evidence retrieved from population-based studies showed that obese men have lower levels of oestradiol compared to lean and non-diabetic men. The lower levels of estradiol have been suggested to induce an increase in total body and intra-abdominal fat mass, which, together with the age-related accumulation of comorbid burden, may contribute to the development of features of androgenic deficiency[42,43].

The neuronal dysregulation of the reproductive axis

Under physiological conditions, leptin interacts with the ventral premammillary neurons[44]. The latter group of neurons induces the function of kisspeptin neurons to upregulate the synthesis of follicle-

Table 1. Epidemiological characteristics of the association between male obesity and hypogonadism

Study	Sample characteristics	Conclusion
Risk for hypogonadism among individuals with obesity		
Aggerholm *et al.*[12]	cross-sectional study of 2,139 men	Obese vs. normal-weight men: T levels 25%-32% lower Overweight *vs.* normal-weight men: Slightly (↓) sperm concentration Slightly (↓) sperm count
Calderon *et al.*[13]	*N* = 35 men pre-bariatric surgery, age 39.5 9.5, mean BMI 42.7 0.7	Prevalence of hypogonadism: TT < 3 ng/mL in 68.5% FT < 65 pg/mL in 45.7%
Calderon *et al.*[14]	Prevalence of MOSH in 100 male patients with moderate to severe obesity	Low TT and/or FT concentrations in 45% (95%CI: 35-55) of patients
Dhindsa *et al.*[15]	HIM study evaluated the prevalence of hypogonadism in 1,451 non-diabetic and 398 diabetic men aged > 45 years	Prevalence of subnormal testosterone levels: Non-diabetes, overweight and obese men 29% *vs.* 40% diabetic, overweight, and obese men, 44% and 50%
Escobar - Morreale *et al.*[16]	Meta-analysis, 382 severely obese men	Prevalence of MOSH in those referred for bariatric surgery: 64% (95%CI: 50-77) of men
Hofstra *et al.*[17]	149 men aged 18-66 years, BMI 42.7 ± 0.7 kg/m^2, T2DM in 37%	Prevalence of hypogonadism: TT< 3 ng/mL in 57.7% FT < 65 pg/mL in 35.6%
Rigon *et al.*[18]	29 obese men who were treated with bariatric surgery and 29 age-matched men	Prevalence of hypogonadism FT < 6.5 ng/dL: 55.56% Both FT < 6.5 ng/dL and TT < 264 ng/dL: 82.75%
Wu *et al.*[19]	Survey of a random population sample of 3,369 men aged 40 to 79 years	LOH prevalence by BMI categories Overweight, prevalence 1.6% Obesity, prevalence 5.2%
Dhindsa *et al.*[20]	Part of the Teen-Longitudinal assessment of bariatric surgery study, 34 males with obesity were referred for bariatric surgery	Subnormal FT (< 0.23 nmol/L) prior to surgery: 73%
Van Hulsteijn *et al.*[21]	Meta-analysis of 68 studies with 19,996 obesity patients	Pooled prevalence of hypogonadism: Low TT 42.8% (95%CI: 37.6 - 48.0) Low FT 32.7% (95%CI: 23.1 - 43.0)
Risk for general or central obesity among individuals assessed for male hypogonadism		
Bonomi *et al.*[22]	Cohort study within the national network of academic or general hospitals, *N* = 503 patients with IHH	Prevalence of overweight: PPO-nIHH, 23.9% KS 31.5% AO-nIHH 42.8% AO-doIHH 50% Prevalence of obesity: PPO-nIHH, 15.6% KS 18.1% AO-nIHH 14.3% AO-doIHH 25%
Kapoor *et al.*[23]	Cross-sectional study of *N* = 355 T2DM aged > 30 years	Prevalence of obesity per the severity of hypogonadism: TT ≤ 8 nmol/L *vs.* 8-12 nmol/L or TT > 12nmol/L: 80% *vs.* 68% *vs.* 51%
Liu *et al.*[24]	Aging men (*N* = 819) aged 43-87 years from Taiwan Overweight defined as 24 < BMI ≤ 27 kg/m^2. Obesity defined as BMI > 27 kg/m^2	Prevalence of overweight and obesity: Biochemical TD, TT < 300 ng/dL and FT < 5 ng/dL: overweight 39.3% and obesity 27% Symptomatic AD: overweight 35.3% and obesity 17.3%
Mulligan *et al.*[25]	Hypogonadism in males study: 2,165 men aged ≥ 45 years	Prevalence of obesity in hypogonadal *vs.* normogonadal men: 32.3% *vs.* 17%

HIM: hypogonadism in males study; TD: testosterone deficiency; FT: free testosterone; BMI: body mass index; AD: androgen deficiency; IHH: isolated hypogonadotrophic hypogonadism; PPO: pre-pubertal onset; AO: adult onset; KS: Kallman syndrome; nIHH: normoosmic; AO-doIHH: adult onset isolated hypogonadotrophic hypogonadism with defective olfaction.

stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary gland and their release into the

systemic circulation[44,45]. Within the testes, LH molecules stimulate Leydig cells and induce testosterone production, while in combination with FSH, they support spermatogenesis[35,40]. In an obesigenic environment, leptin resistance negatively affects the function of the HPT axis[46,47]. Obesity-related leptin resistance upregulates hypothalamic release of the orexigenic agouti-related peptide neurons[48]. The agouti-related peptide is known to suppress the activity of kisspeptin neurons, which reduces the production of kisspeptin [46,49,50]. Simultaneously, obese males are characterized by low-grade inflammation secondary to excessive adiposity and energy storage overload. This low-grade inflammation is characterized by the release of pro-inflammatory cytokines like TNF-a and IL-6[27]. This pro-inflammatory state has been reported to compromise the activity of kisspeptin neurons due to their prolonged exposure to higher concentrations of TNF-a[27,51]. The ensuing suboptimal expression and activation of the kisspeptin receptor disrupt the GnRH pulse frequency, impair LH, and lower testosterone secretion[51,52]. Higher levels of TNF-a are known to further affect steroidogenesis by impairing cholesterol transportation into the mitochondria of Leydig cells, contributing to the state of hypogonadism[27,47,52].

Metabolic endotoxinaemia

The GELDING (Gut Endotoxin Leading to a Decline IN Gonadal function) theory supports that a key inflammatory trigger for developing MOSH is the trans-mucosal passage of bacterial lipopolysaccharide from the lumen of the gut to the circulation[53]. Testicular microbiota is closely linked with the gut microbiota; both exert an immune modifying role in protecting against invasion from pathogens[54]. High fat, with or without a high caloric diet, has been described to result in changes to intestinal wall permeability but also to the flora of the gut microbiome, breakdown of the mucosal barrier, and passage of the altered endotoxins to the circulation[53]. This change appears to lead to the direct or indirect destruction of spermatozoa[53,54]. In addition, metabolic endotoxemia in systemic circulation correlates with the severity of oxidative damage of sperm DNA, even after adjustment for BMI[55]. Moreover, metabolic endotoxemia also correlates with oxidative stress, which affects both the hypothalamus and the pituitary gland and results in subsequent inhibition of the release of LH[53,56]. Simultaneously, exposure of the testis to metabolic endotoxins activates the function of interstitial macrophages. The latter inhibits steroidogenic activity in Leydig cells by further promoting testicular oxidative stress, changes that result in lower testosterone production. Lower testosterone levels and local oxidative stress impair spermatogenesis in the seminiferous tubules and decrease sperm quality[53].

The role of hypogonadism in regulating body fat accumulation

Hypogonadism (also defined as testosterone deficiency; TD) is attributed to other comorbidities, such as T2DM, hypertension, and increased body fat mass, which contribute to low-grade inflammation, and increased secretion of adipocytokines and inflammatory cytokines[27]. Prospective studies have indicated that males with hypogonadism at baseline are at increased risk of visceral obesity and metabolic syndrome[57,58]. Moreover, data from studies in patients with prostate cancer treated with androgen deprivation therapy (ADT) showed that ADT causes an increase in BMI, suggesting that TD contributes to obesity[59,60]. Testosterone plays a crucial role in regulating body composition, exerting various molecular functions. It acts as an anabolic hormone essential for developing muscle mass and strength. Testosterone has been found to inhibit the differentiation of adipocytes while enhancing the expansion of myocytes, as both cell types share a common developmental origin[61,62]. This effect was confirmed in a study where treatment with testosterone or dihydrotestosterone downregulated key regulators of adipogenesis, namely the peroxisomal proliferator-activated receptor gamma (PPAR-γ) and CCAAT/enhancer binding protein alpha (C/EBPα), promoting myogenesis[63]. Testosterone also modulates lipid metabolism by promoting lipolysis in adipocytes, increasing the breakdown of triglycerides into free fatty acids and glycerol[64,65]. Androgens enhance lipolysis by upregulating β-adrenergic receptors in adipocytes, which are stimulated by catecholamines[65,66].

However, the effects of androgens on different fat depots remain controversial[67]. Studies have shown differential effects, with increased lipolysis observed in visceral fat explants but not subcutaneous fat retrieved from obese men treated with dehydroepiandrosterone (DHEA) for 24 h[67]. Moreover, low testosterone levels are associated with increased lipid uptake, as indicated by elevated expression of lipoprotein lipase (LPL), an enzyme with a central role in the lipid uptake process[68]. Testosterone replacement therapy in hypogonadal men has been shown to decrease LPL activity and lipid uptake, particularly in visceral abdominal depots[69,70]. Low testosterone levels contribute to increased adiposity by promoting adipogenesis, particularly in visceral fat depots[28]. In men with hypogonadism, testosterone levels negatively correlate with visceral fat mass and the incidence of obesity-related conditions, including nonalcoholic fatty liver disease (NAFLD) and obstructive sleep apnea (OSA)[71,72].

Hypogonadism and Nonalcoholic fatty liver disease

Earlier data demonstrated a bi-directional association between low testosterone levels and NAFLD in men[54,55]. Both obesity and NAFLD are independent predictors of developing hepatocellular carcinoma or cholangiocarcinoma[73]. Hence early diagnosis and appropriate management are recommended.

Hypogonadism in the setting of primary NAFLD

Andrologic conditions share cardiometabolic risk factors with metabolic syndrome and NAFLD[74]. Apart from the documented associations between low levels of total testosterone and sex hormone binding globulin (SHBG) with NAFLD[75-77], the severity of hepatic fibrosis in patients with nonalcoholic steatohepatitis (NASH) has been associated with diminished serum levels of DHEA[78-80]. NAFLD is associated with a decrease in hepatic synthesis of SHBG. This change results in hypogonadism, secondary to the altered feedback of testosterone to the HPG axis[74,81]. The obesigenic environment contributes to low-grade chronic hepatic inflammation[8,49]. This state is characterized by pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-a) and interleukin-1 (IL-1)[82,83]. In addition, excessive weight accumulation is associated with a high hepatic lipid content[84]. These pathophysiological changes are thought to suppress the hepatic production of sex hormone-binding globulin (SHBG), a molecule that acts as a transporter of sex hormones. SHBG has been described to suppress inflammation and decrease the fat content in adipocytes and macrophages[26]. Eventually, lower levels of SHBG, further suppressed by a state of insulin resistance[85], increase bioavailable testosterone levels, which provide negative feedback to the HPG axis. Suppression of the axis downregulates the release of gonadotrophins; the release of LH is further decreased secondary to the chronic presence of inflammatory cytokines[74]. Eventually, the production of testosterone will decrease, resulting in hypogonadism[74].

Secondary NAFLD in the setting of hypogonadism

A large body of epidemiological evidence indicates that hypogonadal men are at higher risk of NAFLD[71,76,86,87], while testosterone replacement therapy appears to improve both the lipid profile and adiposity measures[80,86,88,89]. A fair amount of data supported an association between low levels of androgens and increased de novo lipogenesis, which is manifested via an increase in enzymes involved in hepatic steatogenesis[90]. Preclinical studies have shown that inhibition of the AMP-activated protein kinase α-1 function results in the upregulation of SREBP-1 (sterol regulatory element-binding transcription factor - 1), fatty acid synthase and Acetyl-CoA carboxylase 1, changes that induce increased production of triglycerides as well as very low-density lipoprotein cholesterol. Simultaneously, the upregulation of SREBP-2 and the hydroxymethyl glutaryl Co-A (HMGCO) synthase and reductase, changes that promote cholesterol production[90]. Furthermore, activating the scavenger receptor class B type 1 (SR-B1) and stimulating hepatic lipase by testosterone can result in the hydrolysis of phospholipids and triglycerides. This process ultimately leads to increased uptake of specific cholesterol from HDL-C lipids by the liver and facilitates cholesterol

efflux from peripheral cells[91]. Serum DHEA plays a role in modulating homeostasis and has been linked to reduced insulin resistance, increased transcription levels of PPAR (peroxisome proliferator-activated receptor) genes, and regulation of tissue sensitivity to oxidative stress[77,78,92,93]. Expression of the transcription factor PPARα regulates procollagen type I, a precursor associated with the development of fibrosing NASH, and lipid metabolism[78,93,94]. Moreover, a large amount of evidence advocates that low gonadal function is also associated with the presence of cardiovascular risk factors such as both general and central adiposity and the ensuing cardiometabolic burden such as dyslipidemia, hypertension, and insulin resistance, which further contribute to the origin and progression of NAFLD[94]. Additionally, hypogonadism is linked to intestinal dysbiosis, as seen in animal studies, which may play a role in the development of NAFLD. Finally, changes in gut microbiota composition, such as alterations in Lactobacillus numbers and Firmicutes/Bacteroidetes ratio, can occur due to androgen loss[95]. The development of steatosis in castrated rodents fed a high-fat diet may be influenced by alterations in the abundance and composition of the intestinal microbiome and changes in hepatic lipid assembly and secretion[96]. Testosterone supplementation in castrated rodents has been shown to ameliorate hepatic steatosis induced by a high-fat diet[96]. These findings highlight the multifaceted influence of androgens on various factors implicated in the pathogenesis of NAFLD.

Role of NAFLD in the progression of obesity phenotypes

The development of hepatic steatosis with or without fibrosis is associated with obesity itself rather than metabolic health status[97]. A growing amount of data supports an association between the presence and severity of NAFLD and the progression of obesity phenotypes[98]. Individuals with a BMI-based definition of MHO have an almost 6 times higher risk for NAFLD, and those with the waist-circumference-based definition of MHO have an almost 7 times higher risk for NAFLD[99]. Patients diagnosed with the MHO phenotype who remain metabolically healthy over time do not appear at risk for NAFLD[100,101]. However, patients who progress to the MUO phenotype over time have a 2 times higher risk of baseline NAFLD[100,101]. Recent evidence highlighted the marked effect of disorders related to metabolic syndrome, such as NAFLD, rather than weight excess upon the progression between obesity-related metabolic phenotypes[98].

The interplay between hypogonadism, NAFLD, and depressive disorders

Low androgen levels occurring either in spontaneous cessation of gonadal function or androgen deprivation therapy are known to be related to mood disorders, including depression and anxiety[102]. In humans, testosterone has been shown to modulate neurobehavioral pathways[103]. Dihydrotestosterone has been shown to exert both neuroprotective and anti-neuroinflammatory effects on microglial cell lines and neurons[104], a group of cells closely related to the development of future depression[105]. Further *in vivo* evidence showed that androgens modulate the degree of neuroinflammation secondary to endotoxemia[106]. Depression is equally common in older hypogonadal men and middle-aged men with low-normal levels of testosterone[107,108]. Moreover, in a cohort retrieved from an erectile dysfunction clinic, hypogonadal middle-aged men have an almost 2 times higher risk for overt depression in comparison to normogonadal men[109].

Cognitive disorders, as well as depression and anxiety, are frequently encountered in patients diagnosed with NAFLD[110-113]. In pathophysiological terms, early stages of chronic liver disease have been shown to affect the cerebellum, prefrontal cortex, and hippocampus. The latter areas are essential for regulating mood, cognition, and memory[114,115]. In addition, NAFLD has been associated with developing a prothrombotic state, neuroinflammation, and dysregulation of the insulin and IGF-1 (insulin growth factor) pathway, expressed specifically in the brain. These changes contribute to neurodegeneration of the hippocampus and the prefrontal cortex, resulting in disorders of the central nervous system[112]. Patients

with biopsy-proven NAFLD present both subclinical and clinical depression (54% and 14%) and anxiety (45% and 25%, respectively). Subclinical and clinical depression were mainly associated with 2.1 times and 3.6 times higher grades of hepatocyte ballooning[116]. Evidence retrieved from murine models of NAFLD highlighted that hepatic lipid metabolism is interrelated with mitochondrial toxicity secondary to oxidative stress as well as with the serotonin pathway[117,118].

Given the above data, hypogonadal men with or without NAFLD are at higher risk for depression, which might require dedicated treatment. Treatment choices should be carefully selected to minimize the risk of further dysregulation of the metabolic profile[119]. Accordingly, the following drugs are known to affect blood pressure control: psychostimulants, antidepressants, antipsychotics, and mood stabilizers. The following drugs can modify insulin resistance and glycemic control, namely antipsychotics, mood stabilizers, and antidepressants. The prevalence of dyslipidemia is modified by antipsychotics and mood stabilizers, which are known to induce hypertriglyceridemia, as well as antidepressants known to induce hypercholesterolemia. Finally, weight gain is exacerbated by antipsychotics, mood stabilizers, and antidepressants[119].

Hypogonadism - visceral adiposity and Chronic kidney disease

Advanced CKD is also a risk factor for future hypogonadism[120]. In pathophysiological terms, renal failure is associated with various alterations of the pituitary and gonadal function, including the cyclic release of gonadotropin-releasing hormone (GnRH)[121], suppressed production of LH[122], and reduced clearance of prolactin[123,124]. The ensuing apparent hyperprolactinemia can further suppress LH production, resulting in a decrease in testosterone production[123]. In addition, the clearance of GnRH, LH, and FSH is downregulating, resulting in an apparent elevation of gonadotrophin levels[122,123]. The latter fails to induce testosterone production, either due to Leydig cell resistance or secondary to the downregulation of LH receptors in Leydig cells within a uremic environment[122]. CKD-related hyperparathyroidism also stimulates the synthesis of prolactin, further contributing to the development of hypogonadism.

Commonly prescribed medications in end-stage renal disease settings compete for androgen receptors and directly inhibit the synthesis of sex hormones[123]. Examples of such medications are spironolactone and cimetidine. Another effect observed in patients treated with spironolactone and ketoconazole is the further suppression of testosterone synthesis, achieved by reducing the activity of the 17a hydroxylase and C17-20 lyase enzymes. In addition, various other drugs are known to decrease the production of gonadal steroids through different mechanisms[123,125]: (a) Glucocorticoids, which interact with steroid receptors and the HPG axis, can downregulate steroid production; (b) Immunosuppressants affect the HPG axis and modify the function of Leydig cells, thereby reducing the production of gonadal steroids; (c) Drugs such as benzodiazepines, opiates, and tricyclic antidepressants hinder FSH and LH signaling, thereby blocking their effects.

Hypogonadism has also been highlighted to represent one of the significant hormonal disorders related to future CKD risk[125]. Pathophysiologically, low testosterone levels induce visceral fat accumulation, further downregulating testosterone levels. Through multiple mechanisms[126,127]. These mechanisms include[126,127]: (a) insulin resistance and increased pro-inflammatory cytokines; (b) hyperleptinemia; (c) suppression of the HPG axis; and ultimately, reduced testosterone production. Thus, testosterone deficiency and metabolic disorders create a cyclical relationship, where one condition perpetuates the other in a complex interplay of hormonal and metabolic dysregulation.

Visceral adiposity is a novel predictor of future CKD risk[128-130]. The pathophysiological link remains under investigation, yet there is evidence of a relation between intrahepatic fat accumulation and metabolic risk factors in CKD[131]. A growing amount of data indicate that the NAFLD diagnosis is related to a heightened risk of incident CKD, even after controlling for obesity, diabetes mellitus, and cardiovascular risk factors[132]. The balance of the "kidney-liver" axis in patients with NAFLD is modified by the effect of the following parameters [132]: (a) shared genetic polymorphisms for NAFLD and CKD; (b) modifiable lifestyle factors such as obesity; (c) adipose tissue changes which promote de novo hepatic lipogenesis and steatosis; (d) metabolic dysfunction of skeletal muscles known as myosteatosis; (e) intestinal dysbiosis, a link between physical inactivity and unhealthy dietary habits, which manifests in the form of increased production of a variety of microbial metabolites, nephrotoxins, and hepatotoxins; (f) increased nephrotoxic burden, secondary to the hepatic metabolism of the previously mentioned metabolites.

Hypogonadism and Obstructive sleep apnea

The relation between hypogonadism and obstructive sleep is bi-directional[133]. Patients diagnosed with OSA, a frequent complication encountered in states of obesity, have significant evidence of sleep fragmentation, less REM (rapid eye movement) sleep, reduced deep sleep time and efficiency, and more frequent night-time wakings and arousal[133]. These changes contribute to a lowering of testosterone levels[134]. In turn, OSA and the related sleep disorders are associated with disruption of testosterone's circadian manner, with attenuation of the nocturnal increase in testosterone levels[135,136]. Consequently, the downregulation of the GnRH waves results to lower LH levels, which downregulate the function of Leydig cells, contributing to hypogonadism[133]. In addition, a recent cross-sectional study of young male obese participants reported that a short sleep overnight is associated with a greater risk for MOSH in this population[137].

MANAGEMENT OPTIONS IN OBESITY-RELATED HYPOGONADISM

Treatment options in patients with MOSH

The efficacy of weight loss management in controlling obesity-related hypogonadism largely depends on the extent of weight loss. In this context, preliminary evidence showed that 10% of weight loss, induced by changes in lifestyle as well as physical activity and diet therapy, is associated with beneficial effects on the severity of MOSH[138]. In addition, a diet plan which consists of probiotic and synbiotic supplements can be beneficial, as it has been demonstrated to reduce free radicals in the semen and to enhance sperm quality and motility[54]. However, a low-calorie diet remains inferior to bariatric surgery concerning weight loss efficacy and the related restoration of hypogonadism in male patients with obesity[139].

Weight loss and the role of bariatric surgery

Evidence from a meta-analysis and small prospective studies on weight loss following bariatric surgery showed that the restoration of sex hormones at 12 months post-surgery is related to the percentage of weight lost[13,16,140]. Bariatric surgery is beneficial for severely obese patients, as it results in the resolution of MOSH in 87% of affected men[16]. A small study on severely obese men showed that the weight loss induced by laparoscopic gastric bypass or restrictive bariatric techniques (e.g., sleeve gastrectomy and adjustable gastric banding) is comparable and results in comparable restoration of insulin resistance and increased free testosterone levels[13]. A small prospective study of 12 obese males, who underwent obesity surgery, showed that MOSH was resolved six months post-surgery[141]. A recent meta-analysis demonstrated the beneficial effect of the ketogenic diet, adherence to which improved levels of total testosterone; however, the extent of the effect was mediated by the patient's age and weight loss. More specifically, adherence to very low calorie *vs.* normo-caloric ketogenic diet was associated with a significantly more pronounced increase in testosterone levels[142].

Many studies evaluated the association between weight loss and physical disorders associated with MOSH. For example, bariatric surgery has been reported to improve scores of erectile functions at 12 months after the intervention[143]. Another meta-analysis described that obese males with surgically induced weight loss were associated with improved erectile function, erection, and ejaculation scores, as well as overall sexual satisfaction[129].

The effect of weight loss on the results of the semen analysis remains inconsistent. The majority of studies demonstrated that obese or severely obese men who went through bariatric surgery did not experience a change in semen volume, concentration, motility, and total sperm count after the surgery[143,144]. One more small study showed that laparoscopic roux-en-Y-gastric bypass was associated with an increase in semen viability and semen volume, decreased sperm DNA fragmentation, and seminal interleukin-8 levels[145]. The same study supported that BMI variations correlated with alterations in sperm number and morphology, and semen volume[145]. An earlier meta-analysis showed that gastric bypass surgery was associated with an increase in semen volume, whereas semen morphology was found to be increased after sleeve gastrectomy[144]. Results evaluating the effect of bariatric surgery on sperm morphology are still inconsistent, with small prospective studies reporting a decrease in the percentage of semen with normal morphology[141,146]. On the contrary, a recent meta-analysis described that bariatric surgery was associated with increased sperm morphology 12 months post-surgery[143] Table 2 .

Other options for medical treatment

In an attempt to regulate the severity of the hypogonadism related to MOSH, medications focusing on controlling the enzyme aromatase have started gaining attention. Evaluating the effect of weight loss with and without aromatase inhibition, a small study of 23 male patients with severe obesity described that the combination of weight loss/aromatase inhibition vs. weight loss/placebo is associated with an improved hormonal profile but no significant improvement in symptoms of hypogonadism[147]. In addition, a small study of hypogonadal and subfertile men (BMI ≥ 25 kg/m^2) who received treatment with 1 mg anastrozole for five months evaluated the efficacy of this fourth-generation aromatase inhibitor in features of hypogonadism. This study showed an increase in FSH, testosterone, and testosterone-to-estradiol ratio, as well as an increase in sperm concentration, strict morphology, and total motile count[148].

Testosterone replacement has been proven to be beneficial in the treatment of hypogonadal patients. Although changes in lifestyle aiming to achieve significant weight loss should be the basis of treatment, in some cases, testosterone therapy may be indicated, as in those men with multiple signs and symptoms of hypogonadism and concomitantly reduced levels of testosterone[149]. Furthermore, testosterone therapy in men with TD causes weight loss and reduces BMI. These facts suggest that testosterone treatment contributes to reversing obesi[150]. According to the latest guidelines, treatment with testosterone replacement for the short term (3-6 months) can be offered individually to patients with obesity-related hypogonadism, provided other reasons for hypogonadism have been excluded. The gel preparations are preferred over the depot injections, and treatment should be discontinued if there is no improvement in clinical symptoms in 3 months[8,151]. In obese men with hypogonadism, this treatment has been shown to improve body composition and have beneficial effects on metabolic risk factors and the underlying pathophysiological mechanisms. Its use has not been shown to increase the risk of cardiovascular events in this population[27,150].

Personalized medicine approach

Considering the close interrelation between hypogonadism and multiple metabolic manifestations, the evaluation of male hypogonadism in daily clinical praxis will benefit from a personalized medicine approach

Table 2. Practical recommendations for the assessment of patients with suspected or confirmed hypogonadism. Adapted from[151]

Recommendations
(A) If presenting in the obesity clinic: Biochemical assessment of gonadal function (i.e., free testosterone, follicle-stimulating hormone, luteinizing hormone, total testosterone, sex hormone binding globulin, free testosterone) and clinical investigation for hypogonadal symptoms *(B) If presenting in the andrology clinic*: Evaluate anthropometric parameters (i.e., weight, height, waist circumference) for possible generalized obesity or central adiposity
Blood test for assessment of liver and kidney function, blood lipids, and glycemic control
Assess for a possible underlying mood disorder. If needed, treat with a cardiometabolic neutral agent
Investigate for possible obstructive sleep apnea
Detailed medical history for possible intake of medications interfering with gonadal steroid production

concerning the assessment of metabolic disorders[152]. The practical recommendations for assessing patients with suspected or confirmed hypogonadism are outlined in Table 2.

CONCLUSION AND RESEARCH AGENDA

The state of obesity-induced male gonadal dysfunction, most commonly known as MOSH, manifests with various symptoms which can affect not only gonadal function per se but also the overall quality of life. The link between male hypogonadism and weight excess, including the related cardiometabolic and hepatorenal complications, remains bidirectional. We discussed the pathophysiology of these associations and the most indicated management approach. In addition, the extent of additional body weight is associated with the degree of the gonadal compromise, with obese patients experiencing more symptoms and complications compared to their overweight or lean counterparts. Consequently, weight loss remains the most eligible treatment option, which should either be attempted with lifestyle and dietary measures or with the use of medical agents and bariatric surgery. However, further research is required to estimate the BMI and/or WC cut-off, which will predict gonadal dysfunction with reasonable sensitivity and specificity. Moreover, further research is required to explore the role of clinical or subclinical hypogonadism with regard to the balance of the "kidney-liver" axis in patients with a NAFLD diagnosis.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

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