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## REVIEW

Male Health

# Secondary male hypogonadism: a prevalent but overlooked comorbidity of obesity

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Male hypogonadism associated with obesity is a very prevalent condition and is increasing in parallel with the epidemic prevalence of obesity. Low testosterone levels promote higher fat mass with reduced lean mass. Male hypogonadism is related to an increase in associated cardiometabolic complications, such as hypertension, type 2 diabetes mellitus, the metabolic syndrome, and cardiovascular disease. Its influence as a comorbidity of obesity is becoming more evident and should be evaluated and treated in at-risk patients. Mechanisms involved in this relationship include body composition changes, the presence of adipokines, insulin resistance, and other factors, some of which are still unknown. Weight loss and treatment to replace testosterone levels improve the metabolic profile and quality of life in patients with obesity and hypogonadism; these beneficial effects depend on treatment modality and duration of therapy. The use of testosterone replacement therapy may be indicated, as it has not been shown to increase cardiovascular risk, and retrospective studies suggest a reduction in events in men with metabolic syndrome and type 2 diabetes.

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## INTRODUCTION

In recent decades, the prevalence of obesity and overweight has increased substantially. Globally, the number of overweight and obese individuals increased from 857 million in 1980 to 2.1 billion in 2013.<sup>1</sup> To explain this pronounced increase, the influence of factors such as increased caloric intake, dietary changes, decreased physical activity, and alterations in the intestinal microbiome must be considered.<sup>2</sup> Obesity is directly related to a large number of comorbidities, such as type 2 diabetes (T2DM), nonalcoholic fatty liver disease, osteoarthritis, cardiovascular disease, and cancer arising from the severe metabolic alterations caused by excess weight.<sup>3</sup>

Obesity is considered the most frequent cause of male hypogonadism.<sup>4,5</sup> Male hypogonadism is the clinical syndrome resulting from the inability to produce physiological concentrations of testosterone, normal amounts of sperm, or both. It can adversely affect multiple organ functions and quality of life.<sup>6,7</sup>

The increase in life expectancy and prevalence of obesity in Western industrialized countries has given rise to an increasing number of cases of male hypogonadism. Hypogonadism is estimated to affect between 2.1% and 12.8% of adult men in the general population, and its prevalence will increase to 6.5 million by 2025 as a result of an aging population.<sup>8</sup> Androgen deficiency leads to reduced fertility, sexual dysfunction, decreased muscle mass, alterations in bone mineralization, and lipid metabolism disorders in men.

Numerous epidemiological studies have shown a negative correlation between obesity and testosterone levels, and several meta-analyses have shown that weight loss produces a proportional increase in testosterone concentrations.<sup>9</sup> Furthermore, an increase in adipose tissue has been observed in patients with hypogonadism. Patients in testosterone replacement therapy have shown a reduction in abdominal circumference and adipose tissue, together with an increase in muscle mass.<sup>10</sup> The relationship between hypogonadism and obesity is, therefore, bidirectional.

There is also a greater prevalence of hypogonadism in patients with conditions directly related to obesity, such as T2DM and metabolic syndrome (MS).<sup>11,12</sup> The pathophysiological links between all these disorders are complex, but adipose tissue plays an important role, especially when localized to the abdomen.<sup>10</sup>

In this review, we summarize current knowledge about the close relationship between obesity and male hypogonadism.

## MECHANISMS INVOLVED IN THE RELATIONSHIP BETWEEN MALE HYPOGONADISM AND OBESITY

Obesity-associated hypogonadism is characterized by normal or low levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and decreased plasma testosterone.<sup>5</sup>

The gonadal axis (hypothalamus–pituitary–gonadal axis) is regulated by a set of hypothalamic neurons that respond to stimulation by the kisspeptin peptide hormones. These neurons produce

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gonadotropin-releasing hormone (GnRH), which is released in pulses every 60–90 min, stimulating the pulsatile secretion of the pituitary gonadotropins, LH and FSH, into the bloodstream. LH stimulates Leydig cells to produce testosterone, while FSH, in conjunction with intratesticular testosterone, acts on Sertoli cells and seminiferous tubules to stimulate spermatogenesis. In turn, the hormone inhibin is produced in Sertoli cells, which provides negative feedback on the production of FSH in the pituitary gland. Testosterone acts directly through androgen receptors and by its conversion into two active metabolites, dihydrotestosterone, by the enzyme 5- $\alpha$  reductase, and estradiol, by the enzyme aromatase. Testosterone and estradiol provide negative feedback to the hypothalamus and pituitary gland to suppress the secretion of gonadotropins.<sup>7</sup>

Obesity in men is associated with an increase in the aromatase enzyme activity of adipocytes, which results in a higher peripheral conversion of testosterone to estradiol and, traditionally, it has been thought that the consequent rise in serum estradiol exerts negative feedback on the secretion of LH from the pituitary gland, due to the presence of estrogen receptors in the hypothalamus–pituitary–gonadal axis, thereby suppressing the axis and leading to a reduction in testosterone levels. Reduced plasma testosterone worsens obesity since it promotes changes in body composition, stimulating an increase in adipose tissue, mainly in the abdomen. Obesity, in turn, may have a direct impact on testosterone levels, contributing to reduced testosterone and increased adipose tissue, creating a negative cycle called the hypogonadism-obesity cycle. The extension of this theory is based on the fact that adipose tissue is an endocrine organ that secretes various factors that influence the pathogenesis of obesity and affect testosterone production, contributing to the onset of hypogonadism. This is known as the hypogonadism-obesity-adipokine hypothesis.<sup>10</sup>

However, the role of estradiol is controversial in light of recent findings. Since in men, most of the circulating estradiol (80%) derive from peripheral aromatization of testosterone or conversion of estrone and only 10%–20% is directly secreted by the testes,<sup>13</sup> lower testosterone levels should lead to lower estradiol levels. In a meta-analysis studying the relationship between body mass index (BMI) and reproductive hormones, MacDonald *et al.*<sup>14</sup> found a direct relationship between BMI and estradiol in only 4 of 10 studies determining estradiol levels. In fact, large population-based studies using liquid chromatography–tandem mass spectrometry (LC-MS/MS) have reported lower estradiol levels in hypogonadal men compared with eugonadal men.<sup>15,16</sup> Indeed, increased estradiol levels have only been reported in extremely obese men,<sup>17,18</sup> suggesting that increased estradiol contributes to the development of hypogonadism only in extremely obese men.

## TESTOSTERONE AND BODY COMPOSITION

Testosterone influences metabolism. One of the mechanisms is through changes in body composition. In fact, testosterone inhibits fat accumulation through its binding to the androgen receptor, which has a higher density in visceral adipose tissue than in subcutaneous adipose tissue.<sup>19</sup> In addition, testosterone plays an inhibitory role in lipoprotein lipase activity by inhibiting lipid accumulation and favoring lipolysis in visceral adipocytes.

By contrast, decreased testosterone levels could be implicated in the lack of negative regulation of both the differentiation of preadipocytes into mature adipocytes and pluripotent mesenchymal stem cells into adipocytes, which leads to increased adipose tissue related to hypogonadism.<sup>20</sup> Central or abdominal fat is more closely related to testosterone levels than other forms of obesity.<sup>21</sup> Abate *et al.*<sup>22</sup> showed that the accumulation of subcutaneous fat in the trunk was highly

predictive of low levels of free testosterone (FT). Couillard *et al.*<sup>23</sup> in the HERITAGE study, which included 217 men aged 17–64 years, found that abdominal fat was the most important parameter related to testosterone levels. Vermeulen *et al.*<sup>24</sup> found that testosterone levels negatively correlated with body fat percentage and abdominal fat in a study of 57 men between 70 and 80 years old. Garaulet *et al.*<sup>25</sup> carried out a study with 80 obese people (29 men), between 30 and 70 years old. They found an inverse relationship between testosterone levels and fat mass percentage and total abdominal fat. Finally, Dhindsa *et al.*<sup>26</sup> conducted a study on 138 men with T2DM, with a mean age of 59 years and a mean BMI of 31.8 kg m<sup>-2</sup>, finding an inverse correlation between FT and total testosterone (TT) levels and total subcutaneous and trunk fat.

Visceral fat is the most metabolically active fraction of body fat mass. It constitutes a significant proportion of intra-abdominal fat. Testosterone in men has been shown to be a lipolytic hormone, with selective activity at the intra-abdominal level.<sup>27</sup> In 1990, Seidell *et al.*<sup>28</sup> found a negative correlation between FT and visceral fat determined by computed tomography in 23 healthy men between 25 and 50 years old. Subsequently, Tsai *et al.*<sup>29</sup> showed an inverse relationship between TT levels and visceral fat accumulation (also determined by computed tomography), but not other fatty deposits, in a population of 110 males after 7.5 years of follow-up. In the previously mentioned study by Couillard *et al.*,<sup>23</sup> in addition to increased abdominal adiposity, they also found greater accumulation of visceral fat in patients with low testosterone. In 2007, Nielsen *et al.*<sup>30</sup> in a population of 685 young men, 70 of them obese, found that the degree of visceral fat measured by dual-energy X-ray absorptiometry and magnetic resonance imaging was inversely related to free and bioavailable TT. Furthermore, in a multiple linear regression analysis, visceral fat was independently and inversely related to FT and bioavailable testosterone.<sup>30</sup> However, Abate *et al.*<sup>22</sup> found that subcutaneous fat in the trunk, but not visceral fat, was highly predictive of plasma concentrations of testosterone. In fact, patients with prostate cancer who were on antiandrogen hormone treatment develop an increase in central adiposity and percentage of fat mass, with a decrease in lean mass. While Smith *et al.*<sup>31</sup> observed that this change in body fat affected mainly subcutaneous and nonvisceral depots, Hamilton *et al.*<sup>32</sup> reported a higher increase in visceral abdominal fat area than in subcutaneous abdominal fat area. With respect to testosterone replacement therapy, some studies show a clear decrease in visceral fat, while others find either no decrease in abdominal or visceral fat mass or a decline in subcutaneous fat in the limbs but not in the abdomen.<sup>9</sup>

Therefore, in conclusion, the evidence suggests the existence of a link between testosterone deficiency and the development and progression of obesity, but it remains unclear if this association is more apparent in visceral or in subcutaneous depots.

In addition to increased fat mass, decreased muscle mass is a key feature in obesity that contributes to several related metabolic disorders. Testosterone is an anabolic hormone and its effect on increase in muscle mass is well documented.<sup>12</sup> The administration of testosterone stimulates the synthesis of muscle proteins, causes hypertrophy of muscle fiber, and increases the myonuclear content per fiber and satellite cells, which give the muscle strength. In addition, testosterone exerts inhibitory effects on the differentiation of multipotent mesenchymal cells into adipogenic cells and promotes their differentiation into cells of myogenic lineage.<sup>20</sup> Multiple cross-sectional studies demonstrate the positive association between testosterone levels and muscle mass in men.<sup>28–30,33–35</sup>

## ROLE OF ADIPOCYTOKINES IN MALE HYPOGONADISM ASSOCIATED WITH OBESITY

Adipose tissue, as an endocrine and metabolic organ, expresses and secretes active metabolites such as leptin, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin-6 (IL-6). Leptin stimulates GnRH-producing cells in the hypothalamus to induce the release of LH and in the testis stimulates the production of testosterone under normal conditions. This stimulation of hypothalamic GnRH-producing neurons is not directly done by leptin, whose receptors are expressed scarcely on them, but by kisspeptins. Hypothalamic cells produce kisspeptins and express the leptin receptor. Obesity is typically associated with higher levels of leptin derived from the high percentage of fat mass, which does not decrease after the exogenous administration of leptin, suggesting that obese individuals are resistant to it.<sup>36</sup>

Most obese individuals have high serum leptin concentrations mainly due to diet-induced expansion of adipocytes.<sup>37,38</sup> Despite hyperleptinemia, these patients are considered to be resistant to the effects of leptin. This hyperleptinemia seen in obesity may play a role in hypogonadism and subfertility due to the development of leptin resistance, akin to insulin resistance. Based on *in vitro* and rodent studies, several mechanisms of leptin resistance have been proposed, including impaired transport across the blood-brain barrier, impaired leptin signaling by suppressor of cytokine signaling 3 (SOCS3), impaired leptin receptor trafficking, saturation of leptin signaling pathways, endoplasmic reticulum stress, and downmodulation of leptin's neural circuitry.<sup>39,40</sup> A few of these mechanisms have been confirmed in human studies.<sup>41</sup> There may be other factors, including genetic factors, that make certain individuals predisposed to the adverse reproductive effects of central leptin resistance. Leptin concentrations have been found to inversely correlate with testosterone concentrations, even after controlling for sex hormone-binding globulin (SHBG) and estradiol, and leptin concentrations were the best hormonal predictor of low androgen concentrations in obesity.<sup>42</sup>

It has been proposed that this resistance to leptin also exists at the central level, favoring hypogonadism.<sup>43</sup> In addition, elevated leptin levels may directly inhibit the production of testosterone in Leydig cells, further decreasing it.<sup>43</sup> Both TNF- $\alpha$  and IL-6 are also expressed in adipose tissue. An elevation in their levels creates a pro-inflammatory state involved in the pathophysiology of obesity and insulin resistance and also negatively influences the secretion of gonadotropins.<sup>44</sup>

Adiponectin is an adipocyte-specific secretory protein which exhibits antiatherogenic, anti-inflammatory, and antidiabetic properties. It is produced mainly by visceral adipose tissue. Interestingly and in contrast to other adipocytokines, for example, leptin and adiponectin levels are reduced among obese individuals in comparison with lean controls and increase concomitantly with weight loss. Compared to eugonadal patients, hypogonadal men have higher adiponectin levels which are reduced by testosterone replacement therapy. Overall, the evidence suggests that testosterone exerts a negative regulatory role on adiponectin secretion in humans.<sup>45</sup> While this is expected to be metabolically unfavorable, testosterone treatment-induced reductions in adiponectin were not accompanied by reduced insulin sensitivity.

In conclusion, the interplay among testosterone, adipocytokines such as leptin and adiponectin, and glucose metabolism is complex, bidirectional, and linked with body composition in a way that makes it difficult to determine the precise role of these factors in the overall regulation of whole body metabolism.

## TESTOSTERONE AND INSULIN RESISTANCE

Most studies suggest that the effects of testosterone on insulin resistance occur through changes in body composition. Many of these studies linking hypogonadism with insulin levels have been performed in men with prostate cancer in antiandrogen hormone therapy. These patients present an increase in visceral fat, which is related to an increase in insulin resistance, aggravated by a concomitant decrease in muscle mass.<sup>21</sup> Increased abdominal fat causes higher concentrations of free fatty acids to be delivered to the liver. With more free fatty acids, there is a higher production of hepatic glucose and a decrease in insulin uptake. This results in hyperinsulinemia and increased insulin resistance in peripheral tissues, which also leads to further release of insulin by  $\beta$ -cells.<sup>46</sup> Several studies of obese hypogonadal patients with T2DM on testosterone treatment versus placebo or diet and exercise found a decrease in insulin resistance (measured by Homeostasis Model Assessment for Insulin Resistance [HOMA-IR]) in the testosterone replacement therapy group.<sup>47-49</sup> Nevertheless, Grossmann *et al.*<sup>50</sup> in a meta-analysis reported that the effect of testosterone in insulin resistance was nonsignificant when measured using a more stringent computer-based equation, different from the simple linear equation used in previously reported studies. On the other side, some studies have found higher prevalence of insulin resistance among patients with hypogonadism compared to those without it<sup>51,52</sup> and negative correlations between insulin resistance and testosterone levels.<sup>53-57</sup>

In summary, the current evidence is consistent with a bidirectional relationship between visceral fat and testosterone levels, creating a self-perpetuated cycle that promotes insulin resistance.

## OTHER MECHANISMS LINKING OBESITY AND HYPOGONADISM

Another proposed mechanism for the influence of obesity on the development of hypogonadism is through its effects on sleep quality. Studies have established that obstructive sleep apnea (OSA) associated with obesity disrupts the gonadal axis, interfering with the secretion of LH at night and, therefore, with testosterone levels. It has been reported that OSA is independently associated with decreased LH pulse amplitude, decreased mean serum LH and testosterone levels, and disruption of serum testosterone levels associated with the onset of the first rapid eye movement (REM) sleep. Men with OSA present higher circulating leptin levels, regardless of age and BMI.<sup>5</sup> In addition, the relationship between obesity and sleep seems to be bidirectional. Lack of sleep has recently been implicated as a risk factor for the development of obesity and its complications. Although the exact mechanism is unclear, it appears to be mediated by alterations in the concentrations of different neuroendocrine modulators, including leptin and cortisol.<sup>58</sup> Nonetheless, other studies establish that OSA is not a factor favoring hypogonadism independent of obesity.<sup>59</sup>

Most circulating testosterone is bound to SHBG or albumin and only 1%–3% circulates as FT. Changes in SHBG greatly affect the interpretation of testosterone concentrations.<sup>60</sup> Obesity is negatively related to SHBG levels, which in turn affect the serum levels of testosterone. Frequently, in moderate obese men, there are “falsely” low levels of TT with normal FT. The liver secretes SHBG into the blood, where it binds testosterone with high affinity, regulating its bioavailability. Traditionally, it has been postulated that the link between obesity and SHBG may be mediated by insulin resistance and compensatory hyperinsulinemia, which suppresses hepatic SHBG production. Nevertheless, more recently, it has been shown that liver fat, but not visceral fat or total body fat, influences



SHBG levels,<sup>61</sup> and fatty liver is considered the main risk for lower SHBG levels. The free hormone hypothesis, which states that only free steroids diffuse into cells, is still the best explanation for the clinical manifestations of steroid hormone deficiency, but it has been proposed that SHBG leaves the blood circulation in some tissues, interacting with proteins on the plasma membranes of specific cell types. This may contribute to the delivery of SHBG-bound sex steroids via endocytotic mechanisms or lead to cell membrane receptor-mediated signaling,<sup>62</sup> so reduced SHBG could result in decreased testosterone action in this situation. On the other side, lower levels of SHBG allow greater availability of FT as a substrate for aromatization to estradiol in adipose tissue.

Due to the direct effect of obesity on reducing circulating SHBG, it is important to consider SHBG levels when diagnosing hypogonadism.<sup>61</sup>

### PREVALENCE OF MALE HYPOGONADISM ASSOCIATED WITH OBESITY

There has been ongoing interest in the relationship between obesity and hypogonadism. As early as 1977, Glass *et al.*<sup>56</sup> observed that testosterone levels were lower in obese patients than in normal-weight controls. Since then, numerous studies have confirmed this relationship and have established a high prevalence of hypogonadism in obese patients.

In 2008, Hofstra *et al.*<sup>63</sup> reported a prevalence of hypogonadism of 57.7% according to TT criteria ( $<3 \text{ ng mL}^{-1}$ ) and 35.6% according to FT criteria ( $<65 \text{ pg mL}^{-1}$ ) in a population of 149 men between 18 and 66 years of age with a mean BMI of 42.7 (standard deviation [s.d.]:  $0.7 \text{ kg m}^{-2}$ ) and a prevalence of T2DM of 37%. Calderón *et al.*<sup>64</sup> found a 68.5% prevalence of hypogonadism according to TT criteria ( $<3 \text{ ng mL}^{-1}$ ) in a population of 35 men prior to bariatric surgery (mean BMI:  $42.7 \text{ [s.d.: } 0.7] \text{ kg m}^{-2}$ , mean age:  $39.5 \text{ [s.d.: } 9.5] \text{ years}$ ) and 45.7% according to FT criteria ( $<65 \text{ pg mL}^{-1}$ ). Although the prevalence of T2DM was not specified, mean fasting glucose was  $>110 \text{ mg dL}^{-1}$ , indicating that a significant percentage of patients could be diabetic. A recent study by the same research group, conducted with 100 men (mean age:  $40.5 \text{ [s.d.: } 9.5] \text{ years}$ , BMI  $\geq 35 \text{ kg m}^{-2}$ ), found a prevalence of hypogonadism according to TT and/or FT criteria (considering normal range for TT to be  $2.88\text{--}8.94 \text{ ng mL}^{-1}$  and for FT to be  $65\text{--}183 \text{ pg mL}^{-1}$ ) of 45%.<sup>65</sup> When considering only TT, the prevalence was 44% and decreased to 34% when considering only FT. Again, the prevalence of T2DM is not specified, but mean fasting glucose in the group of patients with hypogonadism is  $129.7 \text{ (s.d.: } 55.8) \text{ mg dL}^{-1}$ , thus the number of diabetic patients could be significant. In 2009, Caldas *et al.*<sup>66</sup> studied 80 men with MS (mean BMI  $>30 \text{ kg m}^{-2}$ , mean age:  $42 \text{ [s.d.: } 12] \text{ years}$ ) to determine the relationship between insulin and hypogonadism and found a prevalence of hypogonadism of 30%, according to TT criteria  $<3 \text{ ng mL}^{-1}$ . In this case, the prevalence of T2DM was not specified, but it was not an exclusion criterion. However, the largest study on hypogonadism is the Hypogonadism in Males study,<sup>67</sup> which included 2165 men aged  $\geq 45$  years. Defining hypogonadism as TT  $<300 \text{ ng dL}^{-1}$  ( $<3 \text{ ng mL}^{-1}$ ), a prevalence of 38.7% was found. Of the patients with hypogonadism, 32.3% were obese and 30.9% had T2DM. In a substudy of this same study,<sup>67</sup> data from 1849 men (1451 nondiabetic and 398 diabetic) were examined to determine the prevalence of hypogonadism in patients with obesity and T2DM. Of this sample, 489 were nondiabetic obese. A prevalence of hypogonadism, defined as FT  $<50 \text{ pg mL}^{-1}$ , of 34.6% (s.d.: 3.2%) was observed in this group, whereas in obese patients with T2DM, this prevalence increased to 36.4% (s.d.: 3.2%) (Table 1).

### TREATMENT OF HYPOGONADISM ASSOCIATED WITH OBESITY

#### Weight loss: changes in lifestyle and bariatric surgery

Several studies have shown that in people at risk, intensive lifestyle interventions, including nutritional counseling and physical activity, can reduce body weight and insulin resistance and improve hypogonadism associated with obesity. Loss of body weight is associated with an increase in gonadotropins, TT, and FT, and in most studies with a decrease in estrogen levels.<sup>68</sup>

Few randomized clinical trials have specifically assessed the impact of diet and physical activity on testosterone levels in obese men, and those available have obtained contradictory results. Some show an increase in testosterone, while others find no change or even a decrease.<sup>68</sup> In the studies analyzed in the meta-analysis by Corona *et al.*,<sup>68</sup> the increase in testosterone induced by lifestyle interventions was modest (Table 2). This likely reflects the relatively limited results of diet and physical activity on body weight loss. Changes in lifestyle, however, should be the first measure proposed in patients with obesity-associated hypogonadism.

Nonetheless, most of the weight lost with diet and exercise is regained in the long term in the majority of patients. Consequently, bariatric surgery is another option for reducing body weight and treating hypogonadism associated with obesity.<sup>69</sup> Our knowledge of the long-term effects of bariatric surgery is based only on observational, nonrandomized studies that are often of poor methodological quality. In recent years, several studies have evaluated the impact of bariatric surgery on testosterone levels in men, showing increased levels and even complete recovery of gonadal axis function in most cases.<sup>18</sup> The beneficial effects of weight loss are more striking in younger patients and in nondiabetic controls with a higher degree of obesity presurgery, likely due to greater weight loss.<sup>18,70</sup> At the same time, the normalization of testosterone levels contributes to the reduction in weight, waist circumference, and fat mass, which enhances the beneficial effects of bariatric surgery in terms of decreased development of T2DM, MS, cardiovascular disease, and reduced mortality (Table 2). In a study published in 2014, comparing the effect of bariatric surgery in hypogonadal obese patients versus obese men with normal gonadal status, a greater decrease in waist circumference was observed in the hypogonadal patients with the same weight loss, suggesting that bariatric surgery may have a specific effect on abdominal adiposity in hypogonadal patients.<sup>69</sup> For these reasons, several articles propose hypogonadism associated with obesity as a potential new indication for bariatric surgery.

#### Testosterone treatment

The effect of testosterone treatment in men with hypogonadism is beneficial in most cases, although relatively long periods of time are often required to observe their metabolic effects. In addition, the temporal course of these effects differs depending on the dose or formulation chosen, among other variables. Many studies have demonstrated minimal or moderate effects on body weight and body composition, although the results have been evaluated in the short term. Hoyos *et al.*<sup>71</sup> failed to demonstrate a beneficial effect of testosterone treatment on weight or MS and suggested the need for long-term studies. Systematic reviews of studies with testosterone therapy in men with hypogonadism reveal that changes in fat mass and lean mass occurring at 12–16 weeks of treatment stabilize at 6–12 months and that there is even a marginal improvement for years. In a recently published 56-week clinical trial,<sup>72</sup> it was reported that in men receiving very low energy diet combined with testosterone undecanoate or matching placebo, patients assigned to testosterone

**Table 1: Studies reported hypogonadism prevalence in obese males**

Study	Population characteristics	Diabetes	Hypogonadism prevalence according to TT criteria (%)	Hypogonadism prevalence according to FT criteria (%)
Mulligan <i>et al.</i> <sup>67</sup> 2006	n=2165 Mean age: 60.5 (s.d.: 10.3) years 32.3% obese Mean BMI: 29.7 (s.d.: 5.64) kg m <sup>-2</sup>	30.9%	38.7 <sup>a</sup>	
Hofstra <i>et al.</i> <sup>63</sup> 2008	n=149 Mean age: 43.3 (s.d.: 0.8) years 100% obese Mean BMI: 42.7 (s.d.: 0.7) kg m <sup>-2</sup>	37%	57.7 <sup>a</sup>	35.6 <sup>b</sup>
Caldas <i>et al.</i> <sup>66</sup> 2009	n=80 Mean age: 42 (s.d.: 12) years 100% obese Mean BMI in hypogonadic patients: 34.7 (s.d.: 6) kg m <sup>-2</sup> and in nonhypogonadic patients: 31.9 (s.d.: 4.9) kg m <sup>-2</sup>	Unknown (not exclusion criteria)	30 <sup>a</sup>	
Dhindsa <i>et al.</i> <sup>57</sup> 2010	n=1849 HIM substudy Mean age: 60.9 (s.d.: 10.2) years 38.7% obese Mean BMI: 29.7 (s.d.: 5.6) kg m <sup>-2</sup>	21.5%		35 <sup>c</sup>
	n=489 Nondiabetic obese Mean age: 57.9 (s.d.: 7.1) years Mean BMI: 34.6 (s.d.: 3.2) kg m <sup>-2</sup>	0		40 <sup>c</sup>
Calderón <i>et al.</i> <sup>64</sup> 2014	n=35 Mean age: 39.5 (s.d.: 9.5) years 100% obese Mean BMI: 42.7 (s.d.: 0.7) kg m <sup>-2</sup>	All FPG: 115.6 (s.d.: 47.7) mg dl <sup>-1</sup> (diabetes prevalence not specified)	68.5 <sup>a</sup>	45.7 <sup>b</sup>
Calderón <i>et al.</i> <sup>65</sup> 2016	n=100 Mean age: 40.5 (s.d.: 9.5) years 100% obese Mean BMI in hypogonadic patients: 47.2 (s.d.: 7.2) kg m <sup>-2</sup> and in nonhypogonadic patients: 46.2 (s.d.: 6.6) kg m <sup>-2</sup>	FPG: 129.7 (s.d.: 55.8) mg dl <sup>-1</sup> in hypogonadic patients (diabetes prevalence not specified)	44 <sup>a</sup>	34 <sup>b</sup>

The data of age, BMI, and FPG are displayed as mean±s.d. <sup>a</sup>TT criteria < 3 ng ml<sup>-1</sup>. <sup>b</sup>FT criteria < 65 ng ml<sup>-1</sup>. <sup>c</sup>FT criteria < 50 ng ml<sup>-1</sup>. BMI: body mass index; FPG: fasting plasma glucose; FT: free testosterone; HIM: hypogonadism in males; TT: total testosterone; s.d.: standard deviation

**Table 2: Modifications in anthropometric characteristics, insulin resistance, and testosterone levels after testosterone treatment in male patients with hypogonadism**

Study	Patients (n)	Mean follow-up time (month)	Mean age (year)	Mean initial weight (kg)	Mean weight loss (kg)	Mean BMI change (kg m <sup>-2</sup> )	Mean HbA1c change (%)	Mean HOMA-IR change (unit)	Mean lean mass change (kg)	Mean fat mass change (kg)
Jones <i>et al.</i> <sup>49</sup> 2011	220	12	59.9	NA	NA	+0.03	-0.6	-2.8	NA	NA
Hoyos <i>et al.</i> <sup>71</sup> 2012	67	4.5	48	108	1.5	-0.5	NA	-1.3	+1.2	-3.1
Francomano <i>et al.</i> <sup>74</sup> 2014	40	60	58	NA	15	-2.9	-1.6	-2.8	NA	NA
Gianatti <i>et al.</i> <sup>88</sup> 2014	45	4	62	93	2	-0.6	+0.3	-0.3	+1.6	-0.3
Corona <i>et al.</i> <sup>89</sup> 2016	4513	24	51.7	NA	3.5	NA	NA	-2.8	+0.6	-0.6

BMI: body mass index; HbA1c: hemoglobin A1c; HOMA-IR: Homeostasis Model Assessment for Insulin Resistance; NA: not available

mainly lost body fat, while those receiving placebo lost both fat and lean mass. Cohorts of hypogonadal patients who received long-acting testosterone undecanoate showed a decrease in body weight of almost 5% after 1 year of treatment and more than 13% at 5 years.<sup>73,74</sup> Likewise, a significant reduction in waist circumference has also been reported.<sup>73,75</sup> These effects are most notable in patients with higher BMI.<sup>76</sup> Long-term treatment also produces sustained improvements in weight and waist circumference in a subgroup of obese men with hypogonadism and T2DM.<sup>77</sup>

As a conclusion, the authors suggest that long-term treatment with testosterone produces beneficial effects on weight loss and waist circumference independently of diet and exercise. These effects are superior to other drugs alone or in combination with behavioral and lifestyle modifications (Table 3). However, we have to take into

account that most of these studies were not properly well-designed, double-blind, placebo-controlled trials.

Beyond the relative benefits of different methods of testosterone administration and the duration of treatment, response to treatment also depends on patient demographics. Serum levels of testosterone obtained after intramuscular administration of testosterone correlate with age and body composition. Younger and heavier men have been shown to achieve lower concentrations of total and bioavailable testosterone. Similar results have been described with transdermal testosterone formulations, demonstrating that hypogonadal men with obesity and T2DM have a lower probability of attaining normal gonadal status compared to nonobese, nondiabetic men.<sup>78</sup> The mechanisms underlying this body composition and lower age-dependent response remain to be determined.

**Table 3: Modifications in anthropometric characteristics and testosterone levels after lifestyle intervention or bariatric surgery in male patients with hypogonadism**

Study	Intervention	Control group	Patient (n)	Mean follow-up time (month)	Mean age (year)	Mean initial weight (kg)	Mean weight loss, kg (%)	Mean BMI loss ( $\text{kg m}^{-2}$ )	Mean lean mass loss (kg)	Mean fat mass loss (kg)	Mean total testosterone change ( $\text{ng mL}^{-1}$ )
Kraemer <i>et al.</i> <sup>90</sup> 1999	Diet + exercise	Normal activities	21	3	Mean: 38.8	93.8	9.4 (10)	NA	1.2	8.3	+0.2
Mingrone <i>et al.</i> <sup>91</sup> 2002	Diet + exercise	No	12	12	Range: 30–45	147.3	9.1 (6.2)	3	3.6	5.4	NA
	Bariatric surgery		15			151.8	52.1 (34.3)	17.6	14.5	37.6	NA
Reis <i>et al.</i> <sup>92</sup> 2010	Diet + exercise	No	10	24	Mean: 42.2	160.4	5.4 (3.4)	0.7	NA	NA	–0.5
	Bariatric surgery		10		Mean: 36.7	168.7	74.1 (43.9)	24.7	NA	NA	+3.6
Armamento-Villareal <i>et al.</i> <sup>93</sup> 2016	Diet	Usual dietary and activity habits	10	12	Mean: 68.3	118.8	10.1 (8.5)	NA	NA	NA	+0.7
	Exercise		10		Mean: 71.5	109.7	0.2 (0.2)	NA	NA	NA	–0.2
	Diet + exercise		10		Mean: 68.7	104.2	9.1 (8.7)	NA	NA	NA	+0.5

BMI: body mass index; NA: not available

With regard to the safety of testosterone treatment in these patients, there has been reluctance due to the observation in some studies of a possible increased risk of cardiovascular events.<sup>79,80</sup> In response, the United States Food and Drug Administration and the European Medicine Agency claim that there is no substantial evidence that testosterone treatment has adverse effects on cardiovascular health in men with hypogonadism.<sup>81–83</sup> However, it should be emphasized that there are no long-term safety studies with testosterone. The studies that have raised these concerns are retrospective and with significant methodological limitations. It is also true that in many of these studies, testosterone doses are greater than those recommended in standard clinical practice. On the other hand, in a recent large meta-analysis of major cardiovascular events in placebo-controlled randomized trials, no increase in cardiovascular events was found. In fact, the results suggest a reduction in cardiovascular events in those with MS and T2DM.<sup>84</sup> Another recent large retrospective study has also shown no increase in cardiovascular events.<sup>85</sup>

#### Treatment with aromatase inhibitors

One of the mechanisms involved in the pathophysiology of hypogonadism associated with obesity is the increased aromatase activity in adipose tissue. Aromatase converts testosterone to estradiol, which has an inhibitory effect on the production of LH in the pituitary gland. The use of letrozole, an aromatase inhibitor, has been investigated. De Boer *et al.*<sup>86</sup> analyzed the effect of treatment with letrozole at doses of 7.5 mg and 17 mg per week for 6 weeks in 10 men (mean age of 48.2 [s.d.: 2.3] years and mean BMI of 42.1 [s.d.: 2.6]  $\text{kg m}^{-2}$ ), observing a significant decrease in estradiol levels and a significant increase in LH and TT levels, with stable levels of SHBG. Loves *et al.*<sup>87</sup> reported similar results in a population of 12 men (mean age of 48.4 [s.d.: 3.3] years and mean BMI of 45.7 [s.d.: 3.0]  $\text{kg m}^{-2}$ ) after 6 months of treatment with letrozole at a dose of 2.5 mg weekly. In addition, Loves *et al.*<sup>87</sup> observed that FT levels increased to supraphysiological levels in 50% of patients, suggesting FT levels as the best marker in the follow-up of patients taking letrozole and the need, in some cases, for dose reduction in long-term treatment.

Finally, it is important to note that aromatase inhibitors have been associated with increased osteoporosis risk, and therefore should be used with caution in patients at high risk for bone fractures.

#### CONCLUSION

Male hypogonadism associated with obesity is very prevalent and is increasing in parallel to the increasing prevalence of obesity. Hypogonadism perpetuates obesity, especially central obesity and, as

a consequence, related cardiometabolic complications, such as T2DM and cardiovascular disease. The importance of hypogonadism as a comorbidity of obesity in men is gradually becoming clear.

Our review enabled us to conclude that screening for the presence of hypogonadism is advisable in obese men, especially in those with T2DM. In addition, despite changes in lifestyle 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 concomitant reduced levels of testosterone. In obese men with hypogonadism, this treatment has shown to improve body composition and to 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. The presence of hypogonadism associated with obesity should be taken into account when establishing the indication for bariatric surgery. Randomized controlled clinical trials are needed to reinforce the available evidence.

#### AUTHOR CONTRIBUTIONS

MMV, JCFG and AMG contributed to the manuscript conception, data search, drafting, reviewing, and critically revising the manuscript. MDF contributed to drafting and reviewing the manuscript. FJT contributed to critically revising the manuscript. All authors have read and approved the final manuscript and agree with the order of presentation of the authors.

#### COMPETING INTERESTS

All authors declare no competing interests.

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