

# Obesity and male hypogonadism: Tales of a vicious cycle

David F. Carrageta<sup>1</sup>  | Pedro F. Oliveira<sup>1,2,3</sup>  | Marco G. Alves<sup>1</sup>  | Mariana P. Monteiro<sup>4</sup> 

<sup>1</sup> Department of Microscopy, Laboratory of Cell Biology, Unit for Multidisciplinary Research in Biomedicine (UMIB), Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Porto, Portugal

<sup>2</sup> i3S—Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal

<sup>3</sup> Department of Genetics, Faculty of Medicine, University of Porto, Porto, Portugal

<sup>4</sup> Clinical and Experimental Endocrinology, Unit for Multidisciplinary Research in Biomedicine (UMIB), Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Porto, Portugal

## Correspondence

Mariana P. Monteiro, Clinical and Experimental Endocrinology, Unit for Multidisciplinary Research in Biomedicine (UMIB), Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Rua Jorge Viterbo Ferreira 228, 4050-313, Porto, Portugal.  
Email: mpmonteiro@icbas.up.pt

## Funding information

EU Framework Programme for Research and Innovation H2020, Grant/Award Number: POCI/COMPETE2020; UMIB, Grant/Award Number: PEst-OE/SAU/UI0215/2019; FEDER, Grant/Award Numbers: PTDC/BBB-BQB/1368/2014, IFCT2015, PTDC/MEC-AND/28691/2017 and PTDC/BIM-MET/4712/2014; Fundação para a Ciência e a Tecnologia, Grant/Award Number: SFRH/BD/136779/2018

## Summary

Obesity prevalence, particularly in children and young adults, is perilously increasing worldwide foreseeing serious negative health impacts in the future to come. Obesity is linked to impaired male gonadal function and is currently a major cause of hypogonadism. Besides signs and symptoms directly derived from decreased circulating testosterone levels, males with obesity also present poor fertility outcomes, further evidencing the parallelism between obesity and male reproductive function. In addition, males with androgen deficiency also exhibit increased fat accumulation and reduced muscle and mineral bone mass. Thus, compelling evidence highlights a vicious cycle where male hypogonadism can lead to increased adiposity, while obesity can be a cause for male hypogonadism. On the opposite direction, sustained weight loss can attain amelioration of male gonadal function. In this scenario, a thorough evaluation of gonadal function in men with obesity is crucial to dissect the causes from the consequences in order to target clinical interventions towards maximized improvement of reproductive health. This review will address the causes and consequences of the bidirectional relationship between obesity and hypogonadism, highlighting the implicit male reproductive repercussions.

## KEYWORDS

hypogonadism, male fertility, obesity, steroidogenesis

## 1 | INTRODUCTION

The global number of individuals with obesity has perilously increased in the past decades and has reached pandemic proportions. According to the most recent World Health Organization Data Sheet, in 2016, 1.9 billion adults were identified as overweight, and 650 million of these individuals were identified as having obesity.<sup>1</sup> Alarmingly, the

number of obesity cases among children and adolescents is also steadily increasing, both in developed and developing countries.<sup>2,3</sup> Indeed, the obesity prevalence among European adolescents reached 14.5% in 2017 while among US adolescents<sup>4,5</sup> reached 20.6% in 2016. Obesity is linked to several comorbidities, spanning from psychological, to mechanical and most particularly to metabolic disorders, leading to female and male gonadal dysfunction in addition to the well-recognized increased risk for type 2 diabetes mellitus, dyslipidaemia, hypertension, cardiovascular disorders, and even some types of cancer.<sup>6–11</sup> Moreover, as the number of children and young adults with obesity steadily increases, so does the prevalence of silent consequences resulting from the chronic metabolic imbalance, which will eventually lead to serious negative health impacts in the near

**List of abbreviations:** ADT, androgen deprivation therapy; ATGL, adipose triglyceride lipase; BMI, body mass index; C/EBPα, CCAAT/enhancer binding protein alpha; cAMP, cyclic adenosine monophosphate; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPT, hypothalamic-pituitary-testicular axis; HSL, hormone-sensitive lipase; LH, luteinizing hormone; LPL, lipoprotein lipase; PPAR-γ, peroxisomal proliferator-activated receptor gamma; SHBG, sex hormone-binding globulin

future.<sup>12</sup> One of the silent, yet most relevant consequences of obesity installed in early ages is the impairment of female and male reproductive function. In fact, both clinical and experimental data support that obesity is negatively correlated with normal reproductive function. Notwithstanding, the negative impact of increased body adiposity for female reproductive potential has long been recognized; more recently, the hazard effects on male reproductive function have also been disclosed.<sup>12,13</sup> Indeed, nearly 20% of the subfertility and infertility in males can be directly attributed to overweight and obesity.<sup>14,15</sup> Remarkably, in regions of the globe where obesity is less prevalent, such as non-Western countries, the prevalence of male infertility is also lower, providing additional epidemiological evidence on the parallelism between obesity and male fertility potential.<sup>16</sup>

Male hypogonadism is defined as a syndrome characterized by androgen deficiency, which can be classified as primary or secondary according to the aetiology of testosterone deficiency. Primary hypogonadism is caused by a testicular inability to secrete testosterone in normal amounts in order to sustain the physiological circulating concentrations, while secondary hypogonadism is due to reduced or inappropriately normal gonadotropin release and consequent disruption of the hypothalamic-pituitary-testicular (HPT) axis normal functioning.<sup>17</sup> In brief, the HPT axis is regulated by kisspeptins, a family of peptides coexpressed in the hypothalamus, which are responsible to regulate the secretion and release of hypothalamic gonadotropin-releasing hormone (GnRH). GnRH is ultimately released in pulses into the hypothalamic-pituitary portal vessels to stimulate the secretion of the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary. Then, both gonadotropic hormones are released into the systemic circulation to reach the testis, where LH prompts the production of testosterone by Leydig cells and FSH acts together with testosterone in Sertoli cells in order to vitalize spermatogenesis.<sup>18</sup> Testosterone is then released into the systemic circulation to reach the extragonadal target organs. In the bloodstream, testosterone is mostly transported bound to sex hormone-binding globulin (SHBG) or to serum albumin, where only 1% to 2% of the hormone is transported in the unbound or "free" form and thus biologically active.<sup>19</sup> Testosterone action is mediated through androgen receptor binding or conversion to other two active metabolites, namely, estradiol or dihydrotestosterone (DHT) resulting from testosterone conversion by the aromatase or 5- $\alpha$  reductase enzymes, respectively. Estradiol prompts a negative feedback on the hypothalamus, more specifically through its inhibitory action on kisspeptin-producing KNDy neurons, via oestrogen receptors, which inhibits GnRH production and, subsequently, suppresses the synthesis and secretion of gonadotropins.<sup>20</sup> In addition, inhibin, a peptide hormone secreted by Sertoli cells, also exerts a negative feedback response on the pituitary, decreasing FSH production and secretion.<sup>21</sup> Men with androgen deficiency exhibit reduced libido and erectile dysfunction, in addition to reduced bone mineral mass, reduced muscle mass, and increased fat mass.<sup>22</sup> Thus, hypogonadism, besides clearly affecting quality of life and reproductive function, also disrupts the function of multiple organs.

Men with obesity frequently depict low circulating testosterone levels (usually below 10.5 nM of total testosterone, comparing with

the mean 20 nM found in healthy men).<sup>23</sup> However, assessing testosterone levels in men with obesity to diagnose hypogonadism requires careful interpretation. First of all, circulating testosterone levels depend on several factors, including the circadian rhythm since peak values are usually found in the morning,<sup>24,25</sup> and food ingestion can also decrease testosterone concentrations.<sup>26,27</sup> Thus, it is recommended that circulating testosterone levels should be measured in the morning in fasting condition as a standard operation procedure. In addition, to avoid the risk of false positive results, it is recommended that in the event of finding low testosterone levels, the result should be confirmed by at least two separated measurements.<sup>28,29</sup> Secondly, the laboratorial method used to assess testosterone levels is also very important. In routine laboratories, total testosterone levels are most often measured by competitive immunoassays, which are relatively simple, fast, and cheap methodologies but rather inaccurate within the lower testosterone ranges (usually for concentrations below 10 nM or 300 ng/dL).<sup>30</sup> In contrast, liquid chromatography-tandem mass spectrometry is currently considered the reference methodology for testosterone measurement given the accuracy and high specificity, sensitivity, and precision, although more expensive, labour intensive, and not being widely available in routine laboratories.<sup>31,32</sup> At last but not least, since SHBG concentrations are a major determinant of total testosterone levels, in SHBG-altering conditions, such as obesity and type 2 diabetes mellitus, measuring free testosterone instead of total testosterone should be considered when assessing the gonadal function.<sup>33</sup> In addition, if the concentration of total testosterone is in the 8 to 12 nM range, it is also recommended to measure free testosterone.<sup>34,35</sup> However, currently available laboratory methods for assessing free testosterone concentrations are also challenging in terms of efficiency and limitations, as direct immunoassays are inaccurate and not recommended.<sup>30,35</sup> The equilibrium dialysis is the most reliable method for measuring free testosterone, which if not available, could be replaced by free testosterone estimation using a formula that calculates free testosterone based on total testosterone, SHBG, and albumin concentrations.<sup>36,37</sup> Several epidemiological studies highlighted the positive correlation between obesity and male hypogonadism, with obesity being currently contemplated as a major cause of male gonadal dysfunction.<sup>38,39</sup> In addition, other obesity-related comorbidities, such as type 2 diabetes mellitus and metabolic syndrome, are also directly associated with male hypogonadism.<sup>40,41</sup> Moreover, evidence also alerts for a bidirectional relationship, as hypogonadism per se can lead to increased adiposity, while obesity can also be the cause of hypogonadism. In this sense, a careful evaluation of gonadal function of men with obesity is crucial to select the most adequate and effective interventions to target either the somatic consequences of male hypogonadism or addressing male infertility. Since depending of the aetiology of the male hypogonadism and primary treatment goals, whether considering symptom and metabolic improvement or seeking fertility, different approaches should be applied.

In this review, the causes and consequences of the bidirectional relationship between male obesity and hypogonadism will be highlighted, with a closer look into the implicit male reproductive implications.

## 2 | HYPOGONADISM IS ASSOCIATED WITH INCREASED ABDOMINAL ADIPOSITY

Primary hypogonadism results from the inability of the testes to produce physiological levels of testosterone, leading to an androgen deficiency and increased gonadotropin concentration. Thus, primary hypogonadism is usually designated as hypergonadotropic hypogonadism.<sup>18</sup> Primary hypogonadism can be due to genetic causes, such as Klinefelter syndrome and LH or FSH receptors mutations, or more frequently for testicular lesion, either traumatic, infectious, toxic, neoplastic or iatrogenic.<sup>18</sup> Secondary hypogonadism, or hypogonadotropic hypogonadism, is characterized by suppressed or inappropriately normal gonadotropin levels, which lead to the disruption of the hypothalamic-pituitary normal functioning and, consequently, decreased testosterone secretion by the testes. Secondary hypogonadism can also be due to genetic disorders, such as Kallmann syndrome; anatomical disruption of the hypothalamus and pituitary axis, by trauma or tumours; and other endocrine or metabolic conditions, including hyperprolactinemia, hypercortisolism and obesity, among several other less frequent causes.<sup>42</sup> Regardless the underlying cause, a common clinical feature among hypogonadal men is altered body composition. Although hypogonadism per se usually does not significantly influences total body weight, hypogonadal men exhibit reduced fat-free mass and increased fat mass, which is inversely correlated with testosterone levels. Indeed, there is compelling evidence that correlates low testosterone levels with fat accumulation in men. For instance, data from the Tromsø Study among 1548 men aged 25 to 84 years showed that waist circumference, as a surrogate of central obesity, was inversely related to total and free testosterone and SHBG levels.<sup>43</sup> Dhindsa et al<sup>44</sup> studied the body composition of 138 hypogonadal and eugonadal type 2 diabetic patients and observed an inverse correlation between circulating testosterone and trunk fat accumulation. Remarkably, several studies have shown that abdominal fat accumulation is a common feature among hypogonadal men. However, it is controversial whether the increased adiposity is mainly attributed to increased visceral depots or also subcutaneous. Couillard et al<sup>45</sup> found out a preferential accumulation of abdominal fat, particularly in visceral depots, associated with low testosterone levels. Tsai et al<sup>46</sup> reported an inverse correlation between intra-abdominal fat-specific accumulation and total testosterone after a follow-up study or 7.5 years in 110 men. Nielsen et al,<sup>47</sup> in a study with 783 men aged 20 to 29 years, showed that both visceral and subcutaneous fat accumulation inversely correlated with free testosterone although only visceral fat accumulation was inversely correlated with free testosterone when adjusted for SHBG levels. On the other hand, Smith et al<sup>48</sup> shown that iatrogenic hypogonadism induced by GnRH agonists treatment for prostate cancer led to increased abdominal fat accumulation specifically in subcutaneous depots, while Abate et al<sup>49</sup> reported that subcutaneous fat but not visceral fat accumulation in the truncal region was highly predictive of low testosterone levels. Hence, although the factors that mediate fat accumulation among different depots is still unclear, it is a fact that abdominal depots are the main target for fat accumulation in hypogonadal men.

A unique human model for studying the biological consequences of low testosterone levels is based on the study of men with prostate cancer under androgen deprivation therapy (ADT). Despite the obvious limitations, including age and underlying disease conditions, men under ADT consistently exhibit increased body fat mass and reduced muscle mass. For instance, in a study including 79 men with Stage M0 prostate cancer reported an increased 11% body fat after 12 months of ADT.<sup>50</sup> In another study, van Londen et al<sup>51</sup> reported similar results in men under ADT for 2 years. Besides, men undergoing long-term ADT often develop insulin resistance and metabolic syndrome. In fact, a study by Braga-Basaria et al<sup>52</sup> reported that among 58 men on long-term ADT, more than 50% developed metabolic syndrome due to abdominal obesity and hyperglycaemia. Then, Hamilton et al<sup>53</sup> reported that ADT results in both visceral and subcutaneous fat accumulation, in parallel to increased insulin resistance. Another study by Cheung et al<sup>54</sup> corroborates the increased insulin resistance along with the increased body fat in men undergoing ADT for 12 months, although interestingly, no body weight or visceral fat alterations were observed. Indeed, low testosterone levels seem to display reduced effects on body weight but instead vastly modulates body composition in an unfavourable manner. Additionally, the effects on insulin resistance are thought to be a consequence of very low testosterone levels (less than 2 nM) that arise from ADT. While obesity-associated hypogonadism usually ranges 8 to 12 nM, the first signs of insulin resistance only develop when circulating testosterone falls below 6 to 8 nM.<sup>55,56</sup> Thus, the lower the testosterone levels the more severe seen to be the adverse metabolic effects.

### 2.1 | Testosterone modulates body composition

Testosterone is a key hormone in the regulation of body composition exhibiting wide functions at the molecular level. Testosterone is characterized by acting as an anabolic hormone essential for muscle mass development and strength. Indeed, testosterone is linked with the commitment of multipotent mesenchymal cells into the myogenic lineage.<sup>57,58</sup> As myogenic cells share the same developmental origin with adipogenic cells, testosterone was hypothesized to inhibit differentiation of adipocytes while enhancing myocytes expansion. This hypothesis was confirmed by Singh et al,<sup>59</sup> who observed that treating C3H 10T1/2 pluripotent cells with testosterone or DHT downregulated peroxisomal proliferator-activated receptor gamma (PPAR- $\gamma$ ) and CCAAT/enhancer binding protein alpha (C/EBP $\alpha$ ), two major regulators of adipogenesis, thus prompting myogenesis. In addition, in the same study was demonstrated that the androgen receptor antagonist bicalutamide was able to block those effects, further evidencing that androgens regulate myogenic and adipogenic differentiation through an androgen receptor-mediated pathway. On the other hand, androgens also modulate lipid metabolism through a prolipolytic signalling in adipocytes, while simultaneously reducing lipid uptake and increasing fatty acid  $\beta$ -oxidation.<sup>60</sup> Testosterone is reported to mediate a prolipolytic effect through the upregulation of  $\beta$ -adrenergic receptors in adipocytes, enhancing catecholamines-stimulated lipolysis.<sup>61,62</sup> The

activation of  $\beta$ -adrenergic receptors by catecholamines, such as adrenaline, increases intracellular cyclic adenosine monophosphate (cAMP) levels, which culminates in the stimulation of several lipases responsible for the hydrolysis of triacylglycerol into free fatty acids and glycerol.<sup>63</sup> However, there is evidence that androgens display differential effects among fat depots although with contradictory results. Hernández-Morante et al<sup>64</sup> reported that visceral but not subcutaneous fat explants from men with obesity treated for 24 hours with dehydroepiandrosterone (DHEA), a precursor of testosterone, exhibited an increased lipolysis. These findings are supported by another study by Karbowska and Kochan<sup>65</sup> performed in rats visceral adipose tissue. In this study, increased expression of the adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) were also observed. Moreover, androgen receptor knockout mice present increased visceral fat accumulation, leading to obesity and early insulin resistance.<sup>66,67</sup> Contrastingly, in fully differentiated human preadipocytes isolated from men with obesity treated with different concentrations of testosterone, a concentration-dependent reduction of catecholamine-stimulated lipolysis was observed in cells from subcutaneous depots but not from visceral depots.<sup>68</sup> These results were attributed to the downregulation of  $\beta$ -adrenergic receptors and HSL observed on cells isolated from the subcutaneous fat depot. However, it must be stressed that in vitro conditions do not fully mimic in vivo conditions. Interestingly enough, a previous study reported that men with mild obesity treated with testosterone, either a single injection (500 mg of testosterone propionate) or oral administration (40 mg of testosterone undecanoate, four times) over 6 weeks, showed a decrease in subcutaneous abdominal adipose tissue size but no alterations on the femoral adipose tissue size.<sup>69</sup> Thus, the effects of testosterone within the different location fat depots still needs further investigation.

Testosterone is also involved in lipid uptake regulation, while low testosterone is linked with increased lipid uptake. Indeed, low testosterone levels are associated with increased expression of lipoprotein lipase (LPL), a major enzyme in the lipid uptake process. LPL is a protein present on the extracellular surface of adipocytes, which is responsible for the hydrolysis of circulating triglyceride-rich lipoproteins into smaller fatty acids, enhancing their uptake.<sup>70</sup> For instance, LPL' activity in the abdominal adipose tissue was reported to be inversely correlated with circulating testosterone in men with obesity.<sup>71</sup> These findings are further supported by studies showing that testosterone replacement therapy in hypogonadal men is associated with a decrease in both LPL activity and lipid uptake.<sup>69,72</sup> Interestingly, lipid uptake decrease was more prominent in visceral depot than in the subcutaneous depot of the abdominal region, suggesting that testosterone may be more able to limit lipid accumulation in visceral depots.

In sum, low testosterone levels observed in hypogonadal men lead to increased adiposity through the absence of the inhibitory signal in adipogenesis and lipid uptake, particularly in visceral abdominal depots. However, the opposite can also occur. How obesity may be prompting hypogonadism will be discussed in the subsequent topic.

### 3 | OBESITY PROMPTS HPT AXIS DYSFUNCTION

Obesity may indeed lead to HPT dysfunction and consequently to male hypogonadism. The interest in obesity as a primary cause of male hypogonadism has been intensely studied for the past years and obesity is currently well-recognized as an emerging major cause of male reproductive dysfunction.<sup>18</sup> Obesity is positively linked with reduced total and free testosterone levels. Indeed, when comparing lean men with men with obesity, free testosterone levels are significantly lower in the last group.<sup>73</sup> Besides, several studies reported a high prevalence of hypogonadism in men with obesity. For instance, Zumoff et al<sup>74</sup> observed an inverse correlation between free testosterone and body mass index (BMI) in a population of 48 men with a BMI ranging from 21 to 95 kg/m<sup>2</sup>. In another study, in 149 men aged 18 to 66 years with a mean BMI of 42.7 kg/m<sup>2</sup> Hofstra et al<sup>75</sup> not only reported that BMI was inversely correlated with free testosterone but also that 35.6% of men with obesity exhibited free testosterone levels in the hypogonadism range. Calderón et al<sup>76</sup> reported that among 100 men with a mean age of 40.5 years and BMI  $\geq 35$  kg/m<sup>2</sup>, 45% could be classified as hypogonadal based on low free testosterone levels. In addition, the authors found that low free testosterone levels were associated with increased insulin resistance and low ejaculate volume. Besides obesity, type 2 diabetes mellitus is also associated with male hypogonadism, which furthers evidences the unequivocal link between metabolic imbalance and male gonadal function.<sup>77,78</sup> Although the majority of the studies were conducted in middle-aged men populations, similar results were observed in male adolescents (age ranged from 14 to 20 years), where free testosterone levels were also inversely related to BMI and insulin resistance.<sup>79,80</sup> Thus, evidencing that age is not the only factor that leads to decreased testosterone but indeed increased BMI is also important.<sup>81</sup> Interestingly, although the BMI seems to have a deleterious effect on free testosterone levels, the opposite was not verified.<sup>82</sup> As aforementioned, male hypogonadism results in body composition alterations, but overall, no significant BMI changes are observed. Still, the association of obesity and male hypogonadism is far from being not linear and evidence points to a multifactorial origin.

Obesity is characterized by several adverse metabolic and hormonal alterations that may disrupt the HPT axis, with several possible pathophysiological mechanisms already identified. Among these are some key molecular player such as estradiol and leptin. On the following sections, the effects of estradiol and leptin as well as hormone dysregulation in obesity conditions will be addressed in further detail.

#### 3.1 | Estradiol

Estradiol is known as a critical player in male reproductive function. Estradiol can be secreted in the testis and adipose tissue through the irreversible conversion of testosterone by aromatase. High estradiol concentrations are reported to have deleterious effects on male gonadal function by suppressing the HPT axis.<sup>83,84</sup> The classic view of the

relationship between male obesity and estradiol has the premise that estradiol levels are often increased in men with obesity, which were hypothesized to further contribute for the progression of obesity and enhancement of the metabolic dysfunction.<sup>85,86</sup> The higher estradiol levels observed in men with obesity were attributed to increased testosterone conversion into estradiol by aromatase in peripheral tissues.<sup>87</sup> Aromatase is expressed in adipocytes and due to the increased adipocyte mass, aromatase expression is also increased, thus explaining the higher rate of peripheral conversion of testosterone and thus the higher estradiol levels observed in men with obesity.<sup>88</sup> Then, high estradiol levels would potentially exert a negative feedback on the hypothalamic secretion of GnRH, consequently suppressing the HPT axis and ultimately limiting testosterone secretion in the testis. This hypothesis is further supported by the fact that this is a reversible phenomenon upon weight loss, as testosterone and gonadotropins levels rise while estradiol levels decrease.<sup>89-91</sup> Additionally, aromatase inhibitors were demonstrated to decrease estradiol levels and increase gonadotropins and total testosterone in men with obesity.<sup>92</sup> However, more recent studies challenged this classic premise and kindled the debate on the possible role of estradiol in metabolic regulation. Dhindsa et al<sup>93</sup> reported that total and free estradiol in hypogonadal diabetic men are even lower than in eugonadal diabetic men. This result led some authors to hypothesize that as circulating testosterone is the main substrate for aromatase, low testosterone concentration should be reflected in low estradiol concentration in hypogonadal men.<sup>17,42</sup> In fact, a recent study by Ghanim et al<sup>94</sup> reported that hypogonadal diabetic men's adipocytes expressed less aromatase and oestrogen receptor alpha when compared with eugonadal diabetic men. Additionally, Hammoud et al<sup>95</sup> described an aromatase polymorphism that positively correlated with elevated circulating estradiol and body weight. Interestingly, only men who exhibited the polymorphism had estradiol levels reduced after weight loss. Taken together, the role of estradiol might be more complex than initially hypothesized. Currently, estradiol levels are described as an adaptative and tissue-specific response to obesity.<sup>88</sup> In another words, estradiol levels may reflect an adaptative response to the metabolic state of the individual, regulating lipid metabolism and adipocytes differentiation and function in order to preserve the adipose tissue homeostasis. For instance, Ohlsson et al<sup>96</sup> developed a male mouse model overexpressing aromatase and reported increased estradiol levels in the adipose tissue but both circulating testosterone and estradiol remained unaffected. Besides, aromatase upregulation led to decreased inflammation and improved insulin sensitivity. In light of these recent data, further investigation is required to elucidate the role of estradiol in modulating gonadal function in the presence of obesity.

On a side note, the effects of obesity-related hormonal imbalance on the hypothalamus remain to be fully characterized. It is reported that estradiol may be converted or even synthesized in the central nervous system,<sup>97,98</sup> and that the hypothalamus abundantly expresses oestrogen receptors,<sup>99</sup> but it remains to be elucidated whether obesity alters oestrogen receptors expression or if a high concentration of estradiol is generated specifically in this tissue. Interestingly, estradiol may also take part in leptin regulation. A study by Clegg et al<sup>100</sup> suggests that the pharmacological administration of estradiol increases leptin

sensitivity. Another evidence for the regulation of leptin sensitivity by estradiol is the increased expression of oestrogen receptor alpha in the hypothalamus of leptin-deficient rats with obesity.<sup>101</sup> However, the possible effects of estradiol in leptin still needs further investigation.

### 3.2 | Leptin

Leptin is a hormone predominantly secreted by white adipocytes that acts as a major regulator of male fertility. Leptin has a paramount role in energy homeostasis regulation, first identified for being responsible for promoting satiety among several other endocrine and metabolic functions later disclosed. Overall, leptin is an important mediator between energy reserves, nutritional status, and the HPT axis. Although acting indirectly, leptin stimulates the hypothalamus to secrete and release GnRH and thus regulating the HPT axis. Indeed, leptin administration was demonstrated to dose-dependently stimulate pulsatile GnRH release in rodent models.<sup>102</sup> Although leptin receptor is not expressed by GnRH neurons, its signalling is mediated upstream by intermediate neurons that produce kisspeptin.<sup>103</sup> Since leptin is predominantly secreted by adipocytes, leptin concentrations are usually proportional to the number of adipocytes and size of the adipose tissue.<sup>104</sup> Therefore, despite rare exceptions, obesity is most often associated with high circulating leptin levels due to adipose tissue expansion, while men with decreased adipose tissue mass such as observed in anorexia nervosa present very low circulating leptin levels.<sup>105</sup> Although obesity is often associated with high circulatory leptin levels, individuals with obesity also frequently exhibit leptin resistance. One of the earliest mechanisms identified as being responsible for leptin resistance comprises the saturation of leptin transport through the blood-brain barrier into the central nervous system.<sup>106</sup> In addition, leptin resistance is also linked with leptin receptor down-regulation and inhibition. For instance, the suppressor of cytokine signalling 3 (SOCS3) is activated by leptin and provides a negative feedback mechanism, inhibiting downstream pathways.<sup>107</sup> Besides, leptin resistance is also linked with lipotoxicity, a possible direct consequence of severe obesity, which causes the proteolytic cleavage of the extracellular leptin receptor domain.<sup>108</sup> Another possible explanation for the leptin resistance observed at the HPT axis level is linked to the suppression of kisspeptin gene expression and kisspeptin receptors.<sup>109,110</sup> In support of this hypothesis is the observation that intravenous kisspeptin administration is able to increase testosterone and gonadotropin levels in hypogonadal men.<sup>111</sup> Altogether, these mechanisms culminate in HPT axis dysregulation by decreasing GnRH and gonadotropins release and consequently of testosterone secretion.<sup>112</sup>

Besides hypothalamic actions, leptin also acts at the testis level. Indeed, when present in high levels, leptin acts on Leydig cells that retain leptin sensitivity to inhibit steroidogenesis.<sup>113,114</sup> Interestingly, this modulation seems to be reciprocal as leptin inhibits testosterone production due to the action both at the hypothalamus and testis, but also testosterone suppresses leptin secretion from adipocytes and decreases its circulating levels independently of changes in the adipose tissue size.<sup>115,116</sup> Although the pathways that lead to



metabolism modulation in testicular cells by leptin remains to be fully elucidated, it is well recognized that both leptin and testosterone take part of a vicious cycle, which culminates in the potentiation of increased adiposity and decreased testosterone levels, with negative consequences for men with obesity reproductive function.

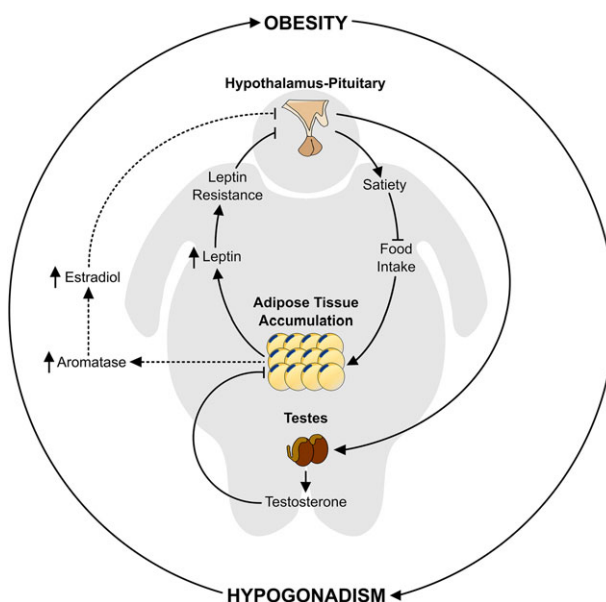
#### 4 | MALE HYPOGONADISM AND OBESITY: CONSEQUENCES FOR MALE FERTILITY POTENTIAL

The primary role of gonadal function is to ensure the species continuity. The testes and epididymis microenvironments are responsible for controlling spermatogenesis and subsequently sperm and semen quality.<sup>12</sup> Alarming, sperm count and quality have been continuously decreasing. In fact, it is estimated that the decline in sperm count is over 50% since the 20th century.<sup>117</sup> Obesity has several negative effects on sperm quality and generally an inverse correlation between BMI and sperm parameters is observed, where men with obesity are more likely to exhibit a reduction in semen quality than men with normal BMI.<sup>14</sup> Several studies show that obesity is linked with abnormal sperm parameters including low sperm concentration and low motility, which results in subfertility. For instance, in 483 subfertile couples, men with a BMI higher than 25 kg/m<sup>2</sup> were reported to have a lower total sperm count when compared with normal weight men.<sup>118</sup> In addition, a negative correlation between BMI and volume of ejaculate was also observed. In another study, among 1558 male military

recruits, a negative correlation between sperm count and BMI was observed.<sup>119</sup> These findings are further supported by a meta-analysis by Sermondade et al,<sup>120</sup> which in a sample of 13 077 men attending fertility clinics observed that overweight and men with obesity displayed an increased prevalence of azoospermia or oligospermia. Moreover, obesity is also positively linked with asthenospermia, ie, low motility of sperm cells. Wang et al<sup>121</sup> reported a negative correlation between BMI and sperm motility, and similar associations were previously observed in smaller studies.<sup>122,123</sup> Undoubtedly, hypogonadism among several other hormonal alterations are important mediators in this process. In addition to reduced libido and erectile dysfunction, hypogonadal men can also present variable degrees of impaired spermatogenesis.<sup>124</sup> Therefore, despite all the previously described effects of male gonadal dysfunction, one of the most negative consequences is related to the reproductive potential and poor fertility outcomes. It is important to highlight that sperm quality and male fecundity potential are of a substantial public health importance, as decreased birth rates will eventually reflect in the progressive aging of the populations and lead to the inevitable steady increase of economic and social burden.<sup>125,126</sup>

#### 5 | MALE HYPOGONADISM AND OBESITY: BREAKING THE VICIOUS CYCLE

The bidirectional relationship of obesity-hypogonadism can easily become a vicious cycle (Figure 1). As aforementioned, low



**FIGURE 1** Schematic illustration of the hypothesized vicious cycle between male hypogonadism and obesity. Fat accumulation in the adipose tissue increases leptin synthesis and secretion. High circulating leptin levels ultimately lead to leptin resistance due to saturation of leptin transport into the central nervous system and decreased expression of leptin receptors. Decreased leptin response will then be responsible not only for reduced satiety, increased food intake, and energy accumulation but also for the disruption of the hypothalamic-pituitary-testes axis, resulting in decreased testosterone production. While testosterone antagonizes lipid accumulation in the adipose tissue, low testosterone levels in hypogonadal men result in the loss of this inhibitory signal, which then results in further fat accumulation. Simultaneously, an increased aromatase expression in the adipose tissue leads to an increased aromatization of testosterone into estradiol, which triggers a negative feedback mechanism on the hypothalamus. However, this classical role of estradiol in the obesity-hypogonadism cycle (represented by dotted lines) has been recently challenged [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

testosterone levels lead to alterations in body composition and abdominal fat accumulation while obesity, in turn, directly disrupts the HPT axis and further reduces testosterone levels. Therefore, in each given individual with obesity and male hypogonadism, a careful dissection of causes and consequences is necessary for a correct diagnosis that will warrant that the most adequate therapeutic approach will be properly selected.<sup>127</sup> Testosterone replacement therapy can only be recommended in cases of confirmed low testosterone levels in the presence of clinical features of hypogonadism in order to maintain secondary sex characteristics and correct the symptoms. To ensure patient safety, testosterone treatment should only be considered if there are no unfavourable conditions for replacement therapy, such as the risk of prostate cancer or established cardiovascular disease, according to the most recent Endocrine Society Clinical Practice Guideline.<sup>127</sup> Besides, in those men seeking to conceive in the near future, an additional care must be taken since testosterone treatment may halt spermatogenesis, and therefore, treatment with gonadotropins should be the first line therapy in order to ensure or recover spermatogenesis.<sup>128</sup> For those cases of obesity-related male hypogonadism, weight loss should be the primary approach aiming to reverse the condition. Several studies have addressed the effect of lifestyle changes and weight loss as a first measure to promote HPT axis recovery and increasing testosterone levels.<sup>54,90</sup> However, studies that assessed the impact of diet and physical activity on testosterone levels yielded conflicting results. Accordingly to a meta-analysis,<sup>90</sup> lifestyle changes, such as diet and increased physical activity, have only moderate effects on body weight reduction and testosterone levels. Kim et al<sup>129</sup> observed that intensive lifestyle intervention for 12 months in middle-aged men with obesity only resulted in a slight increase in total testosterone levels but no significant changes on free testosterone. Besides, as weight regain after lifestyle interventions is very common, it limits the ability to sustain the metabolic and endocrine benefits of weight loss. Lifestyle intervention along with testosterone treatment was also attempted, although the results achieved were limited to moderate fat reduction, which were almost entirely regained after study completion.<sup>130,131</sup> Taking into account the limited evidence for the benefits of testosterone therapy together with the potential risks, testosterone therapy is not recommended in patients with obesity-related hypogonadism.<sup>127,132</sup> In contrast to conservative interventions, bariatric surgery is reported as a very effective means of achieving significant and sustained weight loss in severely patients with obesity. In addition, observational data derived from several studies showed that bariatric surgery is also very effective in increasing testosterone levels and recovering the HPT axis function.<sup>89,133</sup> Interestingly, hypogonadal men were reported to lose more weight than eugonadal men when submitted to bariatric surgery.<sup>134</sup> Thus, it is hypothesized that the weight loss reverts the vicious cycle, as allows the recovery of testosterone to physiological levels, while in turn increased testosterone decreases weight gain due to its inhibitory effects on adipocytes differentiation and lipid uptake and ultimately allowing to recover the metabolic balance.

## 6 | CONCLUSION

As obesity prevalence increases worldwide, so does the prevalence of worrisome comorbidities increases. Obesity-related hypogonadism is an emerging condition that affects the quality of life, disrupts several metabolic functions, and limits male reproductive potential by impairing sexual function and reducing fertility. Moreover, as obesity in young men increases, obesity-related male infertility is likely to become a serious health issue in the near future. In addition, obesity and male hypogonadism are intimately related in a manner that one condition perpetuates the other. Despite the bidirectional relationship between obesity and male hypogonadism, breaking the vicious cycle is undoubtedly achievable, as sustained weight loss allows the reversal of the negative effects of obesity on reproductive function. These data confer obesity treatment an imperative status, which can span from lifestyle modifications, including caloric-restriction and increased physical activity as the backbone of any weight loss intervention, to pharmacological therapy or even bariatric surgery, according to the severity of obesity. Nevertheless, further studies are still needed to elucidate the molecular mechanisms behind the vicious cycle of obesity and HPT axis dysfunction. Novel data will then prompt the development of new and more effective interventions and drug therapies in order to dismiss this cycle and achieve optimal clinical outcomes for men with obesity with gonadal and reproductive dysfunction.

## ACKNOWLEDGEMENTS

This work was supported by “Fundação para a Ciência e a Tecnologia”—FCT to David F. Carrageta (SFRH/BD/136779/2018). The work was cofunded by FEDER through the COMPETE/QREN, FSE/POPH to Marco G. Alves (IFCT2015, PTDC/BIM-MET/4712/2014, and PTDC/MEC-AND/28691/2017) and Pedro F. Oliveira (IFCT2015 and PTDC/BBB-BQB/1368/2014); UMIB (PEst-OE/SAU/UI0215/2019); cofunded by the EU Framework Programme for Research and Innovation H2020 (POCI/COMPETE2020).

## CONFLICT OF INTEREST

No conflict of interest was declared.

## ORCID

David F. Carrageta  <https://orcid.org/0000-0002-0546-3480>

Pedro F. Oliveira  <https://orcid.org/0000-0002-4989-5699>

Marco G. Alves  <https://orcid.org/0000-0001-7635-783X>

Mariana P. Monteiro  <https://orcid.org/0000-0002-0662-1831>

## REFERENCES

1. WHO. Obesity and overweight data sheet. 2018.
2. Poobalan A, Aucott L. Obesity among young adults in developing countries: a systematic overview. *Curr Obes Rep*. 2016;5(1):2-13.
3. Kumar S, Kelly AS. Review of childhood obesity: from epidemiology, etiology, and comorbidities to clinical assessment and treatment. *Mayo Clin Proc Elsevier*. 2017;92(2):251-265.

4. WHO. Situation of child and adolescent health in Europe. *Situation of child and adolescent health in Europe*. 2018.
5. Hales CM, Carroll MD, Fryar CD, Ogden CL. *Prevalence of Obesity Among Adults and Youth: United States, 2015-2016*. US Department of Health and Human Services, Centers for Disease Control and Prevention; 2017.
6. MacDonald AA, Herbison GP, Showell M, Farquhar CM. The impact of body mass index on semen parameters and reproductive hormones in human males: a systematic review with meta-analysis. *Hum Reprod Update*. 2010;16(3):293-311.
7. Alves MG, Jesus TT, Sousa M, Goldberg E, Silva BM, Oliveira PF. Male fertility and obesity: are ghrelin, leptin and glucagon-like peptide-1 pharmacologically relevant? *Curr Pharm Des*. 2016;22(7):783-791.
8. Quail DF, Dannenberg AJ. The obese adipose tissue microenvironment in cancer development and progression. *Nat Rev Endocrinol*. 2019;15:139-154.
9. Csige I, Ujvarosy D, Szabo Z, et al. The impact of obesity on the cardiovascular system. *J Diabetes Res*. 2018;2018:3407306.
10. Michelet X, Dyck L, Hogan A, et al. Metabolic reprogramming of natural killer cells in obesity limits antitumor responses. *Nat Immunol*. 2018;19(12):1330-1340.
11. Lavie CJ, Laddu D, Arena R, Ortega FB, Alpert MA, Kushner RF. Healthy weight and obesity prevention: JACC Health Promotion Series. *J Am Coll Cardiol*. 2018;72(13):1506-1531.
12. Oliveira PF, Sousa M, Silva BM, Monteiro MP, Alves MG. Obesity, energy balance and spermatogenesis. *Reproduction*. 2017;153(6):R173-R185.
13. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. *Fertil Steril*. 2017;107(4):840-847.
14. Liu Y, Ding Z. Obesity, a serious etiologic factor for male subfertility in modern society. *Reproduction*. 2017;154(4):R123-R131.
15. du Plessis SS, Cabler S, McAlister DA, Sabanegh E, Agarwal A. The effect of obesity on sperm disorders and male infertility. *Nat Rev Urol*. 2010;7(3):153-161.
16. Swan SH, Elkin EP, Fenster L. The question of declining sperm density revisited: an analysis of 101 studies published 1934-1996. *Environ Health Perspect*. 2000;108(10):961-966.
17. Grossmann M. Hypogonadism and male obesity: Focus on unresolved questions. *Clin Endocrinol*. 2018;89(1):11-21.
18. Basaria S. Male hypogonadism. *Lancet*. 2014;383(9924):1250-1263.
19. Lamm S, Chidake A, Bansal R. Obesity and hypogonadism. *Urol Clin North Am*. 2016;43(2):239-245.
20. Skorupskaitė K, George JT, Anderson RA. The kisspeptin-GnRH pathway in human reproductive health and disease. *Hum Reprod Update*. 2014;20(4):485-500.
21. Molina-Vega M, Munoz-Garach A, Damas-Fuentes M, Fernandez-Garcia JC, Tinahones FJ. Secondary male hypogonadism: a prevalent but overlooked comorbidity of obesity. *Asian J Androl*. 2018;20(6):531-538.
22. Lunenfeld B, Mskhalaya G, Zitzmann M, et al. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. *Aging Male*. 2015;18(1):5-15.
23. Travison TG, Vesper HW, Orwoll E, et al. Harmonized reference ranges for circulating testosterone levels in men of four cohort studies in the United States and Europe. *J Clin Endocrinol Metab*. 2017;102(4):1161-1173.
24. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in Normal men. *J Clin Endocrinol Metab*. 1983;56(6):1278-1281.
25. Brambilla DJ, O'Donnell AB, Matsumoto AM, McKinlay JB. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. *Clin Endocrinol*. 2007;67(6):853-862.
26. Lehtihet M, Arver S, Bartuseviciene I, Pousette A. S-testosterone decrease after a mixed meal in healthy men independent of SHBG and gonadotrophin levels. *Andrologia*. 2012;44(6):405-410.
27. Caronia LM, Dwyer AA, Hayden D, Amati F, Pitteloud N, Hayes FJ. Abrupt decrease in serum testosterone levels after an oral glucose load in men: implications for screening for hypogonadism. *Clin Endocrinol*. 2013;78(2):291-296.
28. Spratt DI, O'Dea LS, Schoenfeld D, Butler J, Rao PN, Crowley WF Jr. Neuroendocrine-gonadal axis in men: frequent sampling of LH, FSH, and testosterone. *Am J Phys*. 1988;254(5 Pt 1):E658-E666.
29. Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. *J Clin Endocrinol Metab*. 2009;94(3):907-913.
30. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab*. 2007;92(2):405-413.
31. Chang YC, Li CM, Li LA, Jong SB, Liao PC, Chang LW. Quantitative measurement of male steroid hormones using automated on-line solid phase extraction-liquid chromatography-tandem mass spectrometry and comparison with radioimmunoassay. *Analyst*. 2003;128(4):363-368.
32. Cawood ML, Field HP, Ford CG, et al. Testosterone measurement by isotope-dilution liquid chromatography-tandem mass spectrometry: validation of a method for routine clinical practice. *Clin Chem*. 2005;51(8):1472-1479.
33. Rastrelli G, O'Neill TW, Ahern T, et al. Symptomatic androgen deficiency develops only when both total and free testosterone decline in obese men who may have incident biochemical secondary hypogonadism: prospective results from the EMAS. *Clin Endocrinol*. 2018;89(4):459-469.
34. Anawalt BD, Hotelling JM, Walsh TJ, Matsumoto AM. Performance of total testosterone measurement to predict free testosterone for the biochemical evaluation of male hypogonadism. *J Urol*. 2012;187(4):1369-1373.
35. Goldman AL, Bhasin S, Wu FC, Krishna M, Matsumoto AM, Jasuja R. A reappraisal of testosterone's binding in circulation: physiological and clinical implications. *Endocr Rev*. 2017;38(4):302-324.
36. Zakharov MN, Bhasin S, Travison TG, et al. A multi-step, dynamic allosteric model of testosterone's binding to sex hormone binding globulin. *Mol Cell Endocrinol*. 2015;399:190-200.
37. Sartorius G, Ly LP, Sikaris K, McLachlan R, Handelsman DJ. Predictive accuracy and sources of variability in calculated free testosterone estimates. *Ann Clin Biochem*. 2009;46(2):137-143.
38. Saboor Aftab SA, Kumar S, Barber TM. The role of obesity and type 2 diabetes mellitus in the development of male obesity-associated secondary hypogonadism. *Clin Endocrinol*. 2013;78(3):330-337.
39. Tajar A, Forti G, O'Neill TW, et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *J Clin Endocrinol Metab*. 2010;95(4):1810-1818.
40. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab*. 2004;89(11):5462-5468.



41. Michalakis K, Mintziori G, Kaprara A, Talaratzis BC, Goulis DG. The complex interaction between obesity, metabolic syndrome and reproductive axis: a narrative review. *Metabolism*. 2013;62(4):457-478.
42. Dhindsa S, Ghanim H, Batra M, Dandona P. Hypogonadotropic hypogonadism in men with diabetes. *Diabetes Care*. 2018;41(7):1516-1525.
43. Svartberg J, von Mühlen D, Sundsfjord J, Jorde R. Waist circumference and testosterone levels in community dwelling men. The Tromsø Study. *Eur J Endocrinol*. 2004;19:657-663.
44. Dhindsa S, Bhatia V, Dhindsa G, Chaudhuri A, Gollapudi GM, Dandona P. The effects of hypogonadism on body composition and bone mineral density in type 2 diabetic patients. *Diabetes Care*. 2007;30(7):1860-1861.
45. Couillard C, Gagnon J, Bergeron J, et al. Contribution of body fatness and adipose tissue distribution to the age variation in plasma steroid hormone concentrations in men: the HERITAGE Family Study. *J Clin Endocrinol Metab*. 2000;85(3):1026-1031.
46. Tsai EC, Boyko EJ, Leonetti DL, Fujimoto WY. Low serum testosterone level as a predictor of increased visceral fat in Japanese-American men. *Int J Obes*. 2000;24(4):485-491.
47. Nielsen TL, Hagen C, Wraae K, et al. Visceral and subcutaneous adipose tissue assessed by magnetic resonance imaging in relation to circulating androgens, sex hormone-binding globulin, and luteinizing hormone in young men. *J Clin Endocrinol Metab*. 2007;92(7):2696-2705.
48. Smith MR, Lee H, McGovern F, et al. Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer: differences from the classic metabolic syndrome. *Cancer*. 2008;112(10):2188-2194.
49. Abate N, Haffner SM, Garg A, Peshock RM, Grundy SM. Sex steroid hormones, upper body obesity, and insulin resistance. *J Clin Endocrinol Metab*. 2002;87(10):4522-4527.
50. Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology*. 2004;63(4):742-745.
51. van Londen GJ, Levy ME, Perera S, Nelson JB, Greenspan SL. Body composition changes during androgen deprivation therapy for prostate cancer: a 2-year prospective study. *Crit Rev Oncol Hematol*. 2008;68(2):172-177.
52. Braga-Basaria M, Dobs AS, Muller DC, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol*. 2006;24(24):3979-3983.
53. Hamilton EJ, Gianatti E, Strauss BJ, et al. Increase in visceral and subcutaneous abdominal fat in men with prostate cancer treated with androgen deprivation therapy. *Clin Endocrinol*. 2011;74(3):377-383.
54. Cheung AS, Hoermann R, Dupuis P, Joon DL, Zajac JD, Grossmann M. Relationships between insulin resistance and frailty with body composition and testosterone in men undergoing androgen deprivation therapy for prostate cancer. *Eur J Endocrinol*. 2016;175(3):229-237.
55. Singh AB, Hsia S, Alaupovic P, et al. The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. *J Clin Endocrinol Metab*. 2002;87(1):136-143.
56. Grossmann M. Testosterone and glucose metabolism in men: current concepts and controversies. *J Endocrinol*. 2014;220(3):R37-R55.
57. Bhasin S, Taylor WE, Singh R, et al. The mechanisms of androgen effects on body composition: mesenchymal pluripotent cell as the target of androgen action. *J Gerontol A Biol Sci Med Sci*. 2003;58:1103-1110.
58. Herbst KL, Bhasin S. Testosterone action on skeletal muscle. *Curr Opin Clin Nutr Metab Care*. 2004;7(3):271-277.
59. Singh R, Artaza JN, Taylor WE, Gonzalez-Cadavid NF, Bhasin S. Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. *Endocrinology*. 2003;144(11):5081-5088.
60. Kelly DM, Jones TH. Testosterone and obesity. *Obes Rev*. 2015;16(7):581-606.
61. Xu XF, de Pergola G, Bjorntorp P. Testosterone increases lipolysis and the number of beta-adrenoceptors in male rat adipocytes. *Endocrinology*. 1991;128(1):379-382.
62. de Pergola G. The adipose tissue metabolism: role of testosterone and dehydroepiandrosterone. *Int J Obes Relat Metab Disord*. 2000;24(Suppl 2):S59-S63.
63. Carrageta DF, Dias TR, Alves MG, Oliveira PF, Monteiro MP, Silva BM. Anti-obesity potential of natural methylxanthines. *J Funct Foods*. 2018;43:84-94.
64. Hernández-Morante JJ, Perez-de-Heredia F, Lujan JA, Zamora S, Garaulet M. Role of DHEA-S on body fat distribution: gender- and depot-specific stimulation of adipose tissue lipolysis. *Steroids*. 2008;73(2):209-215.
65. Karbowska J, Kochan Z. Fat-reducing effects of dehydroepiandrosterone involve upregulation of ATGL and HSL expression, and stimulation of lipolysis in adipose tissue. *Steroids*. 2012;77(13):1359-1365.
66. McInnes KJ, Smith LB, Hunger NI, Saunders PT, Andrew R, Walker BR. Deletion of the androgen receptor in adipose tissue in male mice elevates retinol binding protein 4 and reveals independent effects on visceral fat mass and on glucose homeostasis. *Diabetes*. 2012;61(5):1072-1081.
67. Yanase T, Fan W, Kyoya K, et al. Androgens and metabolic syndrome: lessons from androgen receptor knock out (ARKO) mice. *J Steroid Biochem Mol Biol*. 2008;109(3-5):254-257.
68. Dicker A, Ryden M, Naslund E, et al. Effect of testosterone on lipolysis in human pre-adipocytes from different fat depots. *Diabetologia*. 2004;47(3):420-428.
69. Rebuffe-Scrive M, Marin P, Bjorntorp P. Effect of testosterone on abdominal adipose tissue in men. *Int J Obes*. 1991;15(11):791-795.
70. Olivecrona G. Role of lipoprotein lipase in lipid metabolism. *Curr Opin Lipidol*. 2016;27(3):233-241.
71. Ramirez ME, McMurry MP, Wiebke GA, et al. Evidence for sex steroid inhibition of lipoprotein lipase in men: comparison of abdominal and femoral adipose tissue. *Metabolism*. 1997;46(2):179-185.
72. Marin P, Lonn L, Andersson B, Olbe L, Bengtsson BA, Bjorntorp P. Assimilation of triglycerides in subcutaneous and intraabdominal adipose tissues in vivo in men: effects of testosterone. *J Clin Endocrinol Metab*. 1996;81(3):1018-1022.
73. Vermeulen A, Kaufman JM, Deslypere JP, Thomas G. Attenuated luteinizing hormone (LH) pulse amplitude but normal LH pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. *J Clin Endocrinol Metab*. 1993;76(5):1140-1146.
74. Zumoff B, Strain GW, Miller LK, et al. Plasma free and non-sex-hormone-binding-globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. *J Clin Endocrinol Metab*. 1990;71(4):929-931.
75. Hofstra J, Loves S, van Wageningen B, Ruinemans-Koerts J, Jansen I, de Boer H. High prevalence of hypogonadotropic hypogonadism in men referred for obesity treatment. *Neth J Med*. 2008;66(3):103-109.
76. Calderon B, Gomez-Martin JM, Vega-Pinero B, et al. Prevalence of male secondary hypogonadism in moderate to severe obesity and

- its relationship with insulin resistance and excess body weight. *Andrology*. 2016;4(1):62-67.
77. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, Mcwhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract*. 2006;60(7):762-769.
  78. Dandona P, Dhindsa S, Chaudhuri A, Bhatia V, Topiwala S, Mohanty P. Hypogonadotropic hypogonadism in type 2 diabetes, obesity and the metabolic syndrome. *Curr Mol Med*. 2008;8(8):816-828.
  79. Mogri M, Dhindsa S, Quattrin T, Ghanim H, Dandona P. Testosterone concentrations in young pubertal and post-pubertal obese males. *Clin Endocrinol*. 2013;78(4):593-599.
  80. Vandewalle S, Taes Y, Fiers T, et al. Sex steroids in relation to sexual and skeletal maturation in obese male adolescents. *J Clin Endocrinol Metab*. 2014;99(8):2977-2985.
  81. Cooper LA, Page ST, Amory JK, Anawalt BD, Matsumoto AM. The association of obesity with sex hormone-binding globulin is stronger than the association with ageing—implications for the interpretation of total testosterone measurements. *Clin Endocrinol*. 2015;83(6):828-833.
  82. Eriksson J, Haring R, Grarup N, et al. Causal relationship between obesity and serum testosterone status in men: a bi-directional mendelian randomization analysis. *PLoS ONE*. 2017;12(4):e0176277.
  83. Schulster M, Bernie AM, Ramasamy R. The role of estradiol in male reproductive function. *Asian J Androl*. 2016;18(3):435-440.
  84. Bernardino RL, Carrageta DE, Silva AM, et al. Estrogen modulates glycerol permeability in sertoli cells through downregulation of aquaporin-9. *Cell*. 2018;7(10):153.
  85. Schneider G, Kirschner MA, Berkowitz R, Ertel NH. Increased estrogen production in obese men. *J Clin Endocrinol Metab*. 1979;48(4):633-638.
  86. Cohen P. The hypogonadal-obesity cycle: role of aromatase in modulating the testosterone-estradiol shunt—a major factor in the genesis of morbid obesity. *Med Hypotheses*. 1999;52(1):49-51.
  87. Barakat R, Oakley O, Kim H, Jin J, Ko CJ. Extra-gonadal sites of estrogen biosynthesis and function. *BMB Rep*. 2016;49(9):488-496.
  88. Rubinow KB. Estrogens and body weight regulation in men. In: *Sex and Gender Factors Affecting Metabolic Homeostasis, Diabetes and Obesity*. Springer; 2017:285-313.
  89. Pellitero S, Olaizola I, Alastrue A, et al. Hypogonadotropic hypogonadism in morbidly obese males is reversed after bariatric surgery. *Obes Surg*. 2012;22(12):1835-1842.
  90. Corona G, Rastrelli G, Monami M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. *Eur J Endocrinol*. 2013;168(6):829-843.
  91. Armamento-Villareal R, Aguirre LE, Qualls C, Villareal DT. Effect of lifestyle intervention on the hormonal profile of frail, obese older men. *J Nutr Health Aging*. 2016;20(3):334-340.
  92. Loves S, Ruinemans-Koerts J, de Boer H. Letrozole once a week normalizes serum testosterone in obesity-related male hypogonadism. *Eur J Endocrinol*. 2008;158(5):741-747.
  93. Dhindsa S, Furlanetto R, Vora M, Ghanim H, Chaudhuri A, Dandona P. Low estradiol concentrations in men with subnormal testosterone concentrations and type 2 diabetes. *Diabetes Care*. 2011;34(8):1854-1859.
  94. Ghanim H, Dhindsa S, Abuaysheh S, et al. Diminished androgen and estrogen receptors and aromatase levels in hypogonadal diabetic men: reversal with testosterone. *Eur J Endocrinol*. 2018;178(3):277-283.
  95. Hammoud A, Carrell DT, Meikle AW, et al. An aromatase polymorphism modulates the relationship between weight and estradiol levels in obese men. *Fertil Steril*. 2010;94(5):1734-1738.
  96. Ohlsson C, Hammarstedt A, Vandenput L, et al. Increased adipose tissue aromatase activity improves insulin sensitivity and reduces adipose tissue inflammation in male mice. *Am J Physiol Endocrinol Metab*. 2017;313(4):E450-E462.
  97. Gillies GE, McArthur S. Estrogen actions in the brain and the basis for differential action in men and women: a case for sex-specific medicines. *Pharmacol Rev*. 2010;62(2):155-198.
  98. Roselli CE, Liu M, Hurn PD. Brain aromatization: classical roles and new perspectives. *Semin Reprod Med NIH Public Access*. 2009;207.
  99. Liu X, Shi H. Regulation of estrogen receptor alpha expression in the hypothalamus by sex steroids: implication in the regulation of energy homeostasis. *Int J Endocrinol*. 2015;2015:949085.
  100. Clegg DJ, Brown LM, Woods SC, Benoit SC. Gonadal hormones determine sensitivity to central leptin and insulin. *Diabetes*. 2006;55(4):978-987.
  101. Chakraborty S, Sachdev A, Salton SR, Chakraborty TR. Stereological analysis of estrogen receptor expression in the hypothalamic arcuate nucleus of ob/ob and agouti mice. *Brain Res*. 2008;1217:86-95.
  102. Parent AS, Lebrethon MC, Gerard A, Vandersmissen E, Bourguignon JP. Leptin effects on pulsatile gonadotropin releasing hormone secretion from the adult rat hypothalamus and interaction with cocaine and amphetamine regulated transcript peptide and neuropeptide Y. *Regul Pept*. 2000;92(1-3):17-24.
  103. Quennell JH, Mulligan AC, Tups A, et al. Leptin indirectly regulates gonadotropin-releasing hormone neuronal function. *Endocrinology*. 2009;150(6):2805-2812.
  104. Harris RB. Direct and indirect effects of leptin on adipocyte metabolism. *Biochim Biophys Acta Mol basis Dis*. 2014;1842(3):414-423.
  105. Hebebrand J, Muller TD, Holtkamp K, Herpertz-Dahlmann B. The role of leptin in anorexia nervosa: clinical implications. *Mol Psychiatry*. 2007;12(1):23-35.
  106. Moreira BP, Monteiro MP, Sousa M, Oliveira PF, Alves MG. Insights into leptin signaling and male reproductive health: the missing link between overweight and subfertility? *Biochem J*. 2018;475(22):3535-3560.
  107. Dunn SL, Bjornholm M, Bates SH, Chen Z, Seifert M, Myers MG Jr. Feedback inhibition of leptin receptor/Jak2 signaling via Tyr1138 of the leptin receptor and suppressor of cytokine signaling 3. *Mol Endocrinol*. 2005;19(4):925-938.
  108. Schaab M, Kausch H, Klammt J, et al. Novel regulatory mechanisms for generation of the soluble leptin receptor: implications for leptin action. *PLoS ONE*. 2012;7(4):e34787.
  109. Sanchez-Garrido MA, Ruiz-Pino F, Manfredi-Lozano M, et al. Obesity-induced hypogonadism in the male: premature reproductive neuroendocrine senescence and contribution of Kiss1-mediated mechanisms. *Endocrinology*. 2014;155(3):1067-1079.
  110. Zhai LL, Zhao J, Zhu YM, et al. Downregulation of leptin receptor and kisspeptin/GPR54 in the murine hypothalamus contributes to male hypogonadism caused by high-fat diet-induced obesity. *Endocrine*. 2018;62(1):195-206.
  111. George JT, Veldhuis JD, Tena-Sempere M, Millar RP, Anderson RA. Exploring the pathophysiology of hypogonadism in men with type 2 diabetes: kisspeptin-10 stimulates serum testosterone and LH secretion in men with type 2 diabetes and mild biochemical hypogonadism. *Clin Endocrinol*. 2013;79(1):100-104.
  112. Isidori AM, Caprio M, Strollo F, et al. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. *J Clin Endocrinol Metab*. 1999;84:3673-3680.

113. Ishikawa T, Fujioka H, Ishimura T, Takenaka A, Fujisawa M. Expression of leptin and leptin receptor in the testis of fertile and infertile patients. *Andrologia*. 2007;39(1):22-27.
114. Giovambattista A, Suescun MO, Nessler CC, Franca LR, Spinedi E, Calandra RS. Modulatory effects of leptin on leydig cell function of normal and hyperleptinemic rats. *Neuroendocrinology*. 2003;78(5):270-279.
115. Jockenhövel F, Blum WF, Vogel E, et al. Testosterone substitution normalizes elevated serum leptin levels in hypogonadal men. *J Clin Endocrinol Metab*. 1997;82(8):2510-2513.
116. Ng Tang Fui M, Hoermann R, Grossmann M. Effect of testosterone treatment on adipokines and gut hormones in obese men on a hypocaloric diet. *J Endocr Soc*. 2017;1(4):302-312.
117. Levine H, Jorgensen N, Martino-Andrade A, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. *Hum Reprod Update*. 2017;23(6):646-659.
118. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertil Steril*. 2010;93(7):2222-2231.
119. Jensen TK, Andersson A-M, Jørgensen N, Andersen A-G, Carlsen E, Skakkebaek NE. Body mass index in relation to semen quality and reproductive hormones among 1,558 Danish men. *Fertil Steril*. 2004;82(4):863-870.
120. Sermondade N, Faure C, Fezeu L, et al. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Hum Reprod Update*. 2013;19(3):221-231.
121. Wang EY, Huang Y, Du QY, Yao GD, Sun YP. Body mass index effects sperm quality: a retrospective study in Northern China. *Asian J Androl*. 2017;19(2):234-237.
122. Hofny ER, Ali ME, Abdel-Hafez HZ, et al. Semen parameters and hormonal profile in obese fertile and infertile males. *Fertil Steril*. 2010;94(2):581-584.
123. Hammoud AO, Wilde N, Gibson M, Parks A, Carrell DT, Meikle AW. Male obesity and alteration in sperm parameters. *Fertil Steril*. 2008;90(6):2222-2225.
124. Kumar P, Kumar N, Thakur DS, Patidar A. Male hypogonadism: symptoms and treatment. *J Adv Pharm Technol Res*. 2010;1(3):297-301.
125. Winters BR, Walsh TJ. The epidemiology of male infertility. *Urol Clin North Am*. 2014;41(1):195-204.
126. Hauser R, Skakkebaek NE, Hass U, et al. Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab*. 2015;100(4):1267-1277.
127. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744.
128. Rastrelli G, Corona G, Mannucci E, Maggi M. Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. *Andrology*. 2014;2(6):794-808.
129. Kim C, Barrett-Connor E, Aroda VR, et al. Testosterone and depressive symptoms among men in the diabetes prevention program. *Psychoneuroendocrinology*. 2016;72:63-71.
130. Fui MNT, Prendergast LA, Dupuis P, et al. Effects of testosterone treatment on body fat and lean mass in obese men on a hypocaloric diet: a randomised controlled trial. *BMC Med*. 2016;14:153.
131. Ng Tang Fui M, Hoermann R, Zajac JD, Grossmann M. The effects of testosterone on body composition in obese men are not sustained after cessation of testosterone treatment. *Clin Endocrinol*. 2017;87(4):336-343.
132. Elagizi A, Köhler TS, Lavie CJ. Testosterone and cardiovascular health. *Mayo Clin Proc*. 2018;93(1):83-100.
133. Calderon B, Galdon A, Calanas A, et al. Effects of bariatric surgery on male obesity-associated secondary hypogonadism: comparison of laparoscopic gastric bypass with restrictive procedures. *Obes Surg*. 2014;24(10):1686-1692.
134. Samavat J, Facchiano E, Lucchese M, et al. Hypogonadism as an additional indication for bariatric surgery in male morbid obesity? *Eur J Endocrinol*. 2014;171(5):555-560.

**How to cite this article:** Carrageta DF, Oliveira PF, Alves MG, Monteiro MP. Obesity and male hypogonadism: Tales of a vicious cycle. *Obesity Reviews*. 2019;1-11. <https://doi.org/10.1111/obr.12863>