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Hypogonadism and Male Obesity: Focus on Unresolved Questions

Short title: Obesity-associated hypogonadism

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Abstract

Obesity, increasing in prevalence globally, is the clinical condition most strongly associated with lowered testosterone concentrations in men, and presents as one of the strongest predictors of receiving testosterone treatment. While low circulating total testosterone concentrations in modest obesity primarily reflect reduced concentrations of sex hormone binding globulin, more marked obesity can lead to genuine hypothalamic-pituitary-testicular axis (HPT) suppression. HPT axis suppression is likely mediated via pro-inflammatory cytokine and dysregulated leptin signalling and aggravated by associated comorbidities. Whether estradiol-mediated negative hypothalamic-pituitary feedback plays a pathogenic role requires further study. Although the obesity-hypogonadism relationship is bi-directional, the effects of obesity on testosterone concentrations are more substantial than the effects of testosterone on adiposity. In markedly obese men submitted to bariatric surgery, substantial weight loss is very effective in reactivating the HPT axis. In contrast, lifestyle measures are less effective in reducing weight and generally only associated with modest increases in circulating testosterone. In randomised controlled clinical trials (RCTs), testosterone treatment does not reduce body weight, but modestly reduces fat mass and increases muscle mass. Short-term studies have shown that testosterone treatment in carefully selected obese men may have modest benefits on symptoms of androgen deficiency and body composition even additive to diet alone. However, longer-term, larger RCTs designed for patient-important outcomes and potential risks are required. Until such trials are available, testosterone treatment cannot be routinely recommended for men with obesity-associated non-classical hypogonadism. Lifestyle measures or where indicated bariatric surgery to achieve weight loss, and optimisation of comorbidities remain first line.

Introduction

Obesity was not considered to be an etiological factor in male hypogonadism in authoritative reviews published in the 1980s[1]. However today, obesity has emerged as one of the strongest predictors of receiving testosterone treatment in middle-aged US American men[2]. Global increases in testosterone prescribing[3] and a marked increase in the prevalence of obesity, which has doubled since the 1980s in many countries[4] in conjunction with secular trends of reductions in circulating testosterone[5] likely contribute to an increasing number of obese men receiving testosterone treatment. Recent observational studies have suggested an interaction

between abdominal obesity and low testosterone in predicting an increased risk of mortality[6,7]. Preclinical studies have reported that paternal but not maternal obesity predisposes to obesity and hypothalamic-pituitary-testicular (HPT) axis suppression preferentially in male offspring[8]. An update on obesity-associated hypogonadism is timely for all the above reasons.

This perspective is not intended to cover all the mechanistic and clinical aspects of obesity-associated hypogonadism. I will not discuss the basic clinical assessment and biochemical evaluation that should be made before attributing low testosterone to obesity alone, rather than to coexisting classical hypogonadism. Furthermore, the assessment for and management of important associated comorbidities that may contribute to HPT axis suppression such as sleep apnoea, and the potential risks of testosterone treatment in men with non-classical hypogonadism will not be covered. These aspects have been summarized in a number of comprehensive reviews[9-14]. Instead I will focus on several aspects of obesity-associated hypogonadism that remain unresolved, addressing the following questions:

1) To what extent do obese men without classical hypogonadism have clinically relevant HPT axis dysfunction?
2) In the bidirectional relationship between obesity and hypogonadism, what is cause and consequence?
3) What are the mechanisms underlying the obesity-associated HPT axis suppression?
4) How should obesity-associated hypogonadism be treated? Does the current evidence support testosterone treatment?
5) Is there a role for selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) in the treatment of obesity-associated hypogonadism?

Given the lack of uniform terminology in this area, the terms used in this article are defined in the **Table**.

The material discussed in this paper is based on PubMed searches using the search terms "testosterone", "androgen", "obesity" "hypogonadism", "selective estrogen receptor modulator", "aromatase inhibitor", "estradiol", "leptin" and "kisspeptin", from inception to March 2018.

1) To what extent do obese men without classical hypogonadism have clinically relevant HPT axis dysfunction?

Reductions in circulating testosterone concentrations among obese men were first reported in the 1970s[15,16]. These early studies, while based on small convenience samples are nevertheless instructive because obese subjects were young to middle-aged (range 18-55 years) and were reported to be healthy. Confounding by older age and comorbidities, factors that can be associated with androgen deficiency-like symptoms and low circulating testosterone concentrations independent of obesity, was minimised in these studies. Subjects underwent detailed clinical examination, dynamic HPT axis testing, and free sex steroid concentrations were measured by gold standard equilibrium dialysis. These studies reported two main patterns of HPT axis abnormality[15-21] (**Figure**).

Men with class 1 (body mass index (BMI) 30 to <35 kg/m^2) and class 2 obesity (BMI 35 to <40 kg/m^2) primarily exhibited low total testosterone concentrations (reduced by as much as 50% compared to age-matched non-obese controls), while free testosterone by equilibrium dialysis was not low. Gonadotrophin concentrations were not elevated. Dynamic testing with gonadotrophin releasing hormone (GnRH), the SERM clomiphene and human chorionic gonadotrophin (hCG) respectively revealed normal pituitary and testicular responsiveness[15,17]. Reductions in total testosterone were primarily interpreted as reflecting obesity-associated reductions in its circulating carrier protein SHBG. Not surprisingly therefore, there was no evidence of clinical androgen deficiency or of defective spermatogenesis in these men[15,17].

Studies in men with class 3 obesity (BMI $\geq$40 kg/m^2) however demonstrated not only reductions in total but also in free testosterone concentrations[15,16,18,21]. Gonadotrophin concentrations were not different to or lower than in lean controls. A study of eight obese middle-aged men demonstrated reductions in mean luteinizing hormone (LH) diurnal concentrations and pulse amplitudes compared to lean controls[22]. Obesity-associated decreases in LH pulse amplitudes were confirmed in a controlled study of 22 men with a BMI $\geq$40 kg/m^2 [21]. These findings are consistent with genuine biochemical hypogonadism in men with massive obesity. Interestingly however, none of the studies found evidence of clinical androgen deficiency, or of reduced semen quality even in these massively obese men[15,16,18,19].

Overall, these studies suggested that in otherwise healthy young to middle-aged men, marked obesity (generally class 3, BMI $\geq$40 kg/m^2) is required to genuinely suppress the HPT axis at the biochemical level, but little information was available about practical clinical consequences. The limitations of these studies include their small size and cross-sectional design. These early studies did not evaluate factors known to supress the HPT axis, such as comorbid burden[23] and associated pro-inflammatory states[24], medications (e.g. opioids, glucocorticoids)[25,26], or older age in itself[27]. These factors may make men more susceptible to the development of obesity-associated hypogonadism.

The obesity-hypogonadism relationship has subsequently been examined in large population-based studies that by and large excluded men with classical hypogonadism. These studies included middle-aged and older men with varying degrees of comorbid burden. Given the large size of these studies, clinical assessment for androgen deficiency was less detailed. These studies have confirmed that obesity is the single most important factor associated with low testosterone, overriding the effects of age and comorbidities[28,29]. In a cross-sectional study of 1,849 US American men aged 45 years or older, 40% of obese non-diabetic and 50% of obese diabetic men had low free testosterone concentrations measured by equilibrium dialysis, compared to 26% of lean men without diabetes[30]. BMI is even more closely correlated with testosterone than diabetic status that is itself closely associated with low testosterone[31]. In the European Male Ageing Study (EMAS) which included 3,369 men aged 40 to 79 years (mean age 60 years), obese men had a 5.1 nmol/L (30%) lower total testosterone and a 53.7 pmol/L (18%) lower calculated free testosterone compared to lean men (BMI $\leq$ 25 kg/m^2). Gonadotrophin concentrations were generally not elevated in obese men[29].

In many of these epidemiological studies, low testosterone was associated with androgen deficiency-like symptoms and clinical markers of androgen deficiency such as sexual dysfunction, reduced lean mass, reduced physical performance, reduced bone density, and anaemia[32-34]. In EMAS, obesity was associated with a 13-fold increased risk of non-classical or late onset hypogonadism (LOH) defined as the syndromic coexistence of sexual dysfunction and low testosterone concentrations, whereas the presence of two or more comorbidities increased the risk of LOH risk by only 5.2-fold[35]. Among 1,822 men from the Boston Area Community Health (BACH) survey, central obesity was the most important contributor to symptomatic androgen deficiency, more so than the effects of age and overall

health status[36]. The close association of obesity with non-classical hypogonadism is also underscored by the fact that in the T trials which recruited men with evidence of clinical androgen deficiency and low testosterone concentrations of (total testosterone < 9.54 nmol/L), 63% of participants were obese[37].

In summary, these population-based studies suggest that in older men with comorbidities, obesity is strongly associated with non-classical hypogonadism. Although head-to-head studies are lacking, it can be speculated that in the context of older age and high comorbid burden, the HPT axis is more susceptible to obesity-associated suppression than in young otherwise healthy men[23,24,26,27]. Consistent with this, in Australian obese men, the prevalence of low testosterone was 12% in healthy community dwelling men[38], much lower than the 57% prevalence reported in diabetic men attending tertiary hospital outpatient clinics[39], despite their similar age.

Testosterone concentrations in non-classical hypogonadism typically range from 8-12 nmol/L[40]. The clinical implications of these modestly low testosterone concentrations remain uncertain, considering the limited specificity of androgen deficiency-like symptoms. In EMAS, only 9 of 32 candidate symptoms of androgen deficiency were associated with a low testosterone, and only 3 sexual symptoms had a syndromic association[35]. There is also the limited specificity of organ effects due to low testosterone, such as erectile dysfunction, reduced muscle mass or reduced bone density. Therefore, the extent to which androgen deficiency-like features are a direct consequence of the HPT axis suppression or of obesity and associated ill health can only be clarified in randomised controlled trials (RCTs) that are discussed below.

2) In the bidirectional relationship between obesity and hypogonadism, what is cause and consequence?

It is most commonly stated that the relationship between low testosterone and obesity is bi-directional. This is supported by prospective observational studies. On the one hand, obesity is associated with a more rapid age-related decline in serum testosterone[41,42]. On the other hand, a lower testosterone predicts future weight gain[43], especially the development of central adiposity[44] with visceral fat accumulation[45].

However, accumulating evidence suggests that the effects of obesity on testosterone concentrations may be more substantial than the effects of low testosterone on adiposity. Weight loss is associated with marked increases in circulating testosterone that rise in proportion to the amount of weight lost[46]. Bariatric surgery is associated with an increase in total testosterone of 8.73 nmol/L [6.51-10.95] together with increases in gonadotropins and free testosterone, suggesting a genuine reactivation of the HPT axis[47]. In contrast, changes in circulating testosterone concentrations induced either by testosterone deprivation or testosterone treatment have limited effects on body weight; instead, changes in circulating testosterone mostly modulate body composition, albeit modesty. In a controlled study of men with prostate cancer, 12 months of androgen deprivation therapy (ADT) which severely reduces circulating testosterone to near zero had only minor effects on body weight. BMI increased by 0.65 kg/m^2 [0.14, 1.15] compared to matched prostate cancer controls not receiving ADT[48]. Fat mass increased by 3.5 kg [2.0, 5.0] and lean mass decreased by 1.5 kg [0.2, 1.8], suggesting that reliance on body weight alone can mask metabolically adverse changes of androgen deprivation[48]. Similarly, while significant reductions in body weight with testosterone treatment have been reported in registry studies[49], this has to date not been demonstrated in RCTs[14]. Instead, testosterone treatment modestly reduces fat mass by 1.6 kg [2.5, 0.6] and increases lean mass by 1.6 kg [0.6-2.6][50]. Although these body composition changes are expected to be metabolically favourable, testosterone treatment has not consistently been associated with improvements in insulin resistance[51,52]. In contrast, ADT consistently increases insulin resistance[48,53]. However, ADT causes much lower testosterone concentrations (<2 nmol/L) than are seen in non-classical hypogonadism, where testosterone concentrations typically range from 8-12 nmol/L[40]. This suggests that the modest reductions in testosterone seen in most men with non-classical hypogonadism may not be low enough to cause marked changes in glucose metabolism. Consistent with this, observational and experimental studies in men[54] have reported that insulin resistance is increased only if circulating testosterone falls below 8.0 nmol/L[32] or even below 6.1 nmol/L[55]. Given that insulin resistance is considered an important mediator of obesity-associated cardiometabolic disease[56], failure to improve insulin resistance might be related to the uncertain effects of testosterone treatment on cardiovascular outcomes[57]. However, a hyperinsulinaemic-euglycaemic clamp study in 44 diabetic men reported that testosterone treatment increased insulin sensitivity in association with increased expression of insulin signalling genes in adipose tissue[58].

A recent bi-directional Mendelian randomisation analysis including 7,446 Caucasian men genotyped for 97 BMI-associated and three testosterone-associated single nucleotide polymorphisms (SNP) reported that while a genetically instrumented increase in BMI was associated with a reciprocal decrease in circulating testosterone, genetically instrumented circulating testosterone was not associated with BMI[59]. The genetic data predicted that a reduction in BMI from 30 to 25 kg/m^2 would result in a 13% increase in circulating testosterone, similar to the actual increase in testosterone reported in weight loss trials[43,46,47]. Consistent with the foregoing discussion, the authors concluded that BMI has a causal effect on testosterone, whereas testosterone does not impact BMI. Limitations of this study include the cross-sectional design, reliance on single testosterone concentrations, and the absence of data on body composition[59].

In summary, while the evidence suggests that the relationship between obesity and lowered testosterone is bi-directional (**Figure**), changes in adiposity may have more dominant effects on the HPT axis compared to the reverse. In a recent comprehensive Endocrine Society statement on the pathogenesis of obesity, low testosterone was not considered to be an aetiological factor[60].

3) What are the mechanisms underlying the obesity-associated HPT axis suppression?

A tight link between nutritional status and reproductive capacity in men is well documented, and both energy deficit and excess compromise reproductive potential[61]. While exact mechanisms are unknown, the reversal of HPT axis suppression with weight loss[43,46,47] suggests a pathogenic role for excess adipose tissue. Key adipose-derived factors postulated to mediate obesity-associated HPT axis suppression include estradiol, leptin, and pro-inflammatory cytokines. Effects of insulin and other non-adipose derived hormonal factors are reviewed elsewhere[54,61,62].

Role of estradiol

Early studies in otherwise healthy young to middle-aged men have reported increases in circulating estradiol concentrations compared to lean controls[17-19,63]. Therefore, estradiol-mediated central negative feedback was postulated to contribute to the suppression of the HPT axis. However, changes in estradiol concentrations consequent to weight loss have been variable, with some studies showing no decrease despite evidence of weight loss-associated HPT axis reactivation[19,47,63]. In part, this inconsistency is due to the use of immunoassays in

some studies which lack sufficient sensitivity and specificity to accurately quantify the low circulating estradiol concentrations found in men[64]. Moreover, in line with the fact that circulating androgens are substrates for aromatase, more recent larger studies reported low circulating estradiol in obese men, paralleling their low testosterone concentrations[64,65]. Consonant with this, a recent study reported lower aromatase expression in the adipose tissue of obese men with low testosterone compared to controls with normal circulating testosterone[66]. In preclinical studies, increased adipose tissue inflammation and insulin resistance are associated with reduced aromatase expression and overexpression of aromatase specifically in adipose tissue reduces inflammation and increases insulin sensitivity[67]. This is in agreement with experimental studies in men reporting that estradiol, rather than its substrate testosterone, is primarily important in preventing adiposity and insulin resistance[68,69]. Other observations as discussed below further support the notion that adipose-derived pro-inflammatory cytokines can contribute to HPT axis suppression.

The fact that SERM and AI treatment are associated with increases in gonadotrophin and testosterone concentrations in obese men[70,71] has been invoked to postulate a pathogenic role for increased estradiol in the obesity-associated HPT axis suppression. However lean men respond similarly to these agents[72], and evidence for clinical benefit with their use is largely lacking (see below). Given that clinical studies to date have relied on circulating estradiol concentrations which may be different from tissue concentrations (such as in the hypothalamic neurons or pituitary gonadotrophic cells), further work to assess the role of estradiol is necessary. In addition, more comprehensive steroid hormone profiling in the circulation and/or target tissues could be of value in elucidating the role of sex steroids in the pathogenesis of obesity-associated hypogonadism. Currently, the routine measurement of estradiol as part of the clinical assessment for obesity-associated hypogonadism is not recommended. Likewise, the clinical merits of blocking estradiol-mediated negative central HPT axis feedback by using e.g. SERMs or AIs require further study.

Role of leptin

While leptin promotes satiety and increases energy expenditure physiologically, obese men are usually leptin resistant, and circulating leptin concentrations correlate positively with total body weight and adiposity. In a cross-sectional study, among men with BMIs ranging from normal weight to severe obesity, circulating leptin was the hormonal factor most closely associated with low testosterone, and inversely correlated with testicular response to hCG

stimulation[73]. In vitro, leptin inhibited basal and hCG-stimulated testosterone secretion from rodent Leydig cells and from testicular samples via a functional leptin receptor isoform[74,75]. While leptin physiologically stimulates GnRH secretion via kisspeptin, obesity is associated with leptin resistance and supressed hypothalamic kisspeptin gene expression[76]. Therefore, it is possible that hypothalamic resistance to leptin stimulation combined with preserved testicular sensitivity to leptin inhibition may contribute to HPT axis suppression in male obesity. Consistent with this notion, testosterone treatment decreases circulating leptin, but early RCTs did not adjust for testosterone-treatment changes in body composition[77]. A more recent RCT reported that testosterone treatment reduced leptin concentrations independent of changes in fat mass, above and beyond the effects of caloric restriction, suggesting that testosterone effects on leptin are not simply an indirect consequence of testosterone-mediated reductions in fat mass[78]. The inference that testosterone directly inhibits leptin production is supported by in vitro observations that testosterone suppresses leptin mRNA and leptin secretion from human adipose tissue[79]. Overall the data suggest that circulating leptin and testosterone could interact in a self-perpetuating cycle promoting adiposity and reproductive dysfunction. While it is tempting to speculate that testosterone treatment may restore HPT axis responsiveness to leptin, further study is required to find out whether this will result in a clinically important effect on adiposity.

Pro-inflammatory cytokines

Observational studies have demonstrated an inverse relationship of circulating pro-inflammatory cytokine and testosterone concentrations in older men[80]. In preclinical studies, cytokines have been shown to supress the HPT axis both at the level of the hypothalamus and the Leydig cell[81-83]. In addition, in experimental studies, even relatively low doses of the pro-inflammatory interleukin-2 reduce the LH feedforward drive on testosterone secretion, and inhibit GnRH and/or LH secretion in older men[24]. The relevance of obesity in this context is underscored by a study in male rabbits demonstrating that high fat diet-induced hypogonadotrophic hypogonadism was associated with increased hypothalamic inflammation, increased expression of pro-inflammatory cytokines and reduced expression of the kisspeptin-1 receptor[84].

Overall, these mechanistic studies support the concept that obesity, especially if marked, leads to genuine hypogonadism. However, in contrast to classical hypogonadism, obesity-associated hypogonadism is functional and therefore potentially reversible.

Upstream regulators of the HPT axis

Although GnRH neurons play a central role in the HPT axis via secretion of GnRH, they do not express receptors for leptin and insulin, and do not express the androgen receptor or the estrogen receptor alpha[61]. This suggests that metabolic signals and sex steroid feedback regulate GnRH neurons indirectly. It is now known that a major hypothalamic regulatory network integrates peripheral metabolic and hormonal cues to regulate the HPT axis, including among others, KNDy (kisspeptin/neurokinin B/dynorphin) neurons in the arcuate nucleus of the mediobasal hypothalamus[61,85]. Whether manipulation of such upstream regulators can be exploited clinically is not known. Proof-of-principle studies have demonstrated that kisspeptin administration can increase LH pulse frequency and LH secretion in obese men with low testosterone[86]. Conversely, administration of a neurokinin receptor 3 antagonist decreased gonadotrophin and testosterone secretion in healthy men[87].

4) How should obesity-associated hypogonadism be treated? Does the current evidence support testosterone treatment?

Most reviews emphasize the importance of lifestyle measures, especially weight loss as an important first line measure[9-14,88]. Indeed, especially in markedly obese men, successful weight loss is very effective in reactivating the HPT axis[46,47], and commonly associated with improvements in androgen deficiency-like clinical features. However, whether the weight loss-associated increases in testosterone are causally related to the clinical improvements is not known[88]. For example, in one longitudinal study among obese men submitted to bariatric surgery, the degree of weight loss was closely associated with improvements in sexual function, but the increase in testosterone was not[89].

In most men, at least 10% of weight loss is required to achieve an increase in circulating testosterone. The largest study examining the effects of weight changes on testosterone concentrations was a secondary analysis of 886 men participating in the diabetes prevention program (DPP) trial[90]. Obese (mean BMI 32 kg/m^2) middle-aged (mean age 55 years) men who were randomised to an intensive lifestyle intervention (n = 293) lost 7.9 kg over 12 months. Total testosterone increased only slightly, by 1.15 nmol/L, along with SHBG, but bioavailable testosterone did not change significantly[90]. There were no significant associations between changes in testosterone and mood. However, baseline testosterone was not clearly low (11.6 nmol/L) in these men[90].

In a recent RCT of middle-aged obese men with low testosterone (6.9 nmol/L) randomised to testosterone or placebo in combination with a concomitant intensive diet program for all participants, the placebo group lost 11% of body weight and this was associated with only a modest increase in endogenous total and free testosterone by 2.9 nmol/L and by 30.3 pmol/L, respectively[91]. Perhaps not surprisingly, at follow-up more than one year after completion of the RCT, these men had regained two-thirds of their weight, and testosterone concentrations fell back to baseline concentrations[92]. These studies confirmed what is known; that while weight loss is difficult to achieve, sustaining weight loss and maintaining the associated increases in testosterone is even more difficult. Low testosterone may however contribute to fatigue and inertia[93], making it more difficult for such men to engage in healthy lifestyle measures. Several studies in obese men have reported that more intensive physical activity is required to increase endogenous testosterone[94,95], an intensity that can be difficult to achieve even in dedicated clinical studies. Moreover, benefits of caloric restriction may be limited by loss of muscle mass, even in the context of concomitant exercise[96].

Overall, while bariatric surgery for severely obese men is very effective, achieving a sustained increase in testosterone with lifestyle measures is challenging. While lifestyle measures and optimisation of chronic disease remain cornerstone management tools, the question arises as to whether testosterone treatment can augment the benefits of lifestyle interventions and prevent the diet-associated loss of muscle mass. Previous RCTs combining exercise interventions and testosterone treatment in healthy older men have reported equivocal results[97,98]. One RCT combining very low energy diet (VLED) and testosterone treatment in obese men with obstructive sleep apnoea failed to show effects of testosterone treatment additive to diet[99]. However, this study achieved only a very modest, ~2kg loss of body weight[99], limiting conclusions regarding combined benefits.

In a recent 56-week RCT, middle-aged (median age 53 years) obese men with a low testosterone (mean total testosterone 6.9 nmol/L) were subjected to a rigorous 10-week VLED phase followed by 46 weeks of weight maintenance and additionally randomized to testosterone treatment or placebo. Both groups lost similar amount of body weight at the end of the VLED phase (testosterone group -12.0 kg, placebo group -13.5 kg) and these were largely sustained at RCT end (testosterone group -11.4 kg, placebo group -10.9 kg) with no significant between group differences[91]. However, men randomised to testosterone had,

compared to placebo, greater reductions in fat mass (between group difference -2.9kg [-5.7, -0.2]) and visceral fat (-2678 mm^2 [-5180, -176]), but preservation of lean mass (+ 3.4kg [1.3, 5.5]). Thus, although testosterone treatment did not augment diet-associated weight loss, it prevented the diet-associated loss in lean mass. While placebo-treated men lost both lean and fat mass, the weight loss with testosterone treatment was almost exclusively due to loss of body fat[91]. These changes in body composition may have been due to androgen receptor signalling in adipose and skeletal muscle cells[100], and/or increased physical activity observed among testosterone-treated men[91]. As discussed above, testosterone treatment decreased leptin over and above the effects of weight loss suggesting a lessening of leptin resistance[78]. In contrast, testosterone treatment did not augment weight loss-associated effects on circulating concentrations of ghrelin, glucagon like peptide-1, gastric inhibitory polypeptide, peptide YY, pancreatic polypeptide, and amylin[78]. This suggests that the effects of testosterone treatment on body composition are unlikely to be mediated by effects on these key modulators of appetite and energy homeostasis.

Interestingly, in this RCT[91] the metabolically favourable changes in body composition consequent to testosterone treatment did not augment weight loss-associated improvements in glucose metabolism, consistent with testosterone treatment RCTs that did not incorporate weight loss measures[51,52]. However, testosterone treatment improved constitutional symptoms and sexual function over and above the effects of weight loss alone[101]. Baseline testosterone (total 6.9 nmol/L, free 166 pmol/L) was markedly lower than that of unselected community dwelling obese men; in the obese subgroup of the EMAS cohort, mean total and free testosterone concentrations were 13.5 nmol and 280 pmol/L[102], and among obese US American men, they ranged from 11.5nmol/L to 12.2 nmol/L and 176 pmol/L to 193 pmol/L respectively, depending on diabetic status[30]. Therefore, the benefits reported with testosterone treatment in this cohort[91,101] cannot be extended to unselected obese men.

When re-evaluated 20 months after the end of the RCT[91,101], the testosterone treatment effects on body composition were not sustained, and the former between group differences in fat and lean mass were no longer apparent[92]. This suggests, consistent with other studies[103,104], that testosterone treatment needs to be given long term to maintain benefits. There were no differences in testosterone concentrations between previously testosterone- and placebo-treated men[92], suggesting that relatively short term (56 weeks) testosterone treatment was not associated with a prolonged iatrogenic suppression of the HPT axis.

Interestingly, in an RCT using the same questionnaires as Ng Tang Fui's study[91,101], but in a cohort of older men with longstanding diabetes (mean duration 8 to 9 years) and a high comorbid burden, testosterone treatment did not improve androgen deficiency-like symptoms or sexual function[105]. This discrepancy is consistent with the notion that in older men with multiple comorbidities, androgen deficiency-like symptoms are less specific, and that sexual dysfunction is more likely to be contributed to by non-endocrine causes compared to younger and healthier men. In the large T Trials, sexual function improved modestly with testosterone treatment, suggesting that even older men with a relatively high comorbid burden (37% had diabetes and 15% a previous myocardial infarction) can respond to testosterone[37].

Overall, larger, longer-term studies are needed to assess whether testosterone treatment has patient important benefits if added to rigorously implemented lifestyle measures.

5) Is there a role for selective estrogen modulators (SERMs) or aromatase inhibitors (AIs) in the treatment of obesity-associated hypogonadism?

SERMs and AIs require residual hypothalamic-pituitary responsiveness for their action and they are therefore ineffective in classical hypogonadotrophic hypogonadism[106]. However, as discussed above, obesity-associated hypogonadism is functional and the question arises as to whether SERMs and AIs could be effective in this context. There are however caveats to their use in obese older men. Experimental studies demonstrate reduced LH and testosterone secretion in response to SERMs[27,72] or AIs[107] in older compared to young men, and this is exacerbated by obesity[108] and a pro-inflammatory state[24] that commonly coexists with obesity. SERMs and AIs may have undesirable effects. In contrast to testosterone treatment, SERMs via estrogen-like actions in the liver may reduce insulin-like growth factor-1, potentially reducing anabolism, while the increase in SHBG may limit testosterone bioavailability[109]. The physiological relevance of such effects remains speculative, as long-term clinical trials are lacking. Moreover, as discussed below, AIs reduce bone density[110].

Clinical studies with SERMs

Uncontrolled case series, reviewed elsewhere[111], variously reported not only increases in testosterone, but also improvements in self-reported sexual function and androgen deficiency-like symptoms in SERM-treated men. The only placebo-controlled RCT in older men (median age of 61 years) with symptomatic androgen deficiency randomised 17 men with

erectile dysfunction and circulating testosterone < 9.5 nmol/L to clomiphene or placebo for 2 months[112]. Despite robust increases in testosterone with clomiphene (from 8.3 nmol/L to 19.1 nmol/L), sexual function assessed by self-reporting and by nocturnal tumescence did not improve[112].

In younger men (mean age 49 years), the largest RCT randomized 256 obese men (BMI 33 kg/m^2) with biochemical secondary hypogonadism (defined as testosterone <10.4 nmol/L and LH < 9.4 IU/L) to either enclomiphene, testosterone gel or placebo for 16 weeks[71]. In men receiving enclomiphene, gonadotrophin concentrations increased and in men receiving testosterone gonadotrophins decreased. It is likely that this differential effect on gonadotrophins resulted in maintenance of a normal sperm count in enclomiphene-treated men whereas sperm count was modestly reduced from a normal baseline in testosterone-treated men[71]. No other outcome measures were reported[71]. Enclomiphene, the *trans*-isomer of clomiphene is a relatively pure estradiol antagonist[113], and long-term effects on bone health, sexual function and adiposity require scrutiny. A recent cross-over RCT among 24 middle-aged obese men with impaired glucose tolerance or diabetes and baseline testosterone < 10.4 nmol/L reported modest but significant improvements in fasting glucose and insulin resistance (by HOMA-IR) after 3 months of clomiphene treatment, but this small study requires confirmation[114].

Clinical studies with AIs

The largest RCT randomised 88 obese men ≥60 years with symptomatic androgen deficiency to anastrozole or placebo for 12 months. Despite substantial increases in testosterone from 11.2 nmol/L to 18.2 nmol/L with anastrozole, there were no between group differences in symptoms, body composition, strength or lipid levels[115]. Smaller RCTs have similarly reported that despite robust increases in testosterone, AIs had no effect on a large array of psychological and somatic measures in men with age- or obesity-associated reductions in testosterone[116-118]. Of concern, BMD at the spine decreased significantly after 12 months of anastrozole, presumably because of the decrease in circulating estradiol[110]. In addition to bone health[119], estradiol may be important for of sexual function, prevention of abdominal adiposity[68] and insulin sensitivity[69,120]. More work is needed before SERMs or AIs can be considered for the treatment of obesity-associated hypogonadism.

Summary and conclusions

While the relationship between obesity and the HPT axis is to a certain extent bi-directional, changes in adiposity can have marked effects on the HPT axis, whereas changes in circulating testosterone have relatively modest effects on body composition. Both mechanistic and clinical studies have shed new light on the roles for adipose tissue-derived factors such as leptin, pro-inflammatory cytokines and estradiol in the regulation of the HPT axis and their hypothalamic targets. However, these insights have yet to be translated into clinical strategies.

Many men with more modest degrees of obesity have reductions primarily in total testosterone, and their nonspecific androgen deficiency-like symptoms may at least in part be caused by comorbidities. It is clear that marked obesity can lead to genuine biochemical hypogonadism, but the evidence for patient-important clinical consequences is comparatively less well established. While in otherwise healthy younger men, only severe obesity, BMI $\geq$ 40 kg/m^2, leads to genuine HPT axis suppression, older men with comorbidities may be susceptible with lesser degrees of adiposity; however, androgen deficiency-like features are less specific in these older men.

In markedly obese men, substantial loss of excess body weight is very effective in restoring eugonadism, but lifestyle measures are less effective and difficult to sustain. While lifestyle modifications should remain first line therapeutic measures, short-term studies have shown that testosterone treatment in selected men may have modest benefits, even additive to diet alone. Testosterone treatment needs to be maintained long-term, and possibly indefinitely to sustain a benefit. Longer-term, larger RCTs powered for patient-important outcomes and long-term safety are needed to more precisely define the benefits, and potential risks of testosterone treatment. Moreover, further studies are required to determine whether the effects of testosterone treatment can be enhanced by concomitant exercise. Until such trials are available, testosterone treatment cannot be routinely recommended for men with obesity-associated non-classical hypogonadism. In comparison, much less evidence is available to guide the use of agents such as SERMs and AIs, and their use should be restricted to clinical trials.

Figure Legend

Bi-directional relationship between adipose tissue and testosterone

Depicted are potential mechanisms by which increased adiposity, via leptin and pro-inflammatory cytokines leads to suppression of the hypothalamic-pituitary-testicular (HPT axis). Both central leptin resistance and inhibitory leptin action at the testicular level may play a role, and cytokines may inhibit the HPT axis at multiple levels (see main text). Potential effects of insulin and other non-adipose derived hormonal factors on the HPT axis are reviewed elsewhere[54,61,62].

In turn, low testosterone and/or low estradiol may promote adipose tissue accumulation. Androgen deficiency-like clinical features may be due to low sex steroid concentrations (both low testosterone and estradiol), and/or due to age-associated accumulation of comorbid burden and sarcopaenic obesity. Loss of muscle mass is primarily due to low testosterone, whereas accumulation of fat mass may primarily be due to low estradiol. SHBG, sex hormone binding globulin. Adapted from[54].

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Table: Definitions

Term	Definition	Remarks
Androgen deficiency-like symptoms and signs*	Clinical symptoms and signs consistent with, but not necessarily diagnostic of androgen deficiency	Some clinical features can be nonspecific and confounded by comorbidities
Low testosterone	Circulating testosterone concentrations below the reference range established for young healthy men	Age-dependent reference ranges have not been rigorously defined
Hypogonadism	Coexistence of androgen deficiency and low testosterone	Coexistence does not necessarily prove causality
Classical hypogonadism	Hypogonadism due to established HPT axis pathology	For example: pituitary tumour, Klinefelter
Non-classical hypogonadism	Hypogonadism without recognisable (classical) HPT axis pathology	Potential for reversibility (functional hypogonadism)
Clinically relevant HPT axis dysfunction	Clinical androgen deficiency and unequivocally low circulating testosterone concentrations	Dysfunction can be caused by classical (established HPT axis pathology) or non-classical hypogonadism (functional suppression).

HPT: hypothalamic-pituitary-testicular

*androgen deficiency-like symptoms and signs may include sexual dysfunction (such as reduced libido and erectile dysfunction), decreased energy, low mood, reduced bone density, reduced muscle mass and increased fat mass.