

# Asian Journal of Andrology

亚洲男性学杂志  
CN 31-1795/R  
ISSN 1008-682X (Print)  
ISSN 1745-7262 (Online)

**This article is authors' accepted manuscripts for 2014 in  
Asian Journal of Andrology.**

OnlineFirst Author's accepted Manuscripts are PDF versions of manuscripts that have been peer reviewed and accepted for publication, but not yet copyedited or typeset, allowing readers the most rapid access to accepted papers. They appear on the OnlineFirst page as submitted by the authors, subject to the authors' agreement, and do not reflect the changes that will be made before final publication. The Author Manuscript remains on the OnlineFirst page until it is either replaced by the final proof version or when the final version of the paper is published in an online issue.

**Review**

**Lowered Testosterone in Male Obesity: Mechanisms, Morbidity and Management**

Mark Ng Tang Fui<sup>1,2</sup>, Philippe Dupuis<sup>1,2</sup>, Mathis Grossmann<sup>1,2</sup>

<sup>1</sup>Department of Medicine Austin Health, University of Melbourne, Melbourne, Victoria, 3084, Australia

<sup>2</sup>Department of Endocrinology, Austin Health, Melbourne, Victoria, 3084, Australia

**Running title: Lowered Testosterone in Male Obesity**

Correspondence:

A/Prof Mathis Grossmann, Email [mathisg@unimelb.edu.au](mailto:mathisg@unimelb.edu.au)

**Abstract**

With increasing modernisation and urbanisation of Asia, much of the future focus of the obesity epidemic will be in the Asian region. Low testosterone levels are frequently encountered in obese men who do not otherwise have a recognisable hypothalamic-pituitary-testicular (HPT) axis pathology. Moderate obesity predominantly decreases total testosterone due to insulin resistance-associated reductions in sex hormone binding globulin. More severe obesity is additionally associated with reductions in free testosterone levels due to suppression of the HPT axis. Low testosterone by itself leads to increasing adiposity, creating a self-perpetuating cycle of metabolic complications. Obesity-associated hypo-testostonaemia is a functional, non-permanent state, which can be reversible, but this requires substantial weight loss. While testosterone treatment can lead to moderate reductions in fat mass, obesity by itself, in the absence of symptomatic androgen deficiency, is not an established indication for testosterone therapy. Testosterone therapy may lead to a worsening of untreated sleep apnoea and compromise fertility. Whether testosterone therapy augments diet- and exercise-induced weight loss requires evaluation in adequately designed randomised controlled clinical trials.

**Keywords:** Obesity, androgens, testosterone, hypogonadism, weight loss

**Received: 2013-6-5    Revised: 2013-8-12    Accepted: 2013-8-23**

**1. Prevalence and clinical significance of obesity**

Obesity, a worldwide epidemic, is on the rise. Populous developing Asian nations such as China and India have seen increases in the prevalence of overweight (body mass index, BMI 25-29.9 kg/m<sup>2</sup>) and obesity (BMI ≥30 kg/m<sup>2</sup>) in adult men by more than 25% in the last 8 years according to WHO estimates<sup>1</sup> (Table 1). In developed countries including Australia, over 75% of the adult male population is already overweight or obese. The number of overweight people is expected to increase from 937 million in 2005 to 1.35 billion in 2030<sup>2</sup>. Similarly the number of obese people is projected to increase from 396 million in 2005 to 573 million in 2030. By 2030, China alone is predicted to have more overweight men and women than the traditional market economies combined.

In addition to posing significant societal and environmental challenges, obesity is associated with a multitude of adverse health outcomes including cardiovascular disease, sleep apnoea, osteoarthritis, increased risk of certain cancers and in men, lowered testosterone levels<sup>3</sup>. A recent systematic review and meta-analysis including 2.8 million people and 270,000 deaths reported increased overall mortality only in those with extreme obesity (BMI >35 kg/m<sup>2</sup>, HR 1.29, 95% CI 1.18-1.41) but not in grade 1 obesity (BMI 30-34.9 kg/m<sup>2</sup>, HR 0.95, 95% CI 0.88-1.01) compared to their non-obese counterparts<sup>4</sup>. However, this meta-analysis has been subsequently criticized in a series of letters and commentaries<sup>5-7</sup>. For example, the adverse effect of obesity may have been underestimated because the lean comparison group (BMI 18-25 kg/m<sup>2</sup>) included frail and elderly with serious illness and weight loss due to their disease. Therefore, the “obesity paradox” remains a hotly debated, but currently still unresolved issue. In addition, obesity, as measured by BMI, is a relatively crude indicator of metabolic risk with waist circumference providing a better indicator of all-cause (HR 1.19 vs 1.10 per standard deviation) and cardiovascular mortality (HR 1.33 vs 1.23 per standard deviation) compared to BMI<sup>8</sup>. This is because excess weight stored as visceral adipose tissue (VAT) is more closely linked to cardiovascular outcomes than subcutaneous adipose tissue (SAT). Consistent with this, there is evidence that some individuals may be metabolically healthy despite a BMI in the obese range (MHO), because they have lower amounts of VAT. Conversely, others may present with a cluster of obesity-associated risk factors for diabetes and cardiovascular disease despite a BMI in the normal range, the so-called “metabolically obese but normal weight” (MONW). Indeed, a recent prospective cohort study from Korea has shown that MONW individuals have a higher mortality than MHO<sup>9</sup>.

The capacity to store excess energy in SAT vs VAT may be genetically regulated, providing a potential mechanistic explanation for the variability in metabolic risk at a given BMI. Interestingly, diacylglycerol O-acyltransferase 2 (DGAT2), mechanistically implicated in this differential storage<sup>10</sup>, is regulated by dihydrotestosterone<sup>11</sup>, suggesting a potential role for androgens to influence the genetic predisposition to either the MHO or MONW phenotype.

Unfortunately, obesity is a chronic condition that is difficult to treat. Public health measures, lifestyle interventions and pharmacotherapy adopted thus far have neither registered a marked impact on the prevalence of obesity, nor markedly reduced body weight-related disease burden<sup>12</sup>. Although dietary restriction often results in initial weight loss, many obese dieters fail to maintain their reduced weight, and there is increasing evidence that weight is physiologically defended<sup>13</sup>. While bariatric surgery achieves 10-30% long-term weight loss in controlled studies<sup>12</sup>, this therapy is expensive and currently not widely available.

## **2. Obesity and low testosterone: evidence from population-based studies**

The fact that obese men have lower testosterone compared to lean men has been recognised for more than 30 years<sup>14</sup>. Since then, multiple cross-sectional and prospective studies have consistently found negative linear correlations between both total and free testosterone levels and adiposity in men<sup>15</sup>. In a cohort of 3 219 men from the European Male Aging Study (EMAS), obesity was associated with an 8.7-fold, and overweight with a 3.3-fold increased relative risk (RR) of secondary hypogonadism (defined as total testosterone of <10.5 nmol/L and normal LH), relative to normal weight<sup>3</sup>. Both total testosterone (-5.9 nmol/L) and free testosterone (-54 pmol/L) levels were lower in obese compared to lean men, with lesser but still significant reduction in overweight men (total T -2.3 nmol/L, free T -18 pmol/L)<sup>16</sup>. A cross-sectional study of 314 Chinese men similarly found that older obese men (defined by BMI >28 kg/m<sup>2</sup> for these Asian men) had a 3 nmol/L lower testosterone level compared to age-matched lean men<sup>17</sup>. The inverse association of BMI with low testosterone may be compounded by the presence of comorbidities: while one Australian study reported a relatively low 12% prevalence of low testosterone in obese but otherwise healthy men<sup>18</sup>, another study found a 57% prevalence in diabetic men attending tertiary hospital outpatient clinics<sup>19</sup>. In a cross-sectional study of 1 849 community-dwelling obese US American men 40% had low testosterone levels<sup>20</sup>. Reductions in testosterone levels correlate with the severity of obesity, and men with a BMI >35-40 kg/m<sup>2</sup> have >50% reduction in total and free testosterone levels compared to lean men<sup>15</sup>.

Obesity can be an important confounder when testosterone levels are compared across different ethnic groups. For example, in a cross-sectional study, while Japanese and Hong Kong Asian men had higher unadjusted testosterone levels than Swedish and US men, these differences did not persist when adjusted for BMI<sup>21</sup>. Similarly, in a multi-ethnic Malaysian population, the lower (11%) prevalence of low testosterone in Chinese compared Malay and Indian men (21%) was due to a higher burden of obesity and the metabolic syndrome in the latter<sup>22</sup>.

In summary, observational studies consistently show a strong association of obesity with low circulating testosterone levels in men. Indeed, epidemiological data suggest that the single most powerful predictor of low testosterone is obesity, and that obesity is a major contributor of the age-associated decline in testosterone levels<sup>16</sup>. Conversely, there is increasing evidence that healthy ageing by itself is uncommonly associated with marked reductions in testosterone levels<sup>23</sup>. This may be because age-related testicular dysfunction is, at least in part, compensated for by an age-associated increase in pituitary luteinising hormone (LH) secretion<sup>3</sup>. However, because obesity blunts this LH rise, obesity leads to hypothalamic-pituitary suppression irrespective of age which cannot be compensated for by physiological mechanisms<sup>3</sup>.

### **3. Obesity and low testosterone: potential mechanisms and biological plausibility**

Overweight and moderate obesity is predominantly associated with reductions in total testosterone, whereas free testosterone levels remain within the reference range, especially in younger men. Reductions in total testosterone levels are largely a consequence of reductions in sex hormone binding globulin (SHBG) due to obesity-associated hyperinsulinaemia. Indeed, although controversial, measurement of free testosterone levels may provide a more accurate assessment of androgen status than the (usually preferred) measurement of total testosterone in situations where SHBG levels are outside the reference range<sup>24</sup>. However, reference ranges for free testosterone levels are not well established, especially in older men whose SHBG increases with age. Some have argued that the measurement of free testosterone levels merely reintroduces age in a covert form<sup>25</sup>.

More marked obesity however is associated with an unequivocal reduction of free testosterone levels, where LH and follicle stimulating hormone (FSH) levels are usually low or inappropriately normal, suggesting that the dominant suppression occurs at the hypothalamic-pituitary level. This may be because adipose tissue, especially when in the inflamed, insulin-resistant state, expresses aromatase which converts testosterone to estradiol (E<sub>2</sub>). Adipose E<sub>2</sub> in turn may feedback negatively to decrease pituitary gonadotrophin secretion, although, partly due to assay limitations, confirmation of increased circulatory E<sub>2</sub> concentrations is often elusive. In addition, local, tissue-specific increases of E<sub>2</sub> may not be reflected in circulatory concentrations. However, this adipose tissue-aromatase hypothesis is not well supported by other data. Clinical studies showing that treatment of obese men with aromatase inhibitors can increase testosterone levels and restore fertility<sup>26</sup> do not necessarily support the pathophysiological importance of this E<sub>2</sub>-mediated HPT axis suppression, because gonadotrophins and testosterone levels also rise with this treatment. Interestingly, more recent studies suggest that, diabetic obesity is associated with decreases in circulatory E<sub>2</sub><sup>27</sup>. Moreover there is evidence from the European Male Aging Study that even in non-diabetic obese men, E<sub>2</sub> is low and correlated with low testosterone levels<sup>28,29</sup>. In addition to E<sub>2</sub>, increased visceral fat also releases increased amounts of pro-inflammatory cytokines, insulin and leptin, all of which may inhibit the activity of the HPT axis at multiple levels<sup>30</sup>.

#### *Evidence that obesity leads to lower testosterone*

Multiple observational studies in community-dwelling men suggest that obesity leads to decreased testosterone. In the prospective Massachusetts Male Aging Study (MMAS), moving from a non-obese to an obese state resulted in a decline of testosterone levels comparable to that of advancing 10 years in age<sup>31</sup>. Similar findings have been reported in cohort studies of men from Europe<sup>3,32</sup> and Australia<sup>33</sup>. Finally, as discussed in more detail in section 5, weight loss, whether by diet or surgery, increases testosterone levels proportional to the amount of weight lost<sup>19,34</sup>.

#### *Evidence that low testosterone promotes obesity*

While the above discussed studies suggest that obesity leads to reduced testosterone, there is also ample evidence, both from experimental and human studies, to suggest the reverse. Evidence from studies in mice

with genetic deletions of the androgen receptor (AR) (ARKO) is discussed by Rana et al. in more detail elsewhere in this issue. Briefly, ARKO mice develop obesity with increased adipocyte numbers and visceral fat mass suggesting that fat is androgen-responsive<sup>35</sup>. A study of mice with a targeted deletion of the AR in adipose tissue showed that compared to controls, higher visceral fat develops only in the setting of a high fat diet, but not with regular chow, suggesting that low testosterone may augment the effects of a hypercaloric diet<sup>36</sup>. In support of this, transgenic mice with AR overexpression show reduction in adipose tissue volume<sup>37</sup> due to reduction in adipocyte area and adipocyte size. Primate experiments in Japanese macaques show that androgen depletion via castration alters adipocytes size and appearance to an insulin-resistant phenotype which can be rescued by androgen replacement<sup>38</sup>. Consistent with animal experiments linking low testosterone to increases in fat mass are *in vitro* studies showing that testosterone promotes commitment of pluripotent rodent stem cells to the myogenic lineage but inhibits their differentiation into adipocytes via an androgen-receptor mediated pathway<sup>39</sup>. In human male *ex vivo* adipose tissue, testosterone decreased adipocyte differentiation by 50%<sup>40</sup>. Testosterone enhances catecholamine-induced lipolysis *in vitro*, and reduces lipoprotein lipase activity and triglyceride uptake in human abdominal adipose tissue *in vivo*<sup>19</sup>. Moreover, in men with prostate cancer receiving 12 months of androgen deprivation therapy, fat mass increased by 3.4 kg and abdominal visceral adipose tissue by 22%, with the majority of these changes established within six months<sup>41</sup>. Experimental induction of hypogonadism in healthy young men with gonadotrophin-releasing hormone analogue treatment increased fat mass within 10 weeks, suggesting that severe sex steroid deficiency can increase fat mass rapidly<sup>42</sup>.

While evidence reviewed so far suggests that relatively extreme manipulations of testosterone are required to effect changes in fat mass, more moderate variations on testosterone as seen in the majority of men can also impact on fat mass. For example, in a longitudinal study of community-dwelling Japanese-American men, lower baseline testosterone independently predicted increase in intra-abdominal fat after 7.5y of follow-up<sup>43</sup>. Finally, confirmation that testosterone treatment reduces fat mass has been verified in multiple randomized controlled trials (RCT) (see below).

#### *Low testosterone and obesity: a self-perpetuating cycle*

In summary, the current evidence suggests a bi-directional relationship between testosterone and obesity (Fig. 1) in men initiating a self-perpetuating cycle, which may have treatment implications (see sections 5 and 6 below). On the one hand, increasing body fat suppresses the HPT axis by multiple mechanisms<sup>30</sup> via increased secretion of pro-inflammatory cytokines, insulin resistance and diabetes<sup>19,44</sup> while on the other hand low testosterone promotes further accumulation of total and visceral fat mass, thereby exacerbating the gonadotrophin inhibition. Finally there is evidence, reviewed elsewhere<sup>45</sup>, that obesity-associated comorbidities including obstructive sleep apnoea and hypercortisolism may also suppress the HPT axis.

In addition to lowered circulating serum total testosterone levels, obese individuals may have a propensity to lowered androgens in the local fat milieu. Belanger et al<sup>46</sup> found a significant negative correlation of omental testosterone levels with waist circumference ( $r = -0.59$ ,  $P < 0.002$ ). Increased activity of the DHT inactivating enzyme  $3\alpha/\beta$ -ketosteroid reductase ( $3\alpha/\beta$ -HSD) in obese versus non-obese male omental fat biopsies coupled with rat studies showing increased expression of androgen receptor in VAT as opposed to SAT<sup>47</sup> suggests that androgens may play a more significant role in VAT than SAT. Indeed, men undergoing androgen depletion for prostate cancer show more marked increases in visceral compared to subcutaneous fat following treatment<sup>41</sup>. However, RCT studies of testosterone replacement have largely failed to show benefit of selective VAT reduction following testosterone treatment (see section 6 below). In contrast, relatively little is known about the role of androgens in brown fat, since its potential role in energy expenditure in humans has been recognized only more recently. The recently-discovered hormone irisin, derived from muscle, induces brown fat-like properties in rodent white fat<sup>48</sup> and its overexpression led to reduced weight and improved glucose homeostasis<sup>49</sup>. Whether the action of androgens on fat is mediated in part via irisin is yet to be determined although molecular experiments suggest that androgens can act via the PPAR $\gamma$ -pathway<sup>37</sup> which is implicated in the differentiation of precursor fat cells to the energy-consuming phenotype<sup>50</sup>.

#### **4. Low testosterone and obesity beyond testosterone-fat interactions**

Because of its association with sarcopenia<sup>51</sup>, low testosterone may compound the effect of increasing fat mass by making it more difficult for obese men to lose weight via exercise. Conversely, obesity in itself contributes to loss of muscle mass and function, thus escalating the effects of sarcopenia on mobility disability and functional impairment, a concept known as ‘sarcopenic obesity’<sup>52</sup>. Indeed, pro-inflammatory cytokines released by adipose tissue may contribute to loss of muscle mass and function, leading to inactivity and further weight gain in a vicious cycle<sup>53,54</sup>. Sarcopenic obesity, a phenotype recapitulated in men receiving ADT for prostate cancer<sup>55</sup>, may not only be associated with functional limitations, but also aggravate the metabolic risks of obesity; the association of low testosterone with sarcopenia may be an additional mechanism linking low testosterone to insulin resistance beyond its relationship to increased visceral fat<sup>56</sup>.

An important concern related to otherwise desirable weight loss induced by hypocaloric dieting, especially in older obese men who are already at risk of sarcopenia, is the concomitant loss of muscle mass causing altered function of muscle and physical functional decline<sup>52,54</sup>. Although this accelerated loss of muscle mass can be attenuated by exercise<sup>57</sup>, adherence to an exercise program is often difficult to achieve. Whether testosterone treatment will attenuate the catabolic effects of diet restriction on loss of muscle mass and function requires further study. Consistent with this hypothesis is observational evidence associating higher endogenous testosterone with reduced loss of muscle mass and crude measures of muscle function in men losing weight<sup>58</sup>.

In addition to muscle effects, reduced testosterone levels may also lead to obesity via its effects on motivation to exercise. In a study of male mice lacking the androgen-receptor, spontaneous activity was reduced compared to wild-type mice<sup>59</sup> while another animal study reported a positive association between testosterone intake and amount of time spent on a running wheel<sup>60</sup>. In a small RCT, men receiving testosterone undecanoate showed reduced fatigue although the effect of testosterone on exercise motivation and tolerance is to be determined<sup>61</sup>.

## **5. Treatment of obesity leading to increased testosterone**

Observational evidence that weight changes are inversely associated with testosterone levels in community dwelling men have recently been reported in a longitudinal analysis of the EMAS cohort<sup>34</sup>. Minor weight loss (<15%) over 4.4 years was associated with modest increases (+2 nmol/L) in total testosterone, probably as a consequence of increases in SHBG, whereas free testosterone did not change. However, a more substantial weight loss of >15% led not only to a more marked increase (+5.75 nmol/L) of total testosterone, but was also associated with significant increase in free testosterone (+51.78 pmol/L), likely because of HPT activation, evidenced by a significant rise in LH (+2 U/L). This data suggests that while testosterone levels remain relatively stable with small fluctuations in weight, genuine reactivation of the HPT axis in obese men requires more substantial weight-loss, which may be difficult to achieve with lifestyle changes alone.

A number of intervention studies have confirmed that both diet- and surgically-induced weight loss are associated with increased testosterone, with the rise in testosterone generally proportional to the amount of weight lost (Fig. 2). Table 2 lists 15 published trials that have assessed the effects of weight loss interventions on testosterone. The majority of the trials were single-arm cohort studies and included small numbers of subjects. Follow-up in the lifestyle trials was generally shorter than in the surgical trials. Overall, diet led to modest weight loss (6-17%) with modest increases in testosterone (2.9 to 5.1 nmol/L). In comparison to lifestyle, surgical intervention resulted in loss of weight of 28-44% and increases of testosterone from 7.8 - 12.5 nmol/L. While these studies were uncontrolled, a 32-week RCT comparing a very low calorie diet (VLCD) against no intervention reported a 14% weight loss and a 3.0 nmol/L increase in testosterone<sup>62</sup>. Another small RCT comparing lifestyle modification with gastric bypass found that after prolonged follow-up of 2 years, bariatric surgery led to greater weight loss and greater testosterone increments compared to lifestyle<sup>63</sup>. However, not all studies were positive, with a number of studies (Table 2) showing no increase in testosterone, possibly due to small reductions in weight (4-8%)<sup>64,65</sup> or modest baseline obesity in one study (BMI 31 kg/m<sup>2</sup>)<sup>66</sup>.

A recent systematic review and meta-analysis of the effect of weight loss on testosterone reported that lifestyle changes achieve a mean weight reduction of 9.8% versus 32% for surgical intervention<sup>67</sup>. Overall, diet therapy led to an increase in total testosterone of 2.87 nmol/L vs 8.73 nmol/L in the surgical studies. While younger age and higher baseline BMI predicted greater gains in testosterone, in a stepwise logistic regression analysis, only the change in BMI was associated with change in testosterone. This suggests that men, regardless of obesity level, can benefit from the effect of weight loss.

## **6. Intervention studies linking exogenous testosterone to reduction in body fat mass**

Testosterone replacement in men with authentic, pathologically-based hypogonadism reduces fat mass by 10-15%<sup>68,69</sup>. In a meta-analysis of RCTs of older men without confirmed hypogonadism (mean baseline serum testosterone 10.9 nmol/L, BMI 29 kg/m<sup>2</sup>), testosterone treatment reduced total fat mass by 1.6 kg (95% CI 0.6-2.5), corresponding to a relative reduction of fat mass of 6.2% (95% CI 3.3-9.2)<sup>70</sup>. While these effects are relatively modest, more recent RCTs using long-acting testosterone undecanoate formulations in men with higher baseline BMI have found more pronounced effects on total fat mass, ranging from 2.5 to 6kg<sup>71-74</sup>. Uncontrolled studies recently reported larger benefits with progressive weight loss of up to 13% after 5 years of continuous testosterone undecanoate therapy in unselected patients<sup>75</sup>.

While RCTs consistently show that testosterone treatment reduces total body fat mass, effects of testosterone treatment on regional adipose tissue distribution have been less well studied (table 3). RCTs assessing effects of testosterone therapy on VAT have shown inconsistent results with one showing a reduction<sup>76</sup> and others no change<sup>71,77,78</sup>. These inconsistencies may be due to small trial size<sup>79,80</sup>, use of oral testosterone therapy (which did not raise serum testosterone levels)<sup>78</sup> or imprecise methodology to quantify VAT such as dual energy X-ray absorptiometry<sup>77</sup> or ultrasound<sup>78</sup>. Given that VAT is more closely related to insulin resistance and cardiovascular risk than SAT, inconsistent effect of testosterone on VAT may be one possible explanation as to why testosterone treatment, despite reduction of fat mass, has not consistently led to improvements in measures of glucose metabolism<sup>19</sup>. Effects of testosterone therapy on glucose metabolism are discussed in more detail by Allan elsewhere in this issue.

## **7. Clinical consequences of low testosterone in obese men and approach to therapy**

While many obese men have low testosterone levels and non-specific symptoms, it is unclear whether such symptoms are causally related to the hypotestosteronemia. In a study of 181 men with a low testosterone (< 10.4 nmol/L), less than half of men (n=70) reported symptoms consistent with androgen deficiency and these men had higher BMIs than asymptomatic men<sup>81</sup>. A cross-sectional study of older overweight men found that loss of libido occurred at a testosterone level < 15 nmol/L, poor concentration at <10 nmol/L and erectile dysfunction at < 8 nmol/L. However, these thresholds confer neither sensitivity nor specificity for these symptoms, and a high specificity (> 90%) was achieved only when testosterone levels declined to < 3.7 - 6.3nmol/L<sup>82</sup>. In EMAS, while certain end-organ deficits compatible with androgen deficiency, such as reductions in muscle mass, hemoglobin and bone density, occurred more commonly in symptomatic men with a total testosterone of < 12 nmol/L, increased insulin resistance and the metabolic syndrome could only be demonstrated in men with testosterone < 8 nmol/L<sup>29</sup>. Low testosterone either directly or via its metabolite E<sub>2</sub> is a risk factor for osteoporotic fractures<sup>83</sup>. While this may be counterbalanced by the protective effects of obesity on the skeleton<sup>84</sup>, recent evidence suggests that increased VAT may have adverse consequences for skeletal health<sup>56</sup>.

One practical issue for the clinician is when and how to evaluate obese men with lowered testosterone for underlying intrinsic HPT axis pathology, rather than to assume that the lowered testosterone is a non-specific consequence of the obesity. The probability of organic pathology is inversely related to age, BMI, number of comorbidities and testosterone level. We recommend a thorough clinical evaluation for symptoms and signs of androgen deficiency<sup>24</sup> including assessment for end-organ deficits and pituitary pressure symptoms in all men. Mild, otherwise unexplained anaemia<sup>85</sup> and trabecular-predominant osteopenia may be clues to organic androgen deficiency. Measurements of prolactin and, where indicated, iron studies (hemochromatosis is less common in Asian men) should be performed in most men. Provided this evaluation is normal, pituitary imaging can be limited to men with a testosterone of repeatedly <5.2nmol/L and non-raised gonadotrophins<sup>24</sup>.

The presence of both obesity and low testosterone and can have negative impacts on fertility, sleep apnoea, exercise ability, fatigue, mood and feelings of well-being. Weight loss can improve many of these features, and it is conceivable that the associated rise in testosterone may be responsible for salutary effects beyond those achieved by the weight loss itself. However, because of insufficient evidence regarding its risk-benefit ratio, testosterone treatment should not be used for the sole purpose of weight loss. Nevertheless, a reduction in fat mass may be a collateral benefit for men receiving testosterone therapy for treatment of established androgen deficiency. Potential safety concerns with testosterone treatment particularly relevant to obese, older men include sleep apnoea and adverse cardiovascular disease and prostate events<sup>86-89</sup>, in part because such comorbidities are common in this population. However, whether testosterone treatment increases risk is unknown because there are no adequately designed and powered RCTs that have assessed the long-term risk-benefit ratio of testosterone therapy. As testosterone treatment impairs spermatogenesis, it is contra-indicated in obese men seeking to have children who are already at increased risk of impaired fertility<sup>90</sup>. Other approaches using aromatase inhibitors, selective estrogen receptor modulators and gonadotrophins may be considered instead. Studies, reviewed elsewhere have shown that use of such agents can improve the endocrine hormonal profile (increased gonadotrophins and testosterone), semen parameters and sexual function<sup>91</sup>. For example, in one study of men with secondary hypogonadism, clomiphene therapy increased testosterone levels and improved sexual function in 75%; younger men with less comorbidities were more likely to respond<sup>92</sup>. However, their effects on fertility are not proven<sup>91</sup>. In addition, because of the associated lowering of circulating E2 levels, long-term use of such agents may lead to reduced bone mineral density<sup>93</sup>.

## **8. Summary and Conclusions**

The bi-directional, inverse relationship between increased fat mass and testosterone levels suggests that both weight loss as well as testosterone therapy have the potential to break this vicious cycle. While HPT axis reactivation is achievable with weight loss, the degree of weight loss required to achieve this may be difficult to achieve, and to maintain, with usual lifestyle changes for many obese men. However, successful weight loss has many other health benefits and should be first priority. The preclinical and observational data reviewed here suggests that testosterone therapy has the potential to augment diet-induced weight loss, and that it may have additional benefits on other, androgen-responsive tissues beyond its effects on fat mass. While a small, uncontrolled study found that testosterone treatment augmented the reductions in central adiposity and insulin resistance achieved with lifestyle<sup>94</sup>, a recent, preliminary RCT failed to find additive effects of dietary restriction and testosterone therapy on weight loss<sup>88</sup>. Given the increasing prevalence of obesity-associated hypo-testosteronemia, not only the underlying pathophysiology, but also the risk-benefit of testosterone therapy added to lifestyle intervention on long-term outcomes of obesity and its associated adverse health consequences require further study.

## **Conflict of interest**

The authors are primary investigators of an investigator initiated trial "Effect of Testosterone and Diet on Weight", ClinicalTrials.gov Identifier NCT01616732, supported by Bayer HealthCare.

## **Acknowledgements:**

M Grossmann was supported by a National Health and Medical Research Council of Australia Career Development Fellowship (# 1024139), M Ng Tang Fui was supported by a National Health and Medical Research Council of Australia Postgraduate Research Scholarship (#1055305) and P Dupuis was supported by Bourse du Comité des Médecins, Dentistes et Pharmaciens du Centre Hospitalier Universitaire de Québec.

## **References**

- 1) WHO. *WHO Global infobase, estimated overweight and obesity, 2002-2010 in males aged 30-100y*, <<https://apps.who.int/infobase/Comparisons.aspx>>
- 2) Kelly, T., Yang, W., Chen, C. S., Reynolds, K. & He, J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond)* 2008, **32**: 1431-1437.



- 3) Tajar, A., Forti, G., O'Neill, T. W., Lee, D. M., Silman, A. J. *et al.* Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *The Journal of clinical endocrinology and metabolism* 2010, **95**: 1810-1818.
- 4) Flegal, K. M., Kit, B. K., Orpana, H. & Graubard, B. I. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA : the journal of the American Medical Association* 2013, **309**: 71-82.
- 5) Heymsfield, S. B. & Cefalu, W. T. Does body mass index adequately convey a patient's mortality risk? *JAMA : the journal of the American Medical Association* 2013, **309**: 87-88.
- 6) Hughes, V. The big fat truth. *Nature* 2013, **497**: 428-430.
- 7) Willett, W. C., Hu, F. B. & Thun, M. Overweight, obesity, and all-cause mortality. *JAMA : the journal of the American Medical Association* 2013, **309**: 1681.
- 8) Staiano, A. E., Reeder, B. A., Elliott, S., Joffres, M. R., Pahwa, P. *et al.* Body mass index versus waist circumference as predictors of mortality in Canadian adults. *Int J Obes (Lond)* 2012, **36**: 1450-1454.
- 9) Choi, K. M., Cho, H. J., Choi, H. Y., Yang, S. J., Yoo, H. J. *et al.* Higher mortality in metabolically obese normal-weight people than in metabolically healthy obese subjects in elderly Koreans. *Clinical endocrinology* 2013: *in press*.
- 10) Alligier, M., Gabert, L., Meugnier, E., Lambert-Porcheron, S., Chansaume, E. *et al.* Visceral fat accumulation during lipid overfeeding is related to subcutaneous adipose tissue characteristics in healthy men. *The Journal of clinical endocrinology and metabolism* 2013, **98**: 802-810.
- 11) Gupta, V., Bhasin, S., Guo, W., Singh, R., Miki, R. *et al.* Effects of dihydrotestosterone on differentiation and proliferation of human mesenchymal stem cells and preadipocytes. *Molecular and cellular endocrinology* 2008, **296**: 32-40.
- 12) Proietto, J. Why is treating obesity so difficult? Justification for the role of bariatric surgery. *The Medical journal of Australia* 2011, **195**: 144-146.
- 13) Sumithran, P., Prendergast, L. A., Delbridge, E., Purcell, K., Shulkes, A. *et al.* Long-term persistence of hormonal adaptations to weight loss. *The New England journal of medicine* 2011, **365**: 1597-1604.
- 14) Glass, A. R., Swerdloff, R. S., Bray, G. A., Dahms, W. T. & Atkinson, R. L. Low serum testosterone and sex-hormone-binding-globulin in massively obese men. *The Journal of clinical endocrinology and metabolism* 1977, **45**: 1211-1219.
- 15) Allan, C. A. & McLachlan, R. I. Androgens and obesity. *Current opinion in endocrinology, diabetes, and obesity* 2010, **17**: 224-232.
- 16) Wu, F. C., Tajar, A., Pye, S. R., Silman, A. J., Finn, J. D. *et al.* Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *The Journal of clinical endocrinology and metabolism* 2008, **93**: 2737-2745.
- 17) Cao, J., Chen, T. M., Hao, W. J., Li, J., Liu, L. *et al.* Correlation between sex hormone levels and obesity in the elderly male. *The aging male : the official journal of the International Society for the Study of the Aging Male* 2012, **15**: 85-89.
- 18) Allan, C. A., Strauss, B. J., Burger, H. G., Forbes, E. A. & McLachlan, R. I. The association between obesity and the diagnosis of androgen deficiency in symptomatic ageing men. *The Medical journal of Australia* 2006, **185**: 424-427.
- 19) Grossmann, M. Low testosterone in men with type 2 diabetes: significance and treatment. *The Journal of clinical endocrinology and metabolism* 2011, **96**: 2341-2353.
- 20) Dhindsa, S., Miller, M. G., McWhirter, C. L., Mager, D. E., Ghanim, H. *et al.* Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes care* 2010, **33**: 1186-1192.
- 21) Orwoll, E. S., Nielson, C. M., Labrie, F., Barrett-Connor, E., Cauley, J. A. *et al.* Evidence for geographical and racial variation in serum sex steroid levels in older men. *The Journal of clinical endocrinology and metabolism* 2010, **95**: E151-160.
- 22) Tan, W. S., Ng, C. J., Khoo, E. M., Low, W. Y. & Tan, H. M. The triad of erectile dysfunction, testosterone deficiency syndrome and metabolic syndrome: findings from a multi-ethnic Asian men study (The Subang Men's Health Study). *The aging male : the official journal of the International Society for the Study of the Aging Male* 2011, **14**: 231-236.

- 23) Sartorius, G., Spasevska, S., Idan, A., Turner, L., Forbes, E. *et al.* Serum testosterone, dihydrotestosterone and estradiol concentrations in older men self-reporting very good health: the healthy man study. *Clinical endocrinology* 2012, **77**: 755-763.
- 24) Bhasin, S., Cunningham, G. R., Hayes, F. J., Matsumoto, A. M., Snyder, P. J. *et al.* Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism* 2010, **95**: 2536-2559.
- 25) Handelsman, D. J. An old emperor finds new clothing: rejuvenation in our time. *Asian journal of andrology* 2011, **13**: 125-129.
- 26) de Boer, H., Verschoor, L., Ruinemans-Koerts, J. & Jansen, M. Letrozole normalizes serum testosterone in severely obese men with hypogonadotropic hypogonadism. *Diabetes, obesity & metabolism* 2005, **7**: 211-215.
- 27) Dhindsa, S., Furlanetto, R., Vora, M., Ghanim, H., Chaudhuri, A. *et al.* Low estradiol concentrations in men with subnormal testosterone concentrations and type 2 diabetes. *Diabetes care* 2011, **34**: 1854-1859.
- 28) Huhtaniemi, I. T., Tajar, A., Lee, D. M., O'Neill, T. W., Finn, J. D. *et al.* Comparison of serum testosterone and estradiol measurements in 3174 European men using platform immunoassay and mass spectrometry; relevance for the diagnostics in aging men. *European journal of endocrinology / European Federation of Endocrine Societies* 2012, **166**: 983-991.
- 29) Tajar, A., Huhtaniemi, I. T., O'Neill, T. W., Finn, J. D., Pye, S. R. *et al.* Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). *The Journal of clinical endocrinology and metabolism* 2012, **97**: 1508-1516.
- 30) Grossmann, M., Gianatti, E. J. & Zajac, J. D. Testosterone and type 2 diabetes. *Current opinion in endocrinology, diabetes, and obesity* 2010, **17**: 247-256.
- 31) Travison, T. G., Araujo, A. B., Kupelian, V., O'Donnell, A. B. & McKinlay, J. B. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. *The Journal of clinical endocrinology and metabolism* 2007, **92**: 549-555.
- 32) Haring, R., Ittermann, T., Volzke, H., Krebs, A., Zygumt, M. *et al.* Prevalence, incidence and risk factors of testosterone deficiency in a population-based cohort of men: results from the study of health in Pomerania. *The aging male : the official journal of the International Society for the Study of the Aging Male* 2010, **13**: 247-257.
- 33) Yeap, B. B., Chubb, S. A., Hyde, Z., Jamrozik, K., Hankey, G. J. *et al.* Lower serum testosterone is independently associated with insulin resistance in non-diabetic older men: the Health In Men Study. *European journal of endocrinology / European Federation of Endocrine Societies* 2009, **161**: 591-598.
- 34) Camacho, E. M., Huhtaniemi, I. T., O'Neill, T. W., Finn, J. D., Pye, S. R. *et al.* Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. *European journal of endocrinology / European Federation of Endocrine Societies* 2013, **168**: 445-455.
- 35) Rana, K., Fam, B. C., Clarke, M. V., Pang, T. P., Zajac, J. D. *et al.* Increased adiposity in DNA binding-dependent androgen receptor knockout male mice associated with decreased voluntary activity and not insulin resistance. *American journal of physiology. Endocrinology and metabolism* 2011, **301**: E767-778.
- 36) McInnes, K. J., Smith, L. B., Hunger, N. I., Saunders, P. T., Andrew, R. *et al.* 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**: 1072-1081.
- 37) Semirale, A. A., Zhang, X. W. & Wiren, K. M. Body composition changes and inhibition of fat development in vivo implicates androgen in regulation of stem cell lineage allocation. *Journal of cellular biochemistry* 2011, **112**: 1773-1786.
- 38) Varlamov, O., White, A. E., Carroll, J. M., Bethea, C. L., Reddy, A. *et al.* Androgen effects on adipose tissue architecture and function in nonhuman primates. *Endocrinology* 2012, **153**: 3100-3110.

- 39) Singh, R., Artaza, J. N., Taylor, W. E., Gonzalez-Cadavid, N. F. & Bhasin, S. Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. *Endocrinology* 2003, **144**: 5081-5088.
- 40) Blouin, K., Nadeau, M., Perreault, M., Veilleux, A., Drolet, R. *et al.* Effects of androgens on adipocyte differentiation and adipose tissue explant metabolism in men and women. *Clinical endocrinology* 2010, **72**: 176-188.
- 41) Hamilton, E. J., Gianatti, E., Strauss, B. J., Wentworth, J., Lim-Joon, D. *et al.* Increase in visceral and subcutaneous abdominal fat in men with prostate cancer treated with androgen deprivation therapy. *Clinical endocrinology* 2011, **74**: 377-383.
- 42) Mauras, N., Hayes, V., Welch, S., Rini, A., Helgeson, K. *et al.* Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. *The Journal of clinical endocrinology and metabolism* 1998, **83**: 1886-1892.
- 43) Tsai, E. C., Boyko, E. J., Leonetti, D. L. & Fujimoto, W. Y. Low serum testosterone level as a predictor of increased visceral fat in Japanese-American men. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 2000, **24**: 485-491.
- 44) Grossmann, M. Diagnosis and treatment of hypogonadism in older men: proceed with caution. *Asian journal of andrology* 2010, **12**: 783-786.
- 45) Mah, P. M. & Wittert, G. A. Obesity and testicular function. *Molecular and cellular endocrinology* 2010, **316**: 180-186.
- 46) Belanger, C., Hould, F. S., Lebel, S., Biron, S., Brochu, G. *et al.* Omental and subcutaneous adipose tissue steroid levels in obese men. *Steroids* 2006, **71**: 674-682.
- 47) Rodriguez-Cuenca, S., Monjo, M., Proenza, A. M. & Roca, P. Depot differences in steroid receptor expression in adipose tissue: possible role of the local steroid milieu. *American journal of physiology. Endocrinology and metabolism* 2005, **288**: E200-207.
- 48) Pedersen, B. K. & Febbraio, M. A. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nature reviews. Endocrinology* 2012, **8**: 457-465.
- 49) Bostrom, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L. *et al.* A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 2012, **481**: 463-468.
- 50) Petrovic, N., Walden, T. B., Shabalina, I. G., Timmons, J. A., Cannon, B. *et al.* Chronic peroxisome proliferator-activated receptor gamma (PPARgamma) activation of epididymally derived white adipocyte cultures reveals a population of thermogenically competent, UCP1-containing adipocytes molecularly distinct from classic brown adipocytes. *The Journal of biological chemistry* 2010, **285**: 7153-7164.
- 51) Baumgartner, R. N., Waters, D. L., Gallagher, D., Morley, J. E. & Garry, P. J. Predictors of skeletal muscle mass in elderly men and women. *Mechanisms of ageing and development* 1999, **107**: 123-136.
- 52) Srikanthan, P., Hevener, A. L. & Karlamangla, A. S. Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: findings from the National Health and Nutrition Examination Survey III. *PloS one* 2010, **5**: e10805.
- 53) Waters, D. L. & Baumgartner, R. N. Sarcopenia and obesity. *Clinics in geriatric medicine* 2011, **27**: 401-421.
- 54) Jensen, G. L. & Hsiao, P. Y. Obesity in older adults: relationship to functional limitation. *Current opinion in clinical nutrition and metabolic care* 2010, **13**: 46-51.
- 55) Grossmann, M. & Zajac, J. D. Management of side effects of androgen deprivation therapy. *Endocrinology and metabolism clinics of North America* 2011, **40**: 655-671.
- 56) Grossmann, M., Cheung, A. S. & Zajac, D. J. Androgens and prostate cancer; pathogenesis and deprivation therapy. *Best Practice & Research Clinical Endocrinology & Metabolism* 2013: *in press*.
- 57) Chomentowski, P., Dube, J. J., Amati, F., Stefanovic-Racic, M., Zhu, S. *et al.* Moderate exercise attenuates the loss of skeletal muscle mass that occurs with intentional caloric restriction-induced weight loss in older, overweight to obese adults. *The journals of gerontology. Series A, Biological sciences and medical sciences* 2009, **64**: 575-580.

- 58) LeBlanc, E. S., Wang, P. Y., Lee, C. G., Barrett-Connor, E., Cauley, J. A. *et al.* Higher testosterone levels are associated with less loss of lean body mass in older men. *The Journal of clinical endocrinology and metabolism* 2011, **96**: 3855-3863.
- 59) Fan, W., Yanase, T., Nomura, M., Okabe, T., Goto, K. *et al.* Androgen receptor null male mice develop late-onset obesity caused by decreased energy expenditure and lipolytic activity but show normal insulin sensitivity with high adiponectin secretion. *Diabetes* 2005, **54**: 1000-1008.
- 60) Wood, R. I. Oral testosterone self-administration in male hamsters: dose-response, voluntary exercise, and individual differences. *Hormones and behavior* 2002, **41**: 247-258.
- 61) O'Connor, D. B., Archer, J. & Wu, F. C. Effects of testosterone on mood, aggression, and sexual behavior in young men: a double-blind, placebo-controlled, cross-over study. *The Journal of clinical endocrinology and metabolism* 2004, **89**: 2837-2845.
- 62) Kaukua, J., Pekkarinen, T., Sane, T. & Mustajoki, P. Sex hormones and sexual function in obese men losing weight. *Obesity research* 2003, **11**: 689-694.
- 63) Reis, L. O., Favaro, W. J., Barreiro, G. C., de Oliveira, L. C., Chaim, E. A. *et al.* Erectile dysfunction and hormonal imbalance in morbidly obese male is reversed after gastric bypass surgery: a prospective randomized controlled trial. *International journal of andrology* 2010, **33**: 736-744.
- 64) Khoo, J., Piantadosi, C., Duncan, R., Worthley, S. G., Jenkins, A. *et al.* Comparing effects of a low-energy diet and a high-protein low-fat diet on sexual and endothelial function, urinary tract symptoms, and inflammation in obese diabetic men. *The journal of sexual medicine* 2011, **8**: 2868-2875.
- 65) Khoo, J., Piantadosi, C., Worthley, S. & Wittert, G. A. Effects of a low-energy diet on sexual function and lower urinary tract symptoms in obese men. *Int J Obes (Lond)* 2010, **34**: 1396-1403.
- 66) Leenen, R., van der Kooy, K., Seidell, J. C., Deurenberg, P. & Koppeschaar, H. P. Visceral fat accumulation in relation to sex hormones in obese men and women undergoing weight loss therapy. *The Journal of clinical endocrinology and metabolism* 1994, **78**: 1515-1520.
- 67) Corona, G., Rastrelli, G., Monami, M., Saad, F., Luconi, M. *et al.* Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. *European journal of endocrinology / European Federation of Endocrine Societies* 2013, **168**: 829-843.
- 68) Katznelson, L., Finkelstein, J. S., Schoenfeld, D. A., Rosenthal, D. I., Anderson, E. J. *et al.* Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *The Journal of clinical endocrinology and metabolism* 1996, **81**: 4358-4365.
- 69) Brodsky, I. G., Balagopal, P. & Nair, K. S. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men--a clinical research center study. *The Journal of clinical endocrinology and metabolism* 1996, **81**: 3469-3475.
- 70) Isidori, A. M., Giannetta, E., Greco, E. A., Gianfrilli, D., Bonifacio, V. *et al.* Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clinical endocrinology* 2005, **63**: 280-293.
- 71) Allan, C. A., Strauss, B. J. G., Forbes, E. A. & McLachlan, R. I. in *92nd Annual Meeting of the Endocrine Society* Vol. P2 455 (San Diego 2010).
- 72) Aversa, A., Bruzziches, R., Francomano, D., Rosano, G., Isidori, A. M. *et al.* Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *The journal of sexual medicine* 2010, **7**: 3495-3503.
- 73) Kalinchenko, S. Y., Tishova, Y. A., Mskhalaya, G. J., Gooren, L. J., Giltay, E. J. *et al.* Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. *Clinical endocrinology* 2010, **73**: 602-612.

- 74) Svartberg, J., Agledahl, I., Figenschau, Y., Sildnes, T., Waterloo, K. *et al.* Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. *International journal of impotence research* 2008, **20**: 378-387.
- 75) Saad, F., Haider, A., Doros, G. & Traish, A. Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss. *Obesity (Silver Spring)* 2013: *in press*.
- 76) Allan, C. A., Strauss, B. J., Burger, H. G., Forbes, E. A. & McLachlan, R. I. Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men. *The Journal of clinical endocrinology and metabolism* 2008, **93**: 139-146.
- 77) Nair, K. S., Rizza, R. A., O'Brien, P., Dhatariya, K., Short, K. R. *et al.* DHEA in elderly women and DHEA or testosterone in elderly men. *The New England journal of medicine* 2006, **355**: 1647-1659.
- 78) Emmelot-Vonk, M. H., Verhaar, H. J., Nakhai Pour, H. R., Aleman, A., Lock, T. M. *et al.* Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. *JAMA : the journal of the American Medical Association* 2008, **299**: 39-52.
- 79) Munzer, T., Harman, S. M., Hees, P., Shapiro, E., Christmas, C. *et al.* Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. *The Journal of clinical endocrinology and metabolism* 2001, **86**: 3604-3610.
- 80) Schroeder, E. T., Zheng, L., Ong, M. D., Martinez, C., Flores, C. *et al.* Effects of androgen therapy on adipose tissue and metabolism in older men. *The Journal of clinical endocrinology and metabolism* 2004, **89**: 4863-4872.
- 81) Hall, S. A., Esche, G. R., Araujo, A. B., Travison, T. G., Clark, R. V. *et al.* Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. *The Journal of clinical endocrinology and metabolism* 2008, **93**: 3870-3877.
- 82) Zitzmann, M., Faber, S. & Nieschlag, E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *The Journal of clinical endocrinology and metabolism* 2006, **91**: 4335-4343.
- 83) Mellstrom, D., Vandenput, L., Mallmin, H., Holmberg, A. H., Lorentzon, M. *et al.* Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2008, **23**: 1552-1560.
- 84) De Laet, C., Kanis, J. A., Oden, A., Johanson, H., Johnell, O. *et al.* Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 2005, **16**: 1330-1338.
- 85) Grossmann, M. & Zajac, J. D. Hematological changes during androgen deprivation therapy. *Asian journal of andrology* 2012, **14**: 187-192.
- 86) Basaria, S., Coviello, A. D., Travison, T. G., Storer, T. W., Farwell, W. R. *et al.* Adverse events associated with testosterone administration. *The New England journal of medicine* 2010, **363**: 109-122.
- 87) Fernandez-Balsells, M. M., Murad, M. H., Lane, M., Lampropulos, J. F., Albuquerque, F. *et al.* Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *The Journal of clinical endocrinology and metabolism* 2010, **95**: 2560-2575.
- 88) Hoyos, C. M., Killick, R., Yee, B. J., Grunstein, R. R. & Liu, P. Y. Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea: a randomized placebo-controlled trial. *Clinical endocrinology* 2012, **77**: 599-607.
- 89) Zitzmann, M., Mattern, A., Hanisch, J., Gooren, L., Jones, H. *et al.* IPASS: a study on the tolerability and effectiveness of injectable testosterone undecanoate for the treatment of male hypogonadism in a worldwide sample of 1,438 men. *The journal of sexual medicine* 2013, **10**: 579-588.
- 90) Cabler, S., Agarwal, A., Flint, M. & du Plessis, S. S. Obesity: modern man's fertility nemesis. *Asian journal of andrology* 2010, **12**: 480-489.
- 91) Hammoud, A. O., Meikle, A. W., Reis, L. O., Gibson, M., Peterson, C. M. *et al.* Obesity and male infertility: a practical approach. *Seminars in reproductive medicine* 2012, **30**: 486-495.

- 92) Guay, A. T., Jacobson, J., Perez, J. B., Hodge, M. B. & Velasquez, E. Clomiphene increases free testosterone levels in men with both secondary hypogonadism and erectile dysfunction: who does and does not benefit? *International journal of impotence research* 2003, **15**: 156-165.
- 93) Burnett-Bowie, S. A., McKay, E. A., Lee, H. & Leder, B. Z. Effects of aromatase inhibition on bone mineral density and bone turnover in older men with low testosterone levels. *The Journal of clinical endocrinology and metabolism* 2009, **94**: 4785-4792.
- 94) Heufelder, A. E., Saad, F., Bunck, M. C. & Gooren, L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *Journal of andrology* 2009, **30**: 726-733.
- 95) Hammoud, A., Gibson, M., Hunt, S. C., Adams, T. D., Carrell, D. T. *et al.* Effect of Roux-en-Y gastric bypass surgery on the sex steroids and quality of life in obese men. *The Journal of clinical endocrinology and metabolism* 2009, **94**: 1329-1332.
- 96) Omana, J., Tamler, R., Strohmayer, E., Herron, D. & Kini, S. Sex hormone levels in men undergoing bariatric surgery. *Journal of the American College of Surgeons* 2009, **209**: S22–S23.
- 97) Pellitero, S., Olaizola, I., Alastrue, A., Martinez, E., Granada, M. L. *et al.* Hypogonadotropic hypogonadism in morbidly obese males is reversed after bariatric surgery. *Obesity surgery* 2012, **22**: 1835-1842.
- 98) Globerman, H., Shen-Orr, Z., Karnieli, E., Aloni, Y. & Charuzi, I. Inhibin B in men with severe obesity and after weight reduction following gastroplasty. *Endocrine research* 2005, **31**: 17-26.
- 99) Pritchard, J., Despres, J. P., Gagnon, J., Tchernof, A., Nadeau, A. *et al.* Plasma adrenal, gonadal, and conjugated steroids following long-term exercise-induced negative energy balance in identical twins. *Metabolism: clinical and experimental* 1999, **48**: 1120-1127.
- 100) Facchiano, E., Scaringi, S., Veltri, M., Samavat, J., Maggi, M. *et al.* Age as a Predictive Factor of Testosterone Improvement in Male Patients After Bariatric Surgery: Preliminary Results of a Monocentric Prospective Study. *Obesity surgery* 2013, **23**: 167-172.
- 101) Niskanen, L., Laaksonen, D. E., Punnonen, K., Mustajoki, P., Kaukua, J. *et al.* Changes in sex hormone-binding globulin and testosterone during weight loss and weight maintenance in abdominally obese men with the metabolic syndrome. *Diabetes, obesity & metabolism* 2004, **6**: 208-215.
- 102) Stanik, S., Dornfeld, L. P., Maxwell, M. H., Viosca, S. P. & Korenman, S. G. The effect of weight loss on reproductive hormones in obese men. *The Journal of clinical endocrinology and metabolism* 1981, **53**: 828-832.
- 103) Vermeulen, A., Kaufman, J. M. & Giagulli, V. A. Influence of some biological indexes on sex hormone-binding globulin and androgen levels in aging or obese males. *The Journal of clinical endocrinology and metabolism* 1996, **81**: 1821-1826.
- 104) Frederiksen, L., Hojlund, K., Hougaard, D. M., Mosbeck, T. H., Larsen, R. *et al.* Testosterone therapy decreases subcutaneous fat and adiponectin in aging men. *European journal of endocrinology / European Federation of Endocrine Societies* 2012, **166**: 469-476.
- 105) Jones, T. H., Arver, S., Behre, H. M., Buvat, J., Meuleman, E. *et al.* Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes care* 2011, **34**: 828-837.
- 106) Kenny, A. M., Kleppinger, A., Annis, K., Rathier, M., Browner, B. *et al.* Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. *Journal of the American Geriatrics Society* 2010, **58**: 1134-1143.
- 107) Srinivas-Shankar, U., Roberts, S. A., Connolly, M. J., O'Connell, M. D., Adams, J. E. *et al.* Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *The Journal of clinical endocrinology and metabolism* 2010, **95**: 639-650.
- 108) Kapoor, D., Clarke, S., Stanworth, R., Channer, K. S. & Jones, T. H. The effect of testosterone replacement therapy on adipocytokines and C-reactive protein in hypogonadal men with type 2 diabetes. *European journal of endocrinology / European Federation of Endocrine Societies* 2007, **156**: 595-602.

- 109) Kapoor, D., Goodwin, E., Channer, K. S. & Jones, T. H. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *European journal of endocrinology / European Federation of Endocrine Societies* 2006, **154**: 899-906.
- 110) Page, S. T., Herbst, K. L., Amory, J. K., Coviello, A. D., Anawalt, B. D. *et al.* Testosterone administration suppresses adiponectin levels in men. *Journal of andrology* 2005, **26**: 85-92.
- 111) Page, S. T., Amory, J. K., Bowman, F. D., Anawalt, B. D., Matsumoto, A. M. *et al.* Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *The Journal of clinical endocrinology and metabolism* 2005, **90**: 1502-1510.
- 112) Boyanov, M. A., Boneva, Z. & Christov, V. G. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *The aging male : the official journal of the International Society for the Study of the Aging Male* 2003, **6**: 1-7.
- 113) Steidle, C., Schwartz, S., Jacoby, K., Sebree, T., Smith, T. *et al.* AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *The Journal of clinical endocrinology and metabolism* 2003, **88**: 2673-2681.
- 114) Wittert, G. A., Chapman, I. M., Haren, M. T., Mackintosh, S., Coates, P. *et al.* Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. *The journals of gerontology. Series A, Biological sciences and medical sciences* 2003, **58**: 618-625.
- 115) Snyder, P. J., Peachey, H., Hannoush, P., Berlin, J. A., Loh, L. *et al.* Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *The Journal of clinical endocrinology and metabolism* 1999, **84**: 2647-2653.
- 116) Sih, R., Morley, J. E., Kaiser, F. E., Perry, H. M., 3rd, Patrick, P. *et al.* Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *The Journal of clinical endocrinology and metabolism* 1997, **82**: 1661-1667.
- 117) Marin, P., Holmang, S., Gustafsson, C., Jonsson, L., Kvist, H. *et al.* Androgen treatment of abdominally obese men. *Obesity research* 1993, **1**: 245-251.
- 118) Marin, P., Holmang, S., Jonsson, L., Sjostrom, L., Kvist, H. *et al.* The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 1992, **16**: 991-997.

## Figure Legends

Figure 1. Bidirectional relationship between obesity and low testosterone

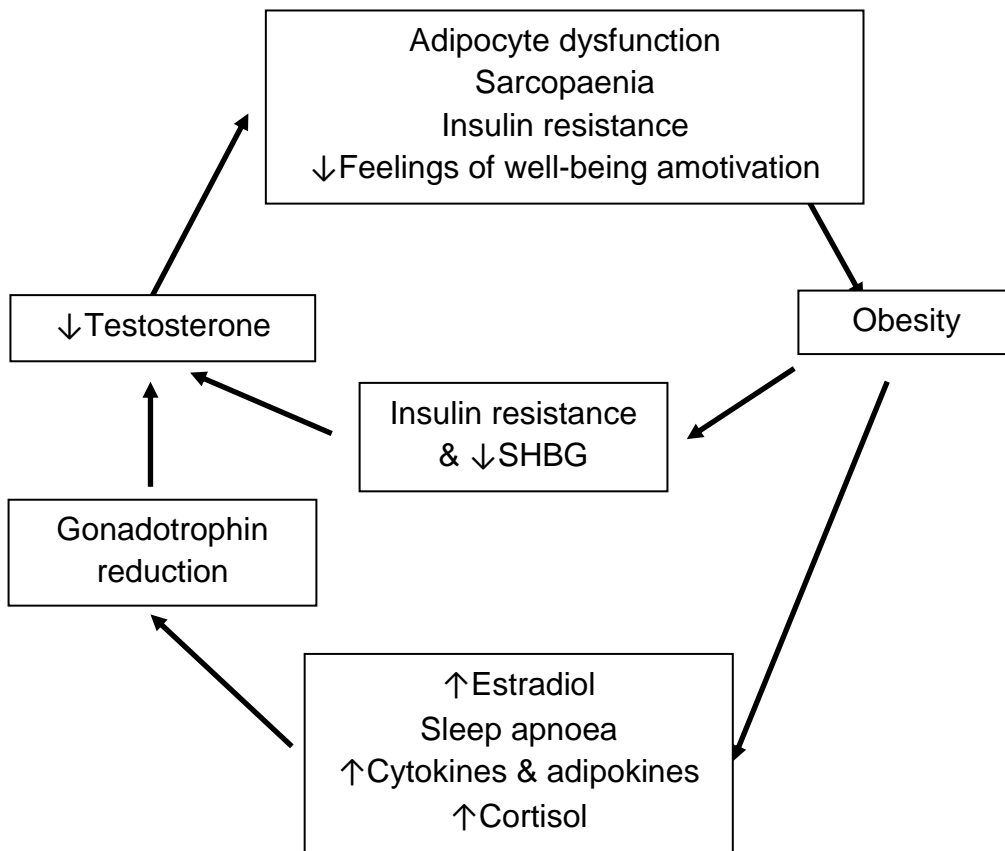




Figure 2. Effect of weight (or BMI) reduction on circulating total testosterone (T). Each circle represents a single longitudinal study. Size of the circle is proportional to study size. Adapted from Grossmann<sup>19</sup>

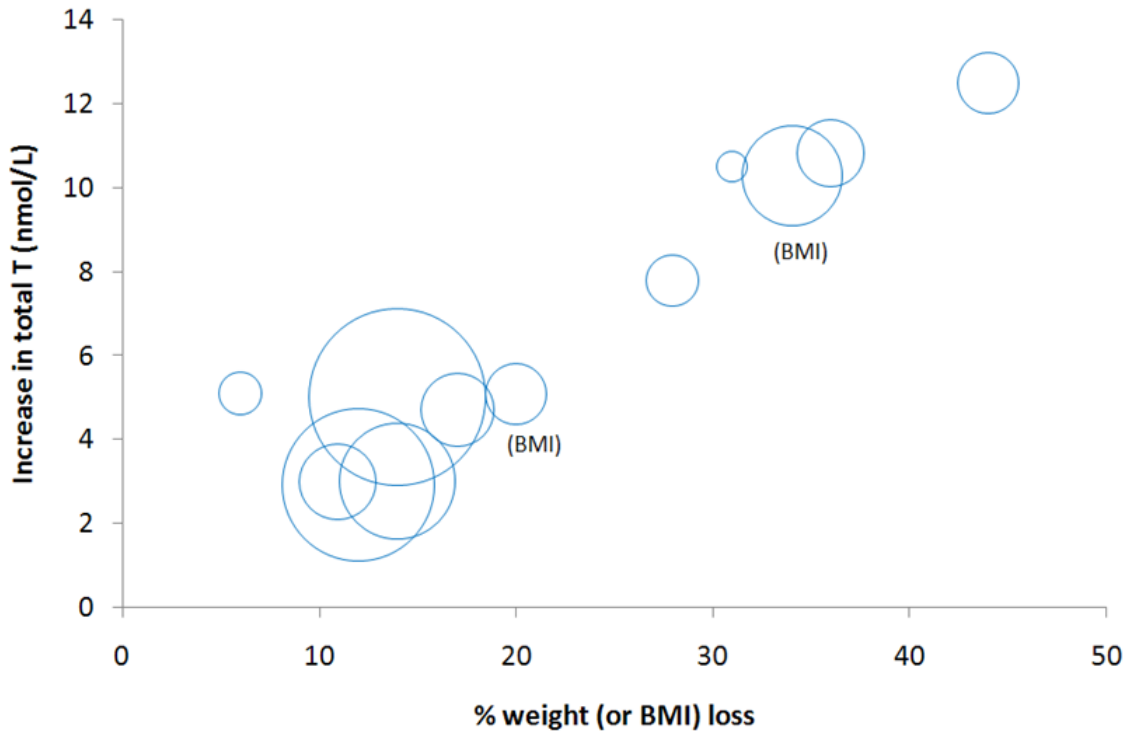


Table 1: World Health Organization estimates of overweight and obesity (BMI >25 kg/m<sup>2</sup>) in males aged 30-100 years in selected Asia-pacific countries<sup>1</sup>

	2002	2010
<b>China</b>	28.9%	45.3%
<b>India</b>	19.9%	26.5%
<b>Australia</b>	71.8%	77.4%
<b>Japan</b>	32.0%	37.7%
<b>Nauru</b>	95.4%	96.2%

Table 2: Effect of weight loss on testosterone: clinical trials

Study, year, design	N	Age (y)	BMI	Baseline T (nmol/L)	Therapy	Weeks	Weight loss	T increase (nmol/L)
Reis <sup>63</sup> 2010 RCT	20	37	56	11.8	Surgery vs. lifestyle	104	44%	12.5
Hammoud <sup>95</sup> 2009 Case-control	22	50	45	11.8	Surgery	104	36% of BMI	10.8
Omana <sup>96</sup> 2009 Cohort	10	48	48	10.6	Surgery	52	31%	10.5
Pellitero <sup>97</sup> 2012 Cohort	33	41	50	8.6	Surgery	52	37%	10.3
Globerman <sup>98</sup> 2005 Cohort	17	38	44	13.4	Surgery	52	28%	7.8
Pritchard <sup>99</sup> 1999 Cohort	14	21	26	12.3	Exercise	13	6%	5.1
Facchiano <sup>100</sup> 2013 Cohort	20	41	44	8.1	Surgery	26	20% of BMI	5.1
Niskanen <sup>101</sup> 2004 Cohort	58	46	36	12	VLCD	9	14%	5.0
Stanik <sup>102</sup> 1981 Cohort	24	30-63	ND	13.9	VLCD	8	17%	4.7
Kaukua <sup>62</sup> 2003 RCT	38	46	39	11.1	VLCD vs control	32	14%	3.0
Khoo <sup>65</sup> (non-DM) 2010 Case-control	25	44	36	28	VLCD	8	11%	3.0
Vermuelen <sup>103</sup> 1996 Case-control	50	25-62	41	14.6	PSMF	6	12%	2.9
Khoo <sup>65</sup> (DM) 2010 Case-control	19	58	35	10	VLCD	8	8%	1.2 n.s
Khoo <sup>64</sup> 2011 RCT	19	58	35	11.7	LCD	8	8%	3.1 n.s
	12	35	36	13.9	HP	8	4%	0.3 n.s
Leenen <sup>66</sup> 1994	37	40	31	12.7	LCD	13	14%	0.6 n.s

Cohort								
--------	--	--	--	--	--	--	--	--

N = number; BMI = body mass index, kg/m<sup>2</sup>; T = testosterone; HP = high protein; VLCD = very low calorie diet; PSMF = protein-sparing modified fast; RCT = randomised controlled trial; DM = diabetes mellitus; n.s = not significant

Table 3: Effect of testosterone therapy on body composition: randomised clinical trials

Study	N	Age (y)	BMI	Baseline T (nmol/L)	Rx	Weeks	Outcome
Frederikson <sup>104</sup> 2012	38	68	30	12.2	gel	26	↔ VAT ↓ SAT by 2%
Jones <sup>105</sup> 2011	220	60	32	9.4	gel	52	nr VAT nr SAT ↔ Total fat
Allan <sup>71</sup> 2010	40	53	34	11.4	im	52	↔ VAT ↓ SAT 9.4% ↓ Total fat by 10.3%
Aversa <sup>72</sup> 2010	50	58	30	8.3	im	52	nr VAT nr SAT ↓ Waist circ by 8.1%
Kalichenko <sup>73</sup> 2010	184	52	35	6.7	im	30	nr VAT nr SAT ↓ Waist circ by 5.1%
Kenny <sup>106</sup> 2010	131	78	27	13.2	gel	52	nr VAT nr SAT ↔ Total fat
Srinivas-Shankar <sup>107</sup> 2010	162	74	28	11.0	gel	26	nr VAT nr SAT ↓ Total fat by 4.2%
Allan <sup>76</sup> 2008	60	62	26	13.6	patch	52	↓ VAT by 8.0% ↔ SAT
Emmelet-Vonk <sup>78</sup> 2008	223	67	27	11.0	oral	26	↔ VAT ↔ SAT ↓ Total fat by 4.3%
Svartberg <sup>74</sup> 2008	35	69	31	8.4	im	52	↔ VAT ↓ SAT 22.2% ↓ Total fat by 16.2%
Kapoor <sup>108</sup> 2007	20	63	33	7.5	im	13	nr VAT nr SAT ↔ Total fat ↓ Waist circ by

							1.7%
Kapoor <sup>109</sup> 2006	24	64	33	8.63	im	13	nr VAT nr SAT ↔ Total fat ↓ WHR by 1.4%
Nair <sup>77</sup> 2006	58	66	28	12.4	patch	156	↔ VAT nr SAT ↔ Total fat
Page <sup>110</sup> 2005	25	73	30	14	im	3	nr VAT nr SAT ↓ BMI by 3.0%
Page <sup>111</sup> 2005	48	71	29	9.9	im	78	nr VAT nr SAT ↓ Total fat by 17.9%
Schroeder <sup>80</sup> 2004	32	72	28	12.8	oral	12	↔ VAT ↔ SAT
Boyanov <sup>112</sup> 2003	48	58	31	9.6	oral	13	nr VAT nr SAT ↓ Total fat by 5.6%
Steidle <sup>113</sup> 2003	20 5	57	30	8.1	gel	13	nr VAT nr SAT ↓ Total fat by 2.8%
Wittert <sup>114</sup> 2003	76	69	27	17.0	oral	52	nr VAT nr SAT ↓ Total fat 1.1%
Munzer <sup>79</sup> 2001	32	71	26	15.3	im	26	↔ VAT ↓ SAT by 9.4%
Snyder <sup>115</sup> 1999	10 8	>65	27	12.7	patch	156	nr VAT nr SAT ↓ Total fat by 12.3%
Sih <sup>116</sup> 1997	32	65	29	10.2	im	52	nr VAT nr SAT ↔ Total fat
Marin <sup>117</sup> 1993	31	57	29	15.1	gel	39	↓ VAT by 9% ↔ SAT
Marin <sup>118</sup> 1992	23	52	29	16.0	oral	35	↓ VAT by 5.5% ↔ SAT

N = number; BMI = body mass index, kg/m<sup>2</sup>; T = testosterone; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; Rx = treatment; im = intramuscular; nr = not reported