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INVITED REVIEW

Male Endocrinology

# Lowered testosterone in male obesity: mechanisms, morbidity and management

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**With increasing modernization and urbanization 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 recognizable 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 hypotestosteronemia 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 apnea and compromise fertility. Whether testosterone therapy augments diet- and exercise-induced weight loss requires evaluation in adequately designed randomized controlled clinical trials.**
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## 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$^{-2}$) and obesity (BMI ≥ 30 kg m$^{-2}$) in adult men by more than 25% in the last 8 years according to WHO estimates[1] (**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.[2] 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 apnea, osteoarthritis, increased risk of certain cancers, and in men, lowered testosterone levels.[3] 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$^{-2}$, hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.18–1.41), but not in grade 1 obesity (BMI 30–34.9 kg m$^{-2}$, HR 0.95, 95% CI 0.88–1.01) compared to their non-obese counterparts.[4] However, this meta-analysis has been subsequently criticized in a series of letters and commentaries.[5-7] For example, the adverse effect of obesity may have been underestimated because the lean comparison group (BMI 18–25 kg m$^{-2}$) 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.[8] 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.[9]

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,[10] is regulated by dihydrotestosterone,[11] 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

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**Table 1: World health organization estimates of overweight and obesity (BMI>25 kg m$^{-2}$) in males aged 30–100 years in selected Asia-Pacific countries**[1]

| | *2002 (%)* | *2010 (%)* |
|---|---|---|
| China | 28.9 | 45.3 |
| India | 19.9 | 26.5 |
| Australia | 71.8 | 77.4 |
| Japan | 32.0 | 37.7 |
| Nauru | 95.4 | 96.2 |

BMI: body mass index

disease burden.[12] 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.[13] While bariatric surgery achieves 10%–30% long-term weight loss in controlled studies,[12] this therapy is expensive and currently not widely available.

## OBESITY AND LOW TESTOSTERONE: EVIDENCE FROM POPULATION-BASED STUDIES

The fact that obese men have lower testosterone compared to lean men has been recognized for more than 30 years.[14] 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.[15] In a cohort of 3219 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$^{-1}$ and normal luteinizing hormone (LH)), relative to normal weight[3]. Both total testosterone (5.9 nmol l$^{-1}$) and free testosterone (54 pmol l$^{-1}$) levels were lower in obese compared to lean men, with lesser but still significant reduction in overweight men (total T 2.3 nmol l$^{-1}$, free T 18 pmol l$^{-1}$)[16]. A cross-sectional study of 314 Chinese men similarly found that older obese men (defined by BMI >28 kg m$^{-2}$ for these Asian men) had a 3 nmol l$^{-1}$ lower testosterone level compared to age-matched lean men.[17] 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;[18] another study found a 57% prevalence in diabetic men attending tertiary hospital outpatient clinics.[19] In a cross-sectional study of 1849 community-dwelling obese US American men 40% had low testosterone levels.[20] Reductions in testosterone levels correlate with the severity of obesity and men with a BMI >35–40 kg m$^{-2}$ have >50% reduction in total and free testosterone levels compared to lean men.[15]

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.[21] 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.[22]

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.[16] Conversely, there is increasing evidence that healthy ageing by itself is uncommonly associated with marked reductions in testosterone levels.[23] This may be because age-related testicular dysfunction is, at least in part, compensated for by an age-associated increase in pituitary LH secretion.[3] However, because obesity blunts this LH rise, obesity leads to hypothalamic-pituitary suppression irrespective of age which cannot be compensated for by physiological mechanisms.[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 hyperinsulinemia. 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.[24] 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.[25]

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 ($E_2$). Adipose $E_2$ in turn may feedback negatively to decrease pituitary gonadotropin secretion; although, partly due to assay limitations, confirmation of increased circulatory $E_2$ concentrations is often elusive. In addition, local, tissue-specific increases of $E_2$ 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[26] do not necessarily support the pathophysiological importance of this $E_2$-mediated hypothalamic-pituitary-testicular (HPT) axis suppression, because gonadotropins and testosterone levels also rise with this treatment. Interestingly, more recent studies suggest that, diabetic obesity is associated with decreases in circulatory $E_2$.[27] Moreover, there is evidence from the EMAS that even in nondiabetic obese men, $E_2$ is low and correlated with low testosterone levels.[28,29] In addition to $E_2$, 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.[30]

### *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.[31] Similar findings have been reported in cohort studies of men from Europe[3,32] and Australia.[33] 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.[19,34]

### *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) (AR knockout (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.[35] 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.[36] In support of this, transgenic mice with AR overexpression show reduction in adipose tissue volume[37] 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.[38] 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.[39] In human male *ex vivo* adipose tissue, testosterone decreased adipocyte differentiation by 50%.[40] Testosterone enhances catecholamine-induced lipolysis *in vitro* and reduces lipoprotein lipase activity and triglyceride uptake in human abdominal adipose tissue *in vivo*.[19] Moreover, in men with prostate cancer receiving 12 months of androgen deprivation therapy, fat mass increased by 3.4 kg and abdominal VAT by 22%, with the majority of these changes established within 6 months.[41] Experimental induction of hypogonadism in healthy young men with gonadotropin-releasing hormone analogue treatment increased fat mass within 10 weeks, suggesting that severe sex steroid deficiency can increase fat mass rapidly.[42]

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 7.5 years of follow-up.[43] 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 bidirectional relationship between testosterone and obesity (**Figure 1**) in men initiating a self-perpetuating cycle, which may have treatment implications (see sections "TREATMENT OF OBESITY LEADING TO INCREASED TESTOSTERONE" and "INTERVENTION STUDIES LINKING EXOGENOUS TESTOSTERONE TO REDUCTION IN BODY FAT MASS" below). On the one hand, increasing body fat suppresses the HPT axis by multiple mechanisms[30] via increased secretion of pro-inflammatory cytokines, insulin resistance and diabetes;[19,44] while on the other hand low testosterone promotes further accumulation of total and visceral fat mass, thereby exacerbating the gonadotropin inhibition. Finally there is evidence, reviewed elsewhere,[45] that obesity-associated comorbidities including obstructive sleep apnea 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.*[46] 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 3α/β-ketosteroid reductase (3α/β-HSD) in obese versus

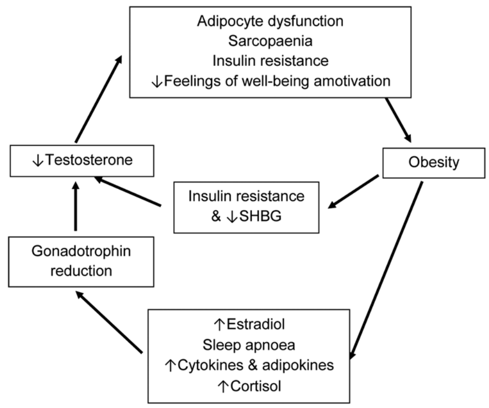


**Figure 1:** Bidirectional relationship between obesity and low testosterone.

non-obese male omental fat biopsies coupled with rat studies showing increased expression of AR in VAT as opposed to SAT[47] 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.[41] However, RCT studies of testosterone replacement have largely failed to show benefit of selective VAT reduction following testosterone treatment (see section "INTERVENTION STUDIES LINKING EXOGENOUS TESTOSTERONE TO REDUCTION IN BODY FAT MASS" 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[48] and its overexpression led to reduced weight and improved glucose homeostasis.[49] 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 PPARγ-pathway[37] which is implicated in the differentiation of precursor fat cells to the energy-consuming phenotype.[50]

## LOW TESTOSTERONE AND OBESITY BEYOND TESTOSTERONE-FAT INTERACTIONS

Because of its association with sarcopenia,[51] 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'.[52] 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.[53,54] Sarcopenic obesity, a phenotype recapitulated in men receiving ADT for prostate cancer,[55] 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.[56]

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.[52,54] Although this accelerated loss of muscle mass can be attenuated by exercise,[57] 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.[58]

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 wildtype mice,[59] while another animal study reported a positive association between testosterone intake and amount of time spent on a running wheel.[60] 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.[61]

## 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.[34] Minor weight loss (<15%) over 4.4 years was associated with modest increases (+2 nmol $l^{-1}$) 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 $l^{-1}$) of total testosterone, but was also associated with significant increase in free testosterone (+51.78 pmol $l^{-1}$), likely because of HPT activation, evidenced by a significant rise in LH (+2 U $l^{-1}$). 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 losses are associated with increased testosterone, with the rise in testosterone generally proportional to the amount of weight lost (**Figure 2**). **Table 2** lists 15 published trials that have assessed the effects of weight loss interventions on testosterone.[62–75] The majority of the trials was 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 (2.9–5.1 nmol $l^{-1}$). In comparison to lifestyle, surgical intervention resulted in loss of weight of 28%–44% and increase of testosterone from 7.8 to 12.5 nmol $l^{-1}$. 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 $l^{-1}$ increase in testosterone.[71] 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.[62] 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%)[72,74] or modest baseline obesity in one study (BMI 31 kg $m^{-2}$).[75]

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% *vs* 32% for surgical intervention.[76] Overall, diet therapy led to an increase in total testosterone of 2.87 *vs* 8.73 nmol $l^{-1}$ 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

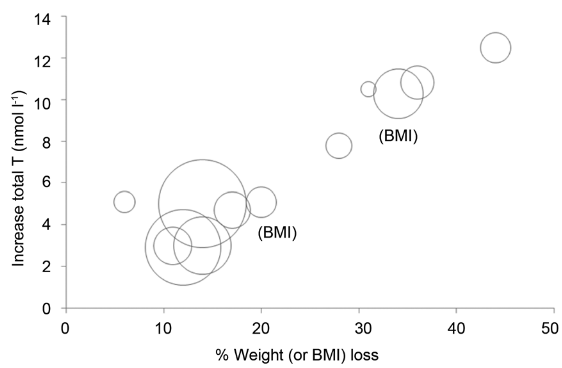


**Figure 2:** Effect of weight (or body mass index (BMI)) reduction on circulating total testosterone. Each circle represents a single longitudinal study. Size of the circle is proportional to study size. Adapted from Grossmann.[19]

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

| *Study, year, design* | *N* | *Age (years)* | *BMI* | *Baseline T (nmol l⁻¹)* | *Therapy* | *Weeks* | *Weight loss (%)* | *T increase (nmol l⁻¹)* |
|---|---|---|---|---|---|---|---|---|
| Reis *et al.*[62] 2010, RCT | 20 | 37 | 56 | 11.8 | Surgery *vs* lifestyle | 104 | 44 | 12.5 |
| Hammoud *et al.*[63] 2009, case-control | 22 | 50 | 45 | 11.8 | Surgery | 104 | 36 of BMI | 10.8 |
| Omana *et al.*[64] 2009, cohort | 10 | 48 | 48 | 10.6 | Surgery | 52 | 31 | 10.5 |
| Pellitero *et al.*[65] 2012, cohort | 33 | 41 | 50 | 8.6 | Surgery | 52 | 37 | 10.3 |
| Globerman *et al.*[66] 2005, cohort | 17 | 38 | 44 | 13.4 | Surgery | 52 | 28 | 7.8 |
| Pritchard *et al.*[67] 1999, cohort | 14 | 21 | 26 | 12.3 | Exercise | 13 | 6 | 5.1 |
| Facchiano *et al.*[68] 2013, cohort | 20 | 41 | 44 | 8.1 | Surgery | 26 | 20 of BMI | 5.1 |
| Niskanen *et al.*[69] 2004, cohort | 58 | 46 | 36 | 12 | VLCD | 9 | 14 | 5.0 |
| Stanik *et al.*[70] 1981, cohort | 24 | 30-63 | ND | 13.9 | VLCD | 8 | 17 | 4.7 |
| Kaukua *et al.*[71] 2003, RCT | 38 | 46 | 39 | 11.1 | VLCD *vs* control | 32 | 14 | 3.0 |
| Khoo *et al.*[72] (non-DM) 2010, case-control | 25 | 44 | 36 | 28 | VLCD | 8 | 11 | 3.0 |
| Vermeulen *et al.*[73] 1996, case-control | 50 | 25-62 | 41 | 14.6 | PSMF | 6 | 12 | 2.9 |
| Khoo *et al.*[72] (DM) 2010, case-control | 19 | 58 | 35 | 10 | VLCD | 8 | 8 | 1.2, n.s. |
| Khoo *et al.*[74] 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 *et al.*[75] 1994, cohort | 37 | 40 | 31 | 12.7 | LCD | 13 | 14 | 0.6, n.s. |

BMI: body mass index, (kg $m^{-2}$); DM: diabetes mellitus; HP: high protein; N: number; n.s.: not significant; PSMF: protein-sparing modified fast; RCT: randomized controlled trial; T: testosterone; VLCD: very low calorie diet; ND: not disclosed change in testosterone. This suggests that men, regardless of obesity level, can benefit from the effect of weight loss.

## 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%.[77,78] In a meta-analysis of RCTs of older men without confirmed hypogonadism (mean baseline serum testosterone 10.9 nmol l$^{-1}$, BMI 29 kg m$^{-2}$), 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).[79] 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 6 kg.[80–83] 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.[84]

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**).[85–104] RCTs assessing effects of testosterone therapy on VAT have shown inconsistent results with one showing a reduction[89] and others no change.[80,90,93] These inconsistencies may be due to small trial size,[96,100] use of oral testosterone therapy (which did not raise serum testosterone levels),[90] or imprecise methodology to quantify VAT such as dual energy X-ray absorptiometry[93] or ultrasound.[90] 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.[19] Effects of testosterone therapy on glucose metabolism are discussed in more detail by Allan elsewhere in this issue.

## CLINICAL CONSEQUENCES OF LOW TESTOSTERONE IN OBESE MEN AND APPROACH TO THERAPY

While many obese men have low testosterone levels and nonspecific 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$^{-1}$), less than half of men ($n = 70$) reported symptoms consistent with androgen deficiency and these men had higher BMIs than asymptomatic men.[105] A cross-sectional study of older overweight men found that loss of libido occurred at a testosterone level <15 nmol l$^{-1}$, poor concentration at <10 nmol l$^{-1}$ and erectile dysfunction at <8 nmol l$^{-1}$. However, these thresholds confer neither sensitivity nor specificity for these symptoms, and a high specificity (> 90%) was achieved only when testosterone levels declined to <3.7–6.3 nmol l$^{-1}$.[106] 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$^{-1}$, increased insulin resistance and the metabolic syndrome could only be demonstrated in men with testosterone <8 nmoll$^{-1}$.[29] Low testosterone either directly or via its metabolite $E_2$ is a risk factor for osteoporotic fractures.[107] While this may be counterbalanced by the protective effects of obesity on the skeleton,[108] recent evidence suggests that increased VAT may have adverse consequences for skeletal health.[56]

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 nonspecific 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[24] including assessment for end-organ deficits and pituitary pressure symptoms in all men. Mild, otherwise unexplained anemia,[109] 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 <5.2 nmol l$^{-1}$ and non-raised gonadotropins.[24]

The presence of both obesity and low testosterone and can have negative impacts on fertility, sleep apnea, 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 apnea and adverse cardiovascular disease and prostate events,[110-113] 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 contraindicated in obese men seeking to have children who are already at increased risk of impaired fertility.[114] Other approaches using aromatase inhibitors, selective estrogen receptor modulators and gonadotropins may be considered instead. Studies, reviewed elsewhere have shown that use of such agents can improve the endocrine hormonal profile (increased gonadotropins and testosterone), semen parameters and sexual function.[115] 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.[116] However, their effects on fertility are not proven.[115] In addition, because of the associated lowering of circulating $E_2$ levels, long-term use of such agents may lead to reduced bone mineral density.[117]

## SUMMARY AND CONCLUSIONS

The bidirectional, 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

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

| *Study* | *N* | *Age (years)* | *BMI* | *Baseline T (nmol l−1)* | *Rx* | *Weeks* | *Outcome* |
|---|---|---|---|---|---|---|---|
| Frederiksen *et al.*[85] 2012 | 38 | 68 | 30 | 12.2 | Gel | 26 | ↔ VAT<br>↓ SAT by 2% |
| Jones *et al.*[86] 2011 | 220 | 60 | 32 | 9.4 | Gel | 52 | n.r. VAT, n.r. SAT<br>↔ Total fat |
| Allan *et al.*[80] 2010 | 40 | 53 | 34 | 11.4 | i.m. | 52 | ↔ VAT<br>↓ SAT 9.4%<br>↓ Total fat by 10.3% |
| Aversa *et al.*[81] 2010 | 50 | 58 | 30 | 8.3 | i.m. | 52 | n.r. VAT, n.r. SAT<br>↓ Waist circ by 8.1% |
| Kalinchenko *et al.*[82] 2010 | 184 | 52 | 35 | 6.7 | i.m. | 30 | n.r. VAT, n.r. SAT<br>↓ Waist circ by 5.1% |
| Kenny *et al.*[87] 2010 | 131 | 78 | 27 | 13.2 | Gel | 52 | n.r. VAT, n.r. SAT<br>↔ Total fat |
| Srinivas-Shankar *et al.*[88] 2010 | 162 | 74 | 28 | 11.0 | Gel | 26 | n.r. VAT, n.r. SAT<br>↓ Total fat by 4.2% |
| Allan *et al.*[89] 2008 | 60 | 62 | 26 | 13.6 | Patch | 52 | ↓ VAT by 8.0%<br>↔ SAT |
| Emmelot-Vonk *et al.*[90] 2008 | 223 | 67 | 27 | 11.0 | Oral | 26 | ↔ VAT<br>↔ SAT<br>↓ Total fat by 4.3% |
| Svartberg *et al.*[83] 2008 | 35 | 69 | 31 | 8.4 | i.m. | 52 | ↔ VAT<br>↓ SAT 22.2%<br>↓ Total fat by 16.2% |
| Kapoor *et al.*[91] 2007 | 20 | 63 | 33 | 7.5 | i.m. | 13 | n.r. VAT, n.r. SAT<br>↔ Total fat<br>↓ Waist circ by 1.7% |
| Kapoor *et al.*[92] 2006 | 24 | 64 | 33 | 8.63 | i.m. | 13 | n.r. VAT, n.r. SAT<br>↔ Total fat<br>↓ WHR by 1.4% |
| Nair *et al.*[93] 2006 | 58 | 66 | 28 | 12.4 | Patch | 156 | ↔ VAT<br>n.r. SAT<br>↔ Total fat |
| Page *et al.*[94] 2005 | 25 | 73 | 30 | 14 | i.m. | 3 | n.r. VAT<br>n.r. SAT<br>↓ BMI by 3.0% |
| Page *et al.*[95] 2005 | 48 | 71 | 29 | 9.9 | i.m. | 78 | n.r. VAT, n.r. SAT<br>↓ Total fat by 17.9% |
| Schroeder *et al.*[96] 2004 | 32 | 72 | 28 | 12.8 | Oral | 12 | ↔ VAT<br>↔ SAT |
| Boyanov *et al.*[97] 2003 | 48 | 58 | 31 | 9.6 | Oral | 13 | n.r. VAT, n.r. SAT<br>↓ Total fat by 5.6% |
| Steidle *et al.*[98] 2003 | 205 | 57 | 30 | 8.1 | Gel | 13 | n.r. VAT, n.r. SAT<br>↓ Total fat by 2.8% |
| Wittert *et al.*[99] 2003 | 76 | 69 | 27 | 17.0 | Oral | 52 | n.r. VAT, n.r. SAT<br>↓ Total fat 1.1% |
| Munzer *et al.*[100] 2001 | 32 | 71 | 26 | 15.3 | i.m. | 26 | ↔ VAT<br>↓ SAT by 9.4% |
| Snyder *et al.*[101] 1999 | 108 | >65 | 27 | 12.7 | Patch | 156 | n.r. VAT, n.r. SAT<br>↓ Total fat by 12.3% |
| Sih *et al.*[102] 1997 | 32 | 65 | 29 | 10.2 | i.m. | 52 | n.r. VAT, n.r. SAT<br>↔ Total fat |
| Marin *et al.*[103] 1993 | 31 | 57 | 29 | 15.1 | Gel | 39 | ↓ VAT by 9%<br>↔ SAT |
| Marin *et al.*[104] 1992 | 23 | 52 | 29 | 16.0 | Oral | 35 | ↓ VAT by 5.5%<br>↔ SAT |

BMI: body mass index. kg m−2; i.m.: intramuscular; N: number; n.r.: not reported; Rx: treatment; SAT: subcutaneous adipose tissue; T: testosterone; VAT: visceral adipose tissue

lifestyle;[118] a recent, preliminary RCT failed to find additive effects of dietary restriction and testosterone therapy on weight loss.[112] Given the increasing prevalence of obesity-associated hypotestosteronemia, 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.

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## COMPETING INTERESTS

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