

Testosterone and glucose metabolism in men: current concepts and controversies

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Abstract

A wealth of observational studies show that low testosterone is associated with insulin resistance and with an increased risk of diabetes and the metabolic syndrome. Experimental studies have identified potential mechanisms by which low testosterone may lead to insulin resistance. Visceral adipose tissue is an important intermediate in this relationship. Actions of testosterone or its metabolite oestradiol on other tissues such as muscle, liver, bone or the brain, and body composition-independent effects may also play a role. However, definitive evidence from randomised controlled trials (RCTs) to clarify whether the association of low testosterone with disordered glucose metabolism is causative is currently lacking. It therefore remains possible that this association is due to reverse causation, or simply originates by association with common health and lifestyle factors. RCTs of testosterone therapy in men with or without diabetes consistently show modest metabolically favourable changes in body composition. Despite this, testosterone effects on glucose metabolism have been inconsistent. Recent evidence suggests that the hypothalamic–pituitary–testicular axis suppression in the majority of obese men with metabolic disorders is functional, and may be, at least in part, reversible with weight loss. Until further evidence is available, lifestyle measures with emphasis on weight reduction, treatment of comorbidities and optimisation of diabetic control should remain the first-line treatment in these men. Such measures, if successful, may be sufficient to normalise testosterone levels in men with metabolic disorders, who typically have only modest reductions in circulating testosterone levels.

Key Words

- ▶ testosterone
- ▶ diabetes
- ▶ glucose metabolism
- ▶ insulin resistance
- ▶ obesity

Journal of Endocrinology
(2014) 220, R37–R55

Introduction: significance of the clinical problem

Around 50% of ageing, obese men presenting to the diabetes clinic have lowered testosterone levels relative to reference ranges based on healthy young men (Grossmann 2011). Many have symptoms consistent with androgen deficiency, but such symptoms are non-specific and overlap with comorbidities. Therefore, the clinician is commonly faced with the question as to whether

testosterone therapy should be considered. There is vigorous debate about this issue. Only a small proportion of these men will have classical hypogonadism due to recognisable hypothalamic–pituitary–testicular (HPT) axis pathology, an important diagnosis not to be missed. In contrast, the risk-benefit ratio of testosterone therapy for the large proportion of men with metabolic disorders,

defined here as type 2 diabetes and or the metabolic syndrome, but without clear-cut classical hypogonadism, is not known. This is because we have insufficient evidence to conclusively answer three key questions: first, is low testosterone a causal factor or a biomarker for metabolic disorders and associated clinical features? Second, even if low testosterone is pathogenic, we do not know whether testosterone treatment meaningfully improves patient-important health outcomes. Third, even if testosterone treatment improves outcomes, we do not know whether we should use this treatment, because this depends on additional factors, such as long-term risks, cost and inconvenience of treatment, and comparisons to established therapies. The absence of high-level evidence in this area is illustrated by the Endocrine Society testosterone therapy in men with androgen deficiency clinical practice guidelines (Bhasin *et al.* 2010), which are appropriate for, but not specific to men with metabolic disorders. All 32 recommendations made in these guidelines are based on either very low or low quality evidence. Compared to other Endocrine Society guidelines, they have the third-lowest evidence backing: only the guidelines on hirsutism and on androgen therapy in women have less (Hazlehurst *et al.* 2013). Appropriately therefore, the Endocrine Society

concludes that ‘the information about the benefits and risks of testosterone therapy in men with type 2 diabetes is either limited or not available’ (Bhasin *et al.* 2010). Similarly, the International Society of Andrology states that it is ‘premature to recommend testosterone therapy for the metabolic syndrome or diabetes’ (Wang *et al.* 2009).

A key concept relates to making a distinction between replacement and pharmacological testosterone therapy, although indications may overlap (Fig. 1; McLachlan 2010, Grossmann 2011, Spitzer *et al.* 2013). On the one hand, in organic androgen deficiency due to intrinsic damage of the gonadal axis, pathological androgen deficiency is treated by normalising circulating testosterone levels. Here, the risk-benefit ratio of treatment is expected to be favourable based on open label studies and almost 70 years of clinical experience. On the other hand, in functional androgen deficiency due to axis suppression because of age-related comorbidities, treatment may aim for a specific health outcome, such as improvement of glucose metabolism, and symptomatic response is a less certain benefit. In this setting, randomised control trial evidence for efficacy and safety is required (Fig. 1). However, it should be noted that, in certain scenarios such as opioid-induced hypogonadism where narcotic analgesia cannot be stopped, functional

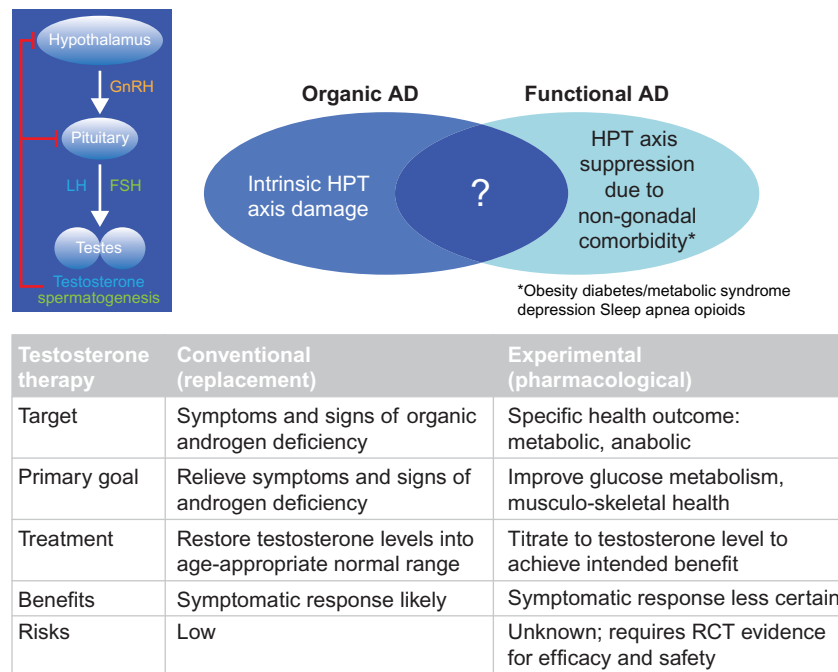


Figure 1

Organic vs functional androgen deficiency. A conceptual framework to distinguish approach to organic and functional androgen deficiency. Both conditions may overlap. It should be noted that even functional androgen deficiency may be associated with profound hypogonadism that requires

testosterone replacement therapy. One example is patients with painful diabetic neuropathy requiring narcotic analgesia. If opioids cannot be stopped, hypogonadism may respond well to testosterone replacement. HPT, hypothalamic–pituitary–testicular; AD, androgen deficiency.

androgen deficiency may require, and respond well to, testosterone replacement.

In this review, I will discuss current concepts and controversies in the relationship between testosterone and metabolic status. I will highlight challenges in the assessment and management of androgen deficiency in men with metabolic disorders, and review observational, mechanistic and therapy studies of testosterone in men with type 2 diabetes and the metabolic syndrome. The material discussed is based on peer-reviewed journals indexes identified by searching the PubMed database from 1970 to September 2013, using the terms 'diabetes', 'metabolic syndrome', 'testosterone', 'androgen', 'insulin resistance and males'. Given several recent reviews in this area (Dandona & Dhindsa 2011, Grossmann 2011, Allan 2013, Rao *et al.* 2013), particular emphasis is given to more recent studies. Articles published before 2012 are highlighted only if they provide essential background data for the more recent studies.

Androgen deficiency in men with metabolic disorders

According to the Endocrine Society, androgen deficiency is a clinical syndrome, diagnosed by the presence of both 'consistent symptoms and signs and unequivocally low serum testosterone levels' (Bhasin *et al.* 2010). Hypogonadism refers to intrinsic pathology of the HPT axis and includes both androgen deficiency and spermatogenic failure. Hypotestosteronaemia denotes biochemical hypoandrogenism, defined as lowered circulating testosterone levels according to an arbitrary cut-off, without reference to symptoms and signs. Although the diagnosis of androgen deficiency is relatively straightforward to make in otherwise healthy younger men, it is more difficult in ageing men with comorbidities.

Symptoms of androgen deficiency

Symptoms of androgen deficiency are non-specific. In ageing obese men with metabolic disorders, they are confounded by comorbidities. Therefore, the presence of symptoms is less specific for the diagnosis of androgen deficiency, compared with otherwise healthy young men with organic androgen deficiency, in whom such confounders are absent. In the European Male Ageing Study (EMAS) of community dwelling men, androgen deficiency was diagnosed according to strict criteria. Despite this, the prevalence of even the most specific sexual symptoms was relatively high in men with normal testosterone levels (Wu *et al.* 2010). In a cross-sectional study of 350 ageing

men with diabetes, 55–70% of men with a clearly low testosterone had symptoms compatible with androgen deficiency. However, even 50–55% of men with clearly normal testosterone also had such symptoms. The presence of symptoms was more closely linked to increasing age than to testosterone levels (Kapoor *et al.* 2007). Similarly, in a more recent study, the inverse association of testosterone levels with symptoms of whether androgen deficiency, erectile dysfunction or quality of life has been found to be weak. The association was not significant if adjusted for age, which again was the best predictor (Biswas *et al.* 2012).

Testosterone levels

In cohort studies from the Framingham Heart study, EMAS, Osteoporotic Fractures in Men study (Bhasin *et al.* 2011b) and the Western Australian Health in Men study (Yeap *et al.* 2012a), men with diabetes were consistently about twice as likely to have lower testosterone levels (determined by liquid chromatography/mass spectrometry (LCMS/MS)) compared with men without diabetes. Cross-sectional studies uniformly show that 30–50% of men with type 2 diabetes have lowered circulating testosterone levels, relative to references based on healthy young men (Dhindsa *et al.* 2004, Kapoor *et al.* 2007, Grossmann *et al.* 2008). However, the extent of hypotestosteronaemia is modest: in meta-analyses of case-control studies, mean unadjusted pooled differences in total testosterone relative to men without diabetes ranged from -2.66 nmol/l (95% CI -3.45 to -1.86) (Ding *et al.* 2006) to -2.99 nmol/l (95% CI -3.59 to -2.40) (Corona *et al.* 2010). This association of low testosterone with type 2 diabetes persists even if adjusted for multiple confounders including age and obesity. However, the adjusted difference between men with and without diabetes becomes less: -1.61 nmol/l (95% CI -2.56 to -0.65) (Ding *et al.* 2006). In a more recent cross-sectional study of 1849 obese men, the presence of diabetes was associated with a significant ($P < 0.05$) but marginal reductions in total testosterone (-0.8 nmol/l) and free testosterone (-13 pmol/l) levels (Dhindsa *et al.* 2010). Indeed, low testosterone is more predictive of the metabolic syndrome in lean men. This suggests that obesity is a dominant risk factor that can override the contribution of the lowered androgen status (Kupelian *et al.* 2006).

Findings similar to type 2 diabetes were reported for men with the metabolic syndrome, which were associated with reductions in total testosterone of -2.2 nmol/l (95% CI -2.41 to 1.94) and in free testosterone of -0.26 pmol/l

(95% CI 0.39 to 0.13) (Corona *et al.* 2011). Thus, both diabetes and the metabolic syndrome are associated with a modest reduction in testosterone, in magnitude comparable with the effect of 10 years of ageing. More marked reductions in testosterone levels are relatively uncommon even in men with diabetes: in a cross-sectional study of 580 men presenting to a tertiary diabetes referral centre, 19% had a total testosterone of <8.0 nmol/l and 5% of <5.0 nmol/l (Grossmann *et al.* 2008). Therefore, marked reductions in circulating testosterone require a thorough clinical evaluation. They should not be dismissed to be a non-specific consequence of diabetes.

As in the general male population, the prevalence of hypotestosteronaemia in men with metabolic disorders increases with age and obesity (Grossmann *et al.* 2008). In a recent cross-sectional study of 240 middle-aged men (mean age 54 years) with either type 2 diabetes, type 1 diabetes or without diabetes (Ng Tang Fui *et al.* 2013b), increasing BMI and age were dominant drivers of low total and free testosterone respectively. This was independent of the presence or absence of diabetes. Prevalence of hypotestosteronaemia (total testosterone <8 nmol/l) in these middle-aged men was low, occurring in 0, 6.2 and 2.5% of men with type 1, type 2 and without diabetes respectively (Ng Tang Fui *et al.* 2013b).

End organ deficits of androgen deficiency

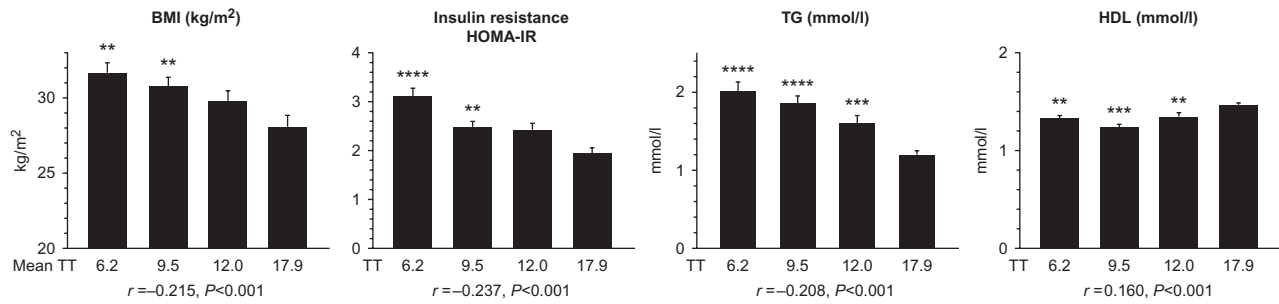
The diagnosis of androgen deficiency in ageing men with comorbidities is difficult. Therefore, there has been increasing interest in identifying objective evidence of androgen deficiency. This has been attempted either by using biomarkers of androgen action or by documenting deficits in androgen-responsive organs. In a cross-sectional survey of 2966 men participating in the EMAS cohort which included 8% of men with type 2 diabetes, the prevalence of late onset hypogonadism (LOH) diagnosed by the presence of three sexual symptoms and a total testosterone of <11 nmol/l or a free testosterone <230 pmol/l was 2.1% (Wu *et al.* 2010). Men with LOH had significantly lower bone density, haemoglobin and lean body mass compared with men who did not meet the diagnostic criteria for LOH (Tajar *et al.* 2012). More recently, prostate-specific antigen (PSA) has been proposed as a tissue marker of testosterone deficiency: in a large cohort of >3000 men, a PSA of <0.65 µg/l predicted a total testosterone of <8 nmol/l with modest sensitivity (65%) and specificity (56%). A low PSA was associated with delayed puberty, lower testicular volume and interestingly, with the presence of the metabolic syndrome

(hazard ratio 1.5 (1.2–1.8), $P<0.001$) and type 2 diabetes (hazard ratio 2.0 (1.7–2.5), $P<0.001$) (Rastrelli *et al.* 2013). In a cohort of 138 men with type 2 diabetes, free testosterone levels were inversely associated with bone density at some but not all sites (Dhindsa *et al.* 2007). In a cross-sectional study of 490 men with type 2 diabetes, there was a strong independent association of low testosterone with anaemia (Grossmann *et al.* 2009). Collectively, these reports suggest that low testosterone is not merely a marker of insulin resistance or obesity, but may be associated with biological consequences of androgen deficiency at the tissue level. However, their cross-sectional design limits inferences about causality. In addition, the aetiology of sarcopaenia, low bone mass and anaemia is multifactorial. It is therefore not known whether such deficits in androgen-dependent organs are causally related to hypotestosteronaemia. Alternatively, a high burden of comorbidities may be responsible for both the lowered testosterone level and these somatic deficits.

In summary, the diagnosis of androgen deficiency in men with metabolic disorders remains challenging. This is due to high prevalence of non-specific symptoms and of modest reductions in testosterone. This may, at least in part, be a non-specific consequence of chronic disease. Stringent diagnostic criteria (Wu *et al.* 2010) or organic markers of androgen deficiency may be helpful to limit over-diagnosis of androgen deficiency in such men. Still, better biomarkers are desirable. Unfortunately, no gold standard for the diagnosis exists. Importantly, such diagnostic criteria do not inform about the risk-benefit ratio of testosterone therapy. Rather they should be helpful in selecting men suited to participate in randomised controlled trials (RCTs) of testosterone therapy.

Low testosterone in men with metabolic disorders: cause or consequence?

In men, low testosterone is a marker of poor health, and may improve our ability to predict risk. For example, in a recent prospective cohort study of men presenting for liver transplantation, low testosterone predicted mortality independently of the model of end-stage liver disease score, the standard score used to prioritise the allocation of liver transplants (Grossmann *et al.* 2012). It is evident from multiple studies that low testosterone identifies men with an adverse metabolic phenotype (Grossmann *et al.* 2010). Diabetic men with low testosterone are significantly more likely to be obese or insulin resistant. Even if aggressively managed to evidence-based targets, they are still more likely to have an adverse lipid profile (Fig. 2). They also

**Figure 2**

Low testosterone is associated with an adverse metabolic phenotype. Data were analysed using simple (Pearson) calculation and multiple regression. HOMA-IR, homeostasis model assessment of insulin resistance; Tg, triglycerides (data from Grossmann *et al.* 2008).

have increased inflammation, evidenced by higher CRP levels (Grossmann *et al.* 2008). Low total testosterone has recently been associated with increased mortality in an observational study of men with diabetes (Muraleedharan *et al.* 2013). Significance, however, was lost when age and sex hormone-binding globulin (SHBG) were taken into account. Bioavailable but not free testosterone was independently predictive of mortality (Muraleedharan *et al.* 2013). These findings may suggest that the increased mortality is driven by imperfect adjustment of confounders. This is consistent with a recent meta-analysis which attributed the increased mortality in men with lowered testosterone to differences in underlying health status between cohorts (Araujo *et al.* 2011). Ultimately, observational studies cannot answer the question to what extent low testosterone causally contributes to alterations in glucose metabolism. It remains possible that low testosterone is a consequence of insulin resistance, or simply a biomarker, co-existing because of in-common risk factors.

In prospective studies, reviewed in detail elsewhere (Grossmann *et al.* 2010) the inverse association of low testosterone with metabolic syndrome or diabetes is less consistent for free testosterone compared with total testosterone. This is because of the confounding effects of SHBG, itself being a strong associate of insulin resistance (Wallace *et al.* 2013). In a study from the Framingham cohort, SHBG but not testosterone was prospectively and independently associated with incident metabolic syndrome (Bhasin *et al.* 2011a). Mendelian randomisation studies, which are less likely to be confounded than traditional observational studies, have associated low SHBG (Ding *et al.* 2009) but not testosterone (Haring *et al.* 2013) with an increased risk of future diabetes. In cross-sectional studies of men with (Grossmann *et al.* 2008) and without (Bonnet *et al.* 2013)

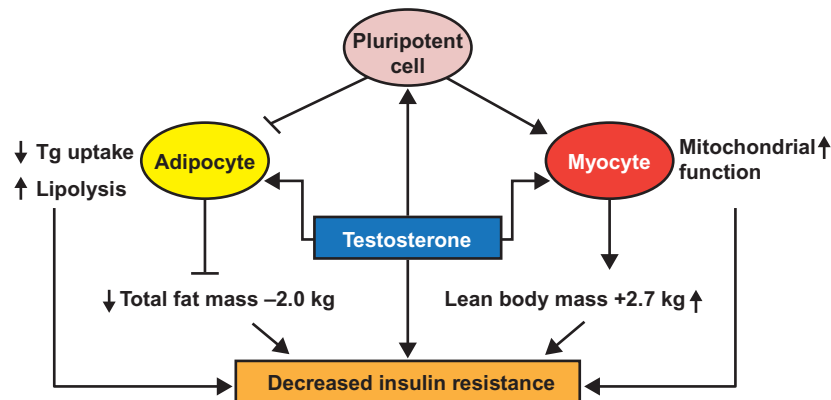
diabetes, SHBG but not testosterone was inversely associated with worse glycaemic control. SHBG may have biological actions beyond serving as a carrier protein for and regulator of circulating sex steroids (Wallace *et al.* 2013). However, this is yet unproven. An interventional study designed to test the effects of altering SHBG levels on glycaemic outcomes will be necessary to confirm causality. However, no intervention readily exists that can modulate SHBG concentrations independent of confounders.

In men with diabetes, free testosterone, if measured by gold standard equilibrium dialysis (Dhindsa *et al.* 2004), is reduced. Low free testosterone remains inversely associated with insulin resistance, independent of SHBG (Grossmann *et al.* 2008). This suggests that the low testosterone–dysglycaemia association is not solely a consequence of low SHBG.

While the association of low testosterone with metabolic disorders is weakened by adjustment for crude measures of adiposity, it becomes non-significant in studies that carefully adjusted for the amount of visceral adipose tissue volume (Grossmann 2011). Experimental evidence reviewed below suggests that visceral adipose tissue is an important intermediate (rather than a confounder) in the inverse association of testosterone with insulin resistance and metabolic disorders.

Evidence that low testosterone leads to increased insulin resistance

Experimental evidence, summarised in Fig. 3, suggests proposed mechanisms by which testosterone decreases insulin resistance: testosterone promotes the commitment of pluripotent stem cells into the myogenic lineage and inhibits their differentiation into adipocytes (Singh *et al.* 2003). This provides a molecular explanation for the

**Figure 3**

Mechanisms by which testosterone may decrease insulin resistance. Mechanisms may include testosterone actions on pluripotent stem cells and differentiated cell function. Data support both body composition-

dependent as well as body composition-independent testosterone actions. For references, see text.

modest reductions in fat mass (-2 kg) and increases in lean body mass ($+2$ – 3 kg) reported in RCTs of testosterone therapy (Isidori *et al.* 2005, Bhasin *et al.* 2006). These changes are expected to be metabolically favourable. In addition, testosterone regulates the metabolic functions of mature adipocytes (Xu *et al.* 1991, Marin *et al.* 1995) and myocytes (Pitteloud *et al.* 2005) in ways that reduce insulin resistance. Pre-clinical evidence (reviewed in Rao *et al.* (2013)) suggests that at the cellular level, testosterone may improve glucose metabolism by modulating the expression of the glucose-transported Glut4 and the insulin receptor, as well as by regulating key enzymes involved in glycolysis. More recently testosterone has been shown to protect murine pancreatic β cells against glucotoxicity-induced apoptosis (Hanchang *et al.* 2013).

Most studies suggest that the effects of testosterone on insulin resistance occur via changes in body composition. There is also evidence that testosterone regulates insulin sensitivity directly and acutely (Yialamas *et al.* 2007). Interestingly, a reciprocal feedback also appears to exist, given that not only chronic (Cameron *et al.* 1990, Allan 2013) but also, as shown more recently (Iranmanesh *et al.* 2012, Caronia *et al.* 2013), acute hyperglycaemia can lower testosterone levels.

In men with prostate cancer commencing androgen deprivation therapy, both total as well as, although not in all studies (Smith 2004), visceral fat mass increases (Hamilton *et al.* 2011) within 3 months. This is associated with increased insulin resistance, which is further aggravated by concurrent loss of muscle mass (Grossmann & Zajac 2011b). More prolonged (>12 months) androgen deprivation therapy has been associated with increased risk

of diabetes in several large observational registry studies. The estimated number to harm to cause one incident CASE of diabetes is ~ 100 (Grossmann & Zajac 2011b). Acute sex steroid withdrawal also induced insulin resistance in healthy men (Yialamas *et al.* 2007). In addition, men with Klinefelter syndrome have an increased risk of metabolic disorders. Interestingly, greater body fat mass is already present before puberty. This indicates that chromosomal factors may also play a role (Groth *et al.* 2013).

Whether testosterone promotes insulin sensitivity via effects on energy expenditure and/or physical activity is less well studied. In rodent models, there is evidence that testosterone may increase the metabolic rate via androgen receptor-dependent actions on skeletal muscle (Fernando *et al.* 2010). Mice lacking the androgen receptor have decreased physical activity, which may, at least in part, be responsible for their sarcopaenic obesity (Rana *et al.* 2011). Data from human studies are less clear, as RCTs of testosterone therapy have, to date, not measured changes in physical activity carefully. A small study investigating the effects of acute biochemical castration in ten healthy younger men (mean age 41 years) did not find any changes in energy expenditure after 4 weeks of castration (Rabiee *et al.* 2010). A larger acute chemical castration study in 54 men aged 50–80 years similarly did not find any change in respiratory exchange ratio or resting energy expenditure after 3 weeks of testosterone suppression (Santosa *et al.* 2010). The authors concluded that, because abrupt changes in sex steroids do not change resting substrate oxidation, changes that can be observed after more prolonged periods of deficiency are most likely due to direct effects of sex steroids on body composition.

Testosterone has also been shown to reduce the concentration of pro-inflammatory cytokines in some, but not all studies, reviewed recently in Kelly & Jones (2013). It is not known whether this effect is independent of testosterone-induced changes in body composition.

Collectively, the observations discussed in this section suggest that it is the decrease in testosterone that causes insulin resistance and diabetes. One important caveat remains: the strongest evidence that low testosterone is the cause rather than consequence of insulin resistance comes from men with prostate cancer (Grossmann & Zajac 2011a) or biochemical castration, and from mice lacking the androgen receptor. How findings with such extreme manipulations of sex steroids (Yialamas *et al.* 2007, Hamilton *et al.* 2011, Rana *et al.* 2011) apply to the majority of men with diabetes who only have modest reductions in testosterone is therefore not known.

Evidence that low testosterone is a consequence of dysglycaemia and associated clinical factors

There is also evidence for reverse causality, demonstrating that low testosterone may be a consequence of disordered glucose metabolism and obesity. In prospective studies, the metabolic syndrome predicts low testosterone (Laaksonen *et al.* 2005). Several large prospective studies have shown that weight gain or development of type 2 diabetes is major drivers of the age-related decline in

testosterone levels (Travison *et al.* 2007, Haring *et al.* 2010). Indeed, there is increasing evidence that healthy ageing by itself is generally not associated with marked reductions in testosterone (Sartorius *et al.* 2012). Circulating testosterone, on an average 30%, is lower in obese compared with lean men, which is more than the purely age-dependent decrease between 40 and 80 years of age (Tajar *et al.* 2010).

Testosterone and insulin resistance: a bilateral relationship

The current evidence is therefore consistent with a bi-directional relationship between visceral fat and testosterone, which may initiate a self-perpetuating cycle promoting insulin resistance (Fig. 4). In addition, interactions of testosterone with other organ systems such as muscle (Pitteloud *et al.* 2005) bone (Lee *et al.* 2007, Oury *et al.* 2011), liver (Lin *et al.* 2008) and the CNS (Yu *et al.* 2013) may also modulate insulin resistance. However, until causality is confirmed by adequately designed intervention trials, it remains possible that this relationship is not pathogenic but an epiphenomenon of shared risk factors. According to this bi-directional model, increased visceral fat not only promotes insulin resistance but also elaborates a variety of circulating mediators that inhibit the HPT axis at multiple levels. Only 5% of men with type 2 diabetes have elevated LH levels (Dhindsa *et al.* 2004, 2011). This is consistent with recent findings that the

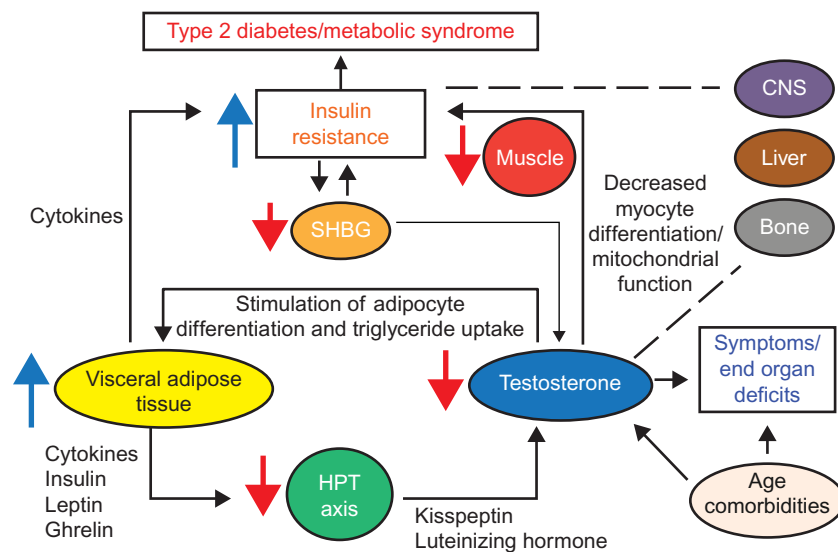


Figure 4

Bi-directional relationship between visceral fat and testosterone: a self-perpetuating cycle promoting insulin resistance. SHBG, sex hormone binding-globulin; HPT, hypothalamic-pituitary-testicular; for references, see text.

inhibition of the gonadal axis predominantly takes place in the hypothalamus, especially with more severe obesity. Metabolic factors, such as leptin, insulin (via deficiency or resistance) and ghrelin are believed to act at the ventromedial and arcuate nuclei of the hypothalamus to inhibit gonadotropin-releasing hormone (GNRH) secretion from GNRH neurons situated in the preoptic area (Navarro & Kaiser 2013). While several putative neurocircuits may link these afferent and efferent signals, kisspeptin has emerged as one of the most potent secretagogues of GNRH release (Navarro & Kaiser 2013). Consistent with the hypothesis that obesity-mediated inhibition of kisspeptin signalling contributes to the suppression of the HPT axis, infusion of a bioactive kisspeptin fragment has been recently shown to robustly increase LH pulsatility, LH levels and circulating testosterone in hypotestosteronaemic men with type 2 diabetes (George *et al.* 2013).

The inhibitory role of oestradiol on LH secretion, inferred by clinical studies demonstrating an increase in circulating testosterone levels with aromatase inhibitors, has recently come under scrutiny. This is because population-based studies have shown that obese men, whether diabetic (Dhindsa *et al.* 2011) or not (Huhtaniemi *et al.* 2012, Yeap *et al.* 2012a), have lower circulating oestradiol levels than non-diabetic and lean men. These observations do not exclude the possibility that aromatase inhibitors counteract increased paracrine oestradiol actions at the hypothalamus. Interestingly, a recent 16-week study of experimentally induced hypogonadism in healthy men with graded testosterone add-back either with or without concomitant aromatase inhibitor treatment has in fact suggested that low oestradiol (but not low testosterone) may be responsible for the hypogonadism-associated increase in total body and intra-abdominal fat mass (Finkelstein *et al.* 2013). A smaller study with a similar experimental design found that acute testosterone withdrawal reduced insulin sensitivity independent of body weight, whereas oestradiol withdrawal had no effects

(Rubinow *et al.* 2012). Clearly, potentially differential actions of testosterone and its metabolite oestradiol on fat mass and insulin sensitivity require further study.

Therapeutic approach to treatment of lowered testosterone levels in men with metabolic disorders

The bi-directional relationship between low testosterone and insulin resistance is mediated, at least in part, by increased visceral fat (Fig. 4). This suggests that both weight loss as well as testosterone treatment have the potential to break this vicious cycle.

Several lines of evidence (Farooqi *et al.* 2002, Zumoff *et al.* 2003, Travison *et al.* 2008, Tajar *et al.* 2010, Grossmann 2011, Sartorius *et al.* 2012, Camacho *et al.* 2013, Corona *et al.* 2013a,b, George *et al.* 2013), summarised in Box 1, suggest that in the majority of men, suppression of the diabetes-associated HPT axis is functional, and may hence be reversible. Obesity and dysglycaemia and associated comorbidities such as obstructive sleep apnoea (Hoyos *et al.* 2012b) are important contributors to the suppression of the HPT axis. Therefore, lifestyle modification, weight reduction and treatment of comorbidities are the most logical approach. This is supported by observational studies showing that weight gain and development of diabetes accelerate the age-related decline in testosterone. This suggests that this decline may be decelerated through management of health and lifestyle factors (Travison *et al.* 2007, Haring *et al.* 2010).

Several observational and randomised studies reviewed in Grossmann (2011) have shown that weight loss, whether by diet or surgery, leads to substantial increases in testosterone, especially in morbidly obese men. The increase in testosterone was highly proportional to the amount of weight lost. It has been estimated that 10% weight loss increases testosterone by 2–3 nmol/l.

Box 1 Evidence suggesting that the hypothalamic–pituitary–testicular axis suppression in obese men with metabolic disorders is functional. For individual references, see main text

- 55% of symptomatic androgen deficiency reverted to a normal testosterone or an asymptomatic state after 8-year follow-up, suggesting that androgen deficiency is not a stable state
- Modifiable risk factors such as obesity and co-morbidities are more strongly associated with a decline in circulating testosterone levels than age alone
- Weight loss can reactivate the hypothalamic–pituitary–testicular axis
- Leptin treatment resolves hypogonadism in leptin-deficient men
- The hypothalamic–pituitary–testicular axis remains responsive to treatment with aromatase inhibitors or selective oestrogen receptor modulators in obese men
- Kisspeptin treatment increases LH secretion, pulse frequency and circulating testosterone levels in hypotestosteronaemic men with type 2 diabetes

More markedly (>30%), body weight loss secondary to bariatric surgery can raise testosterone by >10 nmol/l (Grossmann 2011).

This has been confirmed by a recent systematic review and meta-analysis of studies that have reported the effects of weight loss on testosterone levels (Corona *et al.* 2013b). Non-surgical weight loss achieved a mean weight reduction (9.8%) in body weight. This led to an increase in total testosterone (2.87 nmol/l). Surgical weight loss achieved greater reductions in weight (32%) and more marked increases in circulating testosterone levels (8.73 nmol/l). Men with diabetes experienced a lesser increase in testosterone compared with men without diabetes. This was likely due to the fact that men with diabetes lost lesser amounts of body weight. In a stepwise logistic regression analysis, only the change in BMI was associated with the change in testosterone (Corona *et al.* 2013a,b).

More recently, a retrospective analysis of 891 men with impaired glucose tolerance and a mean BMI of 32 kg/m² participating in the diabetes prevention programme has been reported. Men randomised to lifestyle modification had a 15% (+1.5 nmol/l) increase in their testosterone levels coincident with 7.8 kg weight loss. This reduced the prevalence of hypoandrogenaemia (defined a total testosterone of <10.2 nmol/l) by almost 50% (20.4–11.1% ($P < 0.05$)). In contrast, testosterone levels or hypoandrogenaemia prevalence did not change significantly in men randomised to either placebo or to metformin, who lost <3 kg of weight (Dwyer *et al.* 2012).

The effects of weight changes on the gonadal axis in overweight men (mean BMI 27.6 kg/m²) have also been elegantly demonstrated in a recent observational survey from the EMAS cohort (Camacho *et al.* 2013). In this longitudinal study, weight loss of <10% primarily increased SHBG probably because of improved insulin resistance. This was associated with increases in total but not free testosterone. Weight gain led to the opposite changes. With more substantial weight loss, LH and free testosterone also increased. This suggests that weight loss can lead to genuine reactivation of the gonadal axis by reversal of obesity-associated hypothalamic suppression. Weight loss can also improve quality of life and sexual function in obese men, but whether this is causally related to the associated increase in testosterone levels is not known (Khoo *et al.* 2010).

There is pre-clinical and observational evidence that chronic hyperglycaemia can inhibit the HPT axis (Cameron *et al.* 1990, Iranmanesh *et al.* 2012, Allan 2013). This suggests that improving glycaemic control

may increase testosterone levels. This has been demonstrated in a longitudinal analysis of 265 men with diabetes: in men who improved their glycaemic control over time, testosterone levels increased. By contrast, in those men in whom glycaemic control worsened, testosterone decreased (Grossmann *et al.* 2008).

Men with type 2 diabetes usually have only modest reductions in their testosterone levels. Median circulatory total testosterone levels range from 10.5 to 12.7 nmol/l (Dhindsa *et al.* 2004, Kapoor *et al.* 2007, Grossmann *et al.* 2008). Therefore, successful weight loss combined with optimisation of glycaemic control may be sufficient to normalise circulating testosterone levels in the majority of such men. Although often difficult to achieve, weight loss, optimisation of diabetic control and assiduous care of comorbidities should remain the first-line approach.

However, whether weight loss, even if successful, can fully reverse the HPT axis suppression is not known. A small recently published longitudinal observational study in 13 obese men with low testosterone levels submitted to bariatric surgery has shown that while ten of the men had free testosterone levels in the normal range 1 year after surgery, in three of the men free testosterone remained in the hypogonadal range, despite substantial weight loss (Aarts *et al.* 2013). Therefore, testosterone levels should be measured after successful weight loss to identify men with an insufficient rise in their testosterone levels. Such men may have HPT axis pathology unrelated to their obesity, which will require appropriate evaluation and management.

Testosterone treatment in men with metabolic disorders

Some, but not all uncontrolled studies, reviewed in Grossmann *et al.* (2010) have suggested beneficial effects of testosterone therapy on glucose metabolism. More recently, two observational studies, one in US Veterans (Shores *et al.* 2012) the other in diabetic men from the UK (Muraleedharan *et al.* 2013) have been reported. In both studies, men who were treated with testosterone had a 50% reduced risk of mortality compared with untreated men. In the Veteran population, the difference in hazard ratio for death was particularly noticeable in the subgroup of men with diabetes (Shores *et al.* 2012). A more recent, larger retrospective cohort study has reported findings opposite to those of Shores (Shores *et al.* 2012) and Muraleedharan (Muraleedharan *et al.* 2013). This study evaluated a cohort of 8709 men with a high burden of comorbidities, including a 50% prevalence of diabetes

(Vigen *et al.* 2013). In this cohort, testosterone therapy was associated with an increased risk of adverse outcomes including all-cause mortality, myocardial infarction and ischaemic stroke (adjusted hazard ratio 1.29, 95% CI 1.04 to 1.58) (Vigen *et al.* 2013). In part, the discrepant results may be due to the fact men in the Vigen cohort (Vigen *et al.* 2013) had a higher burden of comorbidities. Given that one (Basaria *et al.* 2010), but not all (Srinivas-Shankar *et al.* 2010), RCTs in men with a similarly high burden of comorbidities reported an increase in cardiovascular events in men randomised to testosterone treatment (see section on Testosterone therapy: potential risks below) (Basaria *et al.* 2010), testosterone should be used with caution in frail men with multiple comorbidities. The retrospective, non-randomised and non-blinded design of these studies (Shores *et al.* 2012, Muraleedharan *et al.* 2013, Vigen *et al.* 2013) leaves open the possibility for residual confounding and multiple other sources of bias. These have been elegantly summarised by Wu (2012).

Evidences from placebo-controlled, double-blind randomised-controlled trials examining glycaemic outcomes have to date been inconsistent. There have been ten RCTs in a total of 907 men not selected for diabetes. These men were ageing, overweight and had borderline low baseline testosterone levels (Table 1; Liu *et al.* 2003, Page *et al.* 2005, Basu *et al.* 2007, Bhasin *et al.* 2007, Allan *et al.* 2008, 2010, Emmelot-Vonk *et al.* 2008, Svartberg *et al.* 2008, Caminiti *et al.* 2009, Huang *et al.* 2013). Effects of

testosterone therapy on body composition were metabolically favourable with modest decreases in fat mass and increases in lean body mass. Despite this, decreases in insulin resistance were found in only two (Emmelot-Vonk *et al.* 2008, Caminiti *et al.* 2009) of the ten trials. This suggests that testosterone has limited effects on glucose metabolism in relatively healthy men with only mildly reduced testosterone.

Six RCTs have been conducted to date specifically in men with diabetes or the metabolic syndrome (Kapoor *et al.* 2006, Gopal *et al.* 2010, Kalinchenko *et al.* 2010, Jones *et al.* 2011; Tables 1 and 2). One was never unpublished (<http://www.solvaypharmaceuticals.com/static/wma/pdf/1/3/4/4/2/S176.2.101.pdf>) and one has been presented in preliminary abstract form (Hackett *et al.* 2013). Compared with unselected men, these men were more obese and had lower testosterone levels (Table 1). Again, beneficial changes in body composition were reported in most trials. However, they did not consistently translate in major improvements of glucose metabolism. Half of the RCTs showed modest improvements in insulin resistance, comparable roughly with metformin monotherapy. The other half showed no effect. One small study reported an improved in HbA1c (Kapoor *et al.* 2006). This was not confirmed by most subsequent larger RCTs. However, men enrolled in these RCTs had reasonably well-controlled diabetes even before testosterone treatment was commenced (Table 2).

Table 1 Effects of testosterone therapy on glucose metabolism in randomised controlled clinical trials. Values are median (range). For references, see main text. Data from Grossmann *et al.* 2010

Target	Number of participants	Baseline characteristics	Outcomes
Older men not selected for abnormal glucose metabolism ^a	58 (38–237)	Age 67 years (47–74) BMI 28 kg/m ² (26–34) TT 11.4 nmol/l (8.4–14.7)	Body composition Fat mass –1.3 kg (no change to –5.7) ^a Lean body mass +1.4 kg (no change to +3.8) ^a Insulin resistance Reduced in two RCTs; no effect in eight RCTs
Men with diabetes and or the metabolic syndrome ^b	182 (22–220)	Age 60 years (44–64) BMI 33 kg/m ² (24–35) TT 9.3 nmol/l (6.7 to <13.0) HbA1c ^c 7.2% (7.0–9.5)	Body composition Fat mass –2 to –2.6 kg; lean body mass +1.9 to 2.0 kg Insulin resistance Reduced in three RCTs; no effect in four RCTs HbA1c Reduced in one RCTs; no effect in six RCTs

TT, total testosterone.

^aThe total population enrolled in the ten randomised controlled trials (RCTs) of unselected men included 907 participants.

^bIn six RCTs of men with type 2 diabetes and or the metabolic syndrome 829 participants were enrolled.

^cMen with diabetes only.

Table 2 Randomised controlled clinical trials in men with type 2 diabetes or the metabolic syndrome. Data from Grossmann 2011

	n	Age (years)	BMI (kg/m ²)	HbA1c baseline (%)	Duration (weeks)	TT (nmol/l) baseline	TT (nmol/l) achieved	HOMA-IR (% reduction)	HbA1c (%)	Effect on lipids
Kapoor <i>et al.</i> (2006)	24	64	33	7.3	12	8.6	12.8	-39*	-0.37*	TC -0.4 nmol/l* No change in LDL, HDL, Tg
Gopal <i>et al.</i> (2010)	22	44	24	7.0	12	10.1	Not reported	No change	No change	No change
Kalinchenko <i>et al.</i> (2010)	184	52	35	Not reported	30	6.7	13.1	-31*	Not reported	No change
Jones <i>et al.</i> (2011)	220	60	32	7.2 [§]	26	9.4	19.5	-15*	No change	Lpa -0.24 µmol/l* HDL -0.049 nmol/l* TC -0.34 mmol/l** ^a LDL -0.21 mmol/l** ^a
Solvay unpublished	180	Not reported	Not reported	7-9.5	26	<13	Not reported	No change	No change	No change in Tg Not reported
Hackett <i>et al.</i> (2013)	199	62	33	7.6	30	9.1	11.2	No change	Significant reduction ^b	Not reported

**P* < 0.05. TT, total testosterone; TC, total cholesterol; Tg, triglycerides; Lpa, lipoprotein a.

^aChanges were significant in the subgroup of men with the metabolic syndrome. Changes in blood pressure were not significant in the randomised controlled trials (RCTs) by Kapoor, Gopal and Jones, but not assessed or reported in the other listed RCTs.

^b-0.42% in men with poorly controlled diabetes. No improvement in HbA1c in men with depression.

Indeed, a recent, yet to be published RCT (Hackett *et al.* 2013) has reported a significant reduction in HbA1c in men with poorly controlled diabetes. Therefore, it is conceivable that testosterone treatment may have more significant effects on glucose metabolism in uncontrolled diabetes, akin to what has generally been shown for conventional anti-diabetic medications.

The study by Hackett *et al.* (2013) also reported that the improvement in HbA1c was observed only in men without depression. This led the authors to hypothesise that depression may mitigate beneficial effects of testosterone therapy on glucose metabolism. Differences in baseline characteristics and baseline circulating testosterone levels among study participants, in the type of testosterone therapy, in the testosterone levels achieved on treatment and in the stringency by which concomitant alterations in anti-glycaemic therapy were controlled for may additionally account for some of the between-trial inconsistencies. Limitations of all RCTs to date include measurement of testosterone by immunoassay rather than by LCMS/MS, and use of surrogate markers of glucose metabolism rather than insulin clamps.

Whether testosterone therapy can enhance the effects of lifestyle measures on glucose metabolism remains unknown. A small, single-blind study found that testosterone treatment augmented the reductions in central adiposity and insulin resistance achieved with lifestyle (Heufelder *et al.* 2009). However, a subsequent RCT failed to find additive effects of dietary restriction and testosterone therapy on weight loss (Hoyos *et al.* 2012a).

In summary, the evidence from controlled studies show that testosterone therapy consistently reduces fat mass and increases lean body mass, but inconsistently decreases insulin resistance. At least in men with adequate control of diabetes, testosterone treatment does not improve glycaemic control. Whether testosterone treatment can improve glycaemic control with poorer glycaemic control, or whether it can reduce the risk of developing diabetes in high-risk men requires further study. This latter hypothesis is currently being tested in a multicentre Australian RCT, 'Testosterone Treatment for the Prevention of Type 2 Diabetes Mellitus in High-Risk Men' (T4DM, Australian New Zealand Clinical Trials Registry: ACTRN12612000287831).

There are several potential reasons why testosterone therapy does not improve glucose metabolism despite preclinical and observational data supporting a plausible hypothesis for such an effect. First, men enrolled in the intervention trials RCT had only modestly lowered baseline testosterone levels around the lower limit of the assay

references range derived from healthy young men (Tables 1 and 2). Profound testosterone deficiency (<1 nmol/l) induced by androgen deprivation therapy consistently induces insulin resistance (Smith *et al.* 2006, Hamilton *et al.* 2011). This suggests a threshold effect. Observational and experimental studies however have failed to identify a consistent threshold. Instead, they show that the testosterone threshold required to prevent fat accumulation and to maintain insulin sensitivity varies across populations and experimental settings (Singh *et al.* 2002, Bhasin *et al.* 2005, Isidori *et al.* 2005, Zitzmann *et al.* 2006, Hamilton *et al.* 2011, Tajar *et al.* 2012; Table 3). Collectively, these data do not exclude the possibility that men with type 2 diabetes and more profound reductions in testosterone may derive a glycaemic benefit with testosterone therapy. However, marked reductions in testosterone levels are uncommon in men with diabetes. They commonly have only modest reductions in circulating testosterone: mean pooled differences in total testosterone relative to men without diabetes range from -1.61 nmol/l (Ding *et al.* 2006) to -2.99 nmol/l (Corona *et al.* 2010) in meta-analyses. Symptomatic men with unequivocal reductions of testosterone levels should, after

an appropriate diagnostic work up, be considered for testosterone therapy irrespective of its effect on glucose metabolism, given the general benefits in such men (Bhasin *et al.* 2010).

Interestingly, testosterone therapy does not consistently improve glucose metabolism despite a reduction in fat mass and an increase in lean mass. It is possible that these metabolically favourable changes in body composition were too small to alter insulin resistance. However, studies that have reported thresholds for both fat mass and insulin sensitivity suggest that the testosterone level required to prevent fat accumulation may be higher than the level below which insulin resistance increases (Table 3). Studies in men with experimentally induced hypogonadism (Singh *et al.* 2002) and in male mice lacking a functional androgen receptor either globally (Rana *et al.* 2011) or selectively in fat (McInnes *et al.* 2012) also show that effects of testosterone on body composition and glucose metabolism can be dissociated. In part, this may be due to the fact that the effects of testosterone therapy on visceral adiposity, the fat compartment most closely associated with insulin resistance, have been inconsistent: the

Table 3 Testosterone thresholds for maintenance of fat mass and insulin sensitivity

Author	Method	Fat mass	Glycaemia
Singh <i>et al.</i> (2002)	Experimental: induced androgen deficiency with graded testosterone add-back (healthy young men)	TT 10.6 fT 110	No change at lowest testosterone concentrations: TT 6.1, fT 80
Bhasin <i>et al.</i> (2005)	Experimental: induced androgen deficiency with graded testosterone add-back (older men)	TT 6.1 fT 65	Not reported
Finkelstein <i>et al.</i> (2013)	Experimental: induced androgen deficiency with graded testosterone add-back (healthy young men) ± aromatase inhibitor co-administration (healthy young men)	TT 13.9 ^a Increase in both total and intra-abdominal fat mass)	Not reported
Zitzmann <i>et al.</i> (2006)	Observational: community-dwelling men presenting to an andrological outpatient department	Obesity TT <12.0	Diabetes TT <10.0
Tajar <i>et al.</i> (2012)	Observational: EMAS cohort	Obesity TT <10.0	Metabolic syndrome/insulin resistance <8.0 TT <1.0 nmol/l
Hamilton <i>et al.</i> (2011)	Observational: men with prostate cancer receiving androgen deprivation therapy	TT <1.0 nmol/l Increase in total fat mass and in visceral adipose tissue volume	TT <1.0 nmol/l
Isidori <i>et al.</i> (2005)	Meta-analysis of randomised controlled trials	Significant decrease with no difference if stratified according to baseline TT (<10 and >10)	Not reported

TT, total testosterone (nmol/l); fT, free testosterone (pmol/l).

^aThis study suggested that oestradiol is more important than testosterone to prevent fat accumulation.

majority of RCTs (recently reviewed in Ng Tang Fui *et al.* (2013a)) showed that testosterone therapy does not reduce visceral fat. Consistent with this, testosterone therapy does not, despite reducing fat mass, increase adiponectin levels, an insulin-sensitising adipokine that is usually inversely associated with fat mass. In fact, androgen deprivation therapy, despite increasing visceral fat mass and in insulin resistance, paradoxically increases adiponectin levels (Hamilton *et al.* 2011). In addition, testosterone therapy decreases SHBG. SHBG may have biological actions that improve glucose metabolism (Wallace *et al.* 2013). Future studies should clarify whether effects of testosterone on adiponectin, SHBG and other potential regulators of glucose metabolism, such as undercarboxylated osteocalcin (Yeap 2011), may limit testosterone therapy-mediated improvements in glucose metabolism.

Testosterone, lipids and blood pressure

In most population-based studies of men with and without metabolic disorders, reviewed recently by Monroe & Dobs (2013), testosterone is inversely associated with total cholesterol, LDL cholesterol and triglyceride (Tg) levels, but positively associated with HDL cholesterol levels, even if adjusted for confounders. Similar findings have been reported in men with diabetes (Fig. 2; Dhindsa *et al.* 2004, Kapoor *et al.* 2007, Grossmann *et al.* 2008). Although observational studies show a consistent association of low testosterone with adverse lipid profiles, whether testosterone therapy exerts beneficial effects on lipid profiles is less clear. The effects of testosterone treatments on lipid levels have been meta-analysed (Fernandez-Balsells *et al.* 2010). In this analysis, HDL cholesterol levels were significantly lower in the testosterone group than in the control group (weighted mean difference -0.49 mg/dl; 95% CI -0.85 to -0.13). There was no statistically significant difference in total cholesterol, LDL cholesterol and Tg levels between the testosterone group and the control group (Fernandez-Balsells *et al.* 2010). The effects of testosterone treatment on lipids in double-blind placebo-controlled RCTs are shown in Table 2. In the TIMES2 study Jones *et al.* (2011) found not only a significant decrease in lipoprotein a (Lpa), an independent risk factor for cardiovascular disease, but also a significant decrease in the theoretically protective HDL cholesterol. Patients with metabolic syndrome additionally had reduced total and LDL cholesterol after 6 months of testosterone therapy compared with placebo (Table 2). A recent

meta-analysis which included both double-blind placebo-controlled RCTs as well as less rigorous intervention trials found that testosterone treatment significantly reduced Tg levels in men with the metabolic syndrome (-0.40 nmol/l; 95% CI -0.66 , -0.14) and in men with diabetes (-0.60 nmol/l; 95% CI -0.83 , -0.37). Effects of testosterone treatment on other lipid fractions were not reported (Corona *et al.* 2013a,b).

In summary, testosterone therapy has been shown to have modest but significant effects on lipid levels in some but not all studies of men with and without disorders of glucose metabolism. Whereas testosterone-induced decreases in total cholesterol, LDL cholesterol and Lpa are expected to reduce cardiovascular risk, testosterone also decreases the levels of the cardio-protective HDL cholesterol. Therefore, the net effect of testosterone therapy on cardiovascular risk remains uncertain.

There is no evidence that testosterone treatment has significant effects on blood pressure, either from the most recent meta-analysis (Fernandez-Balsells *et al.* 2010) or from individual RCTs specifically enrolling men with the metabolic syndrome and/or diabetes (Table 2).

Testosterone therapy: potential risks

Potential risks of testosterone therapy have been reviewed in excellent recent reviews (Cunningham & Toma 2011, Yeap *et al.* 2012b, Huhtaniemi 2013, Matsumoto 2013, Spitzer *et al.* 2013). They are summarised only briefly. It is important to note that RCTs and meta-analyses to date have been underpowered to provide definitive outcome data regarding cardiovascular and prostate events. The long-term risks of testosterone therapy are therefore unknown. The overall frequency of serious adverse events in RCTs, considering that these trials included older men with varying degrees of age-related comorbidities, has been low (Fernandez-Balsells *et al.* 2010).

One meta-analysis has shown increased prostate events, largely driven by PSA increases and protocol-mandated prostate biopsies (Calof *et al.* 2005). Current, albeit limited and preliminary data have not shown evidence that testosterone causes prostate cancer, or that it makes subclinical prostate cancer grow (Grossmann & Wittert 2012). However, it has been estimated that an RCT of 6000 men treated with testosterone or placebo for 3 years is necessary to detect a 30% increase in prostate cancer risk with testosterone therapy (Cunningham & Toma 2011). Yet, the largest completed trials have included <500 men, and most have been short term. Because prostate monitoring is recommended during testosterone therapy

(Bhasin *et al.* 2010), concern remains regarding an increased risk of over-diagnosing pre-existing, clinically insignificant prostate cancer, which is highly prevalent in older men.

One meta-analysis has shown a small increase in haematocrit and decrease in HDL cholesterol (Fernandez-Balsells *et al.* 2010), theoretically unfavourable changes. One RCT has shown an increase in cardiovascular events with testosterone in relatively frail older men (Basaria *et al.* 2010). However, another RCT in a similar population of men has not confirmed this finding (Srinivas-Shankar *et al.* 2010). While previous smaller meta-analyses (Calof *et al.* 2005, Fernandez-Balsells *et al.* 2010) have not shown increased risk, the most recent meta-analysis of RCTs including almost 3000 mainly older men did show an increased risk cardiovascular-related events with testosterone therapy (odds ratio 1.54 (95% CI 1.09 to 2.18)) (Xu *et al.* 2013). Limitations of this meta-analysis include an overall low number of events, 115 events in 1733 testosterone-treated men (6.6 per 100 men) vs 65 events in 1261 men receiving placebo (5.2 per 100 men), and the absence of sensitivity analyses (Xu *et al.* 2013) to exclude outlier studies (Basaria *et al.* 2010). In addition, meta-analysed trials were generally small, short-term, and events

were heterogeneous. The trials were not designed for evaluating cardiovascular outcomes, with suboptimal ascertainment and adjudication of events. Hence, the data are not definitive.

Finally, compared with otherwise healthy young men with organic androgen deficiency, there may be increased risks in older, obese men because of comorbidities and of decreased testosterone clearance (Zitzmann & Nieschlag 2007, Coviello *et al.* 2008, Hoyos *et al.* 2012a).

Low testosterone and metabolic disorders: summary

The relationship between low testosterone and metabolic disorders is complex, multi-directional and may involve a number of different mechanisms. These complex relationships are virtually impossible to disentangle. On central component is the inverse association of circulating testosterone with insulin resistance. Figure 3 shows the best-studied mechanisms by which testosterone (either directly and/or indirectly via its metabolites dihydrotestosterone (DHT) or oestradiol) may decrease insulin resistance. Future studies may clarify additional mechanisms, such as effects on energy

Table 4 Summary of the current evidence and recommendations for clinical assessment and management of lowered testosterone in men with metabolic disorders (type 2 diabetes and/or the metabolic syndrome)

Current evidence	
1	Men with metabolic disorders commonly present with non-specific symptoms and modestly low testosterone levels
2	Low testosterone identifies an adverse metabolic phenotype and may be associated with end-organ deficits suggesting androgen deficiency
3	Testosterone increases with weight loss, suggesting that the hypothalamic–pituitary–testicular axis suppression is functional and reversible
4	In randomised controlled trials of testosterone therapy, metabolically favourable changes in body composition have not consistently translated into improvements of glucose metabolism or other important health outcomes
5	Long-term risks of testosterone therapy in men without classical androgen deficiency remain unknown
Recommendations for assessment and management	
1	Measure testosterone in men with metabolic disorders in whom androgen deficiency is suspected clinically
2	Evaluate unequivocally low testosterone levels for an underlying pathological cause and do not assume that hypogonadism is a consequence of metabolic disorders
3	The first response to the ageing, obese man with metabolic disorders and low-normal testosterone should be the optimisation of life-style measures and glycaemic control, and of established therapies with high level evidence of outcome benefit
4	Indications for testosterone therapy in men with metabolic disorders should be: no difference in men without metabolic disorders reserved for clinically significant symptoms with persistently low testosterone
5	Testosterone therapy should not be routinely given to men with metabolic disorders and low-normal testosterone until clinical benefit is confirmed by well-conducted clinical trials
6	If you treat: discuss uncertainties about risks/benefits set goals evaluate for benefit/adverse events implement standardised monitoring programme reduced insulin resistance potential collateral benefit

expenditure, inflammation or on changes in physical activity and motivation. Figure 4 shows that increased visceral fat is an important component in the association of low testosterone and insulin resistance. However, given the widespread expression of sex steroid receptors in multiple tissues, cross talk between testosterone and/or DHT and oestradiol, and other organs such as bone, liver or the CNS may play a role. Finally age and, probably more importantly, age-associated comorbidities may not only decrease testosterone levels but also promote insulin resistance.

Conclusions and areas of future research

The current evidence and recommendations regarding clinical assessment and management are summarised in Table 4. Given the difficulties in diagnosis of androgen deficiency in men with metabolic disorders, future research should focus on the identification of objective, quantifiable markers of androgen deficiency. Such markers may not only aid in diagnosis but may also predict a response to testosterone therapy. However, this hypothesis requires to be tested in clinical trials.

The vast majority of men with metabolic disorders have functional gonadal axis suppression with modest reductions in testosterone levels. This may be reversible with loss and optimisation of comorbidities. Therefore, identification and treatment of comorbidities and lifestyle measure with emphasis on weight loss remain the first-line approach to therapy of lowered testosterone levels in men with metabolic disorders. However, should well-conducted RCTs provide favourable evidence regarding the risk-benefit ratio, testosterone therapy, be it replacement or pharmacological, may become an option in such men. Future RCTs should evaluate whether, in obese men, testosterone treatment will increase the success rate of a lifestyle programme targeted at weight loss. Currently, testosterone treatment may, after discussion regarding the experimental nature of this treatment, be considered either when lifestyle measures fail or are insufficient to restore circulating testosterone to levels sufficient to prevent deleterious effects of androgen deficiency. However, what constitutes a sufficient circulating testosterone level is unknown. This level will vary not only across individuals depending on age, clinical and genetic characteristics, but also across different tissues. In addition, relative roles of testosterone derivatives such as DHT and oestradiol in regulation of body composition and glucose metabolism should be evaluated: recent evidence that fat accumulation may be oestradiol-, rather than testosterone-dependent (Finkelstein *et al.* 2013). To clarify

the apparent paradox why testosterone therapy-induced metabolically favourable changes in body composition do not consistently translate into improvements in glucose metabolism, testosterone effects on visceral fat mass as well as on potential insulin sensitisers such as adiponectin, SHBG and undercarboxylated osteocalcin (Lee *et al.* 2007) require further study. Future clinical trials assessing the effects of testosterone therapy should focus on men with more marked reductions, larger amount of visceral fat and less well-controlled diabetes. However, marked reductions in testosterone are uncommon even in men with metabolic disorders. They may reflect concomitant authentic androgen deficiency, which requires treatment in its own right. Whether testosterone treatment, be it long term or only temporary, has added benefit to the implementation of lifestyle measures should be assessed in controlled trials.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

M G was supported by a National Health and Medical Research Council of Australia Career Development Fellowship (# 1024139).

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Received in final form 6 December 2013

Accepted 13 December 2013

Accepted Preprint published online 18 December 2013