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Review Article

Testosterone deficiency in men with Type 2 diabetes: pathophysiology and treatment

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What's new?

- Epidemiological studies consistently demonstrate that lowered serum testosterone is common in men with Type 2 diabetes.

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- This review summarizes the current evidence regarding the relationship between endogenous testosterone and Type 2 diabetes, the mechanisms that could mediate this relationship and the impact of exogenous testosterone treatment in men with Type 2 diabetes.
- Although large, well-designed clinical trials are needed, given the benefit–risk ratio of testosterone treatment is not well understood, routine serum testosterone testing or testosterone treatment of asymptomatic men with Type 2 diabetes is currently not recommended.
- A trial of testosterone treatment in symptomatic men with low testosterone should be limited to carefully selected men after discussion of the lack of high-level evidence regarding long-term benefits and risks of treatment.

Abstract

Epidemiological studies consistently demonstrate that lowered serum testosterone is not only common in men with established Type 2 diabetes, but also predicts future diabetic risks and increased mortality. Preclinical studies report plausible mechanisms by which low testosterone could mediate dysglycaemia. Exogenous testosterone treatment consistently reduces fat mass, increases muscle mass and improves insulin resistance in some studies, but the majority of currently available randomized controlled trials (RCTs) do not report a consistent glycaemic benefit. In men with diabetes, testosterone treatment effects on androgen deficiency-like clinical features are inconsistent, and effects on sexual dysfunction may be attenuated compared with men without diabetes. The long-term risks of testosterone treatment in older men without medical disease of the hypothalamic–pituitary–testicular axis are not known. Current RCTs are not definitive, owing to their small size, short duration and enrolment of men with mostly relatively good baseline glycaemic control not specifically selected for the presence of androgen deficiency symptoms. Although large, well-designed clinical trials are needed, given the benefit–risk ratio of testosterone treatment is not well understood, routine serum testosterone testing or testosterone treatment of asymptomatic men with Type 2 diabetes is currently not recommended. Carefully selected, symptomatic men with low testosterone who are informed of the lack of high-level evidence regarding the long-term benefits and risks

of this approach may be offered a trial of testosterone treatment in combination with lifestyle measures, weight loss and optimization of comorbidities.

<H1>Introduction

In this review, we discuss the relationship of endogenous testosterone with Type 2 diabetes, the underlying mechanisms that could mediate this relationship and the impact of exogenous testosterone treatment in men with Type 2 diabetes. The material reviewed is based on a MEDLINE search until 31 August 2018 with no start restriction, and supplemented by the authors' own databases.

<H1>The association between endogenous testosterone levels, obesity and Type 2 diabetes in men

Subnormal testosterone levels in association with non-elevated luteinizing hormone concentrations are common in men with Type 2 diabetes. Such men are characterized by normal gonadotropin responses to gonadotropin-releasing hormone stimulation, and these abnormalities were independent of diabetes duration or severity and were inversely related to BMI [1]. Pituitary-directed magnetic resonance imaging did not demonstrate structural hypothalamic–pituitary disease in these men [1]. Subsequently, it has been established that between 25% and 50% of men with Type 2 diabetes have lowered testosterone levels. An Australian study involving 580 elderly, obese men with Type 2 diabetes found that 43% had low total testosterone levels and 57% had low calculated free testosterone levels, relative to reference ranges from young, reproductively healthy men [2]. Serum testosterone was inversely related to age and BMI in these men; however, lowered testosterone was not restricted to the aged or obese, with 20% of young and 40% of lean men also having low circulating testosterone. In this cohort of men with diabetes, low testosterone predicted mortality, independent of multiple confounders [3]. A meta-analysis of 20 cross-sectional studies with a total of 2900 men (including 850 men with Type 2 diabetes), demonstrated men with diabetes had a modest reduction in total testosterone level compared with men without diabetes (-2.66 nmol/l; $P < 0.001$) [4]. This difference was less when adjusted for age, BMI or waist–hip ratio, but remained significant (-1.61 nmol/l; $P = 0.001$).

Subnormal testosterone levels are relatively uncommon in men with Type 1 diabetes, unless the men are obese. Insulin resistance is the likely common mediator of lowered testosterone levels in men with Type 1 or Type 2 diabetes, given the inverse

relationship between BMI and testosterone levels in both groups. It has been postulated that sex hormone-binding globulin (SHBG) reduction, a hallmark of insulin resistance accounts for the association between total testosterone levels and Type 2 diabetes. In a cross-sectional study of 350 Finnish men, SHBG was associated with insulin resistance independent of total testosterone, whereas the association of total testosterone with insulin resistance was nullified after adjustment for SHBG [5]. Similarly, a euglycaemic-hyperinsulinaemic clamp study in men without diabetes found that the inverse relationship with insulin resistance was more significant for SHBG than for total testosterone concentrations [6]. A Mendelian randomization study reported that SHBG-germline variants that were associated with low serum SHBG concentrations were also predictive of Type 2 diabetes risk [7]. Interestingly, SHBG may not just be a passive carrier protein for circulating sex hormones but may have biological actions that could modulate glucose metabolism, although this requires further study [7]. Moreover, not all studies are consistent; in a hyperglycaemic-euglycaemic clamp study total testosterone levels remained inversely associated with insulin resistance even after adjustment for SHBG [8] and there are reports that low free testosterone (which is not confounded by circulating SHBG concentrations) is independently associated with a diagnosis of metabolic syndrome and/or Type 2 diabetes [9].

In epidemiological studies, adjustments for BMI or waist-hip ratio diminished but did not nullify inverse associations between serum testosterone and impairments in glucose metabolism. Residual confounding cannot be excluded, as these are crude measures of adiposity. Indeed, in studies that carefully quantified body composition, the inverse relationships between circulating testosterone and measures of insulin resistance (including the hyperglycaemic-euglycaemic insulin clamp) lost significance after adjustment for visceral fat and/or truncal fat [10,11]. However, it is possible that the beneficial effects of testosterone on insulin resistance are causally mediated by reduction of central fat mass. In this case, adjusting for fat mass would represent an over-adjustment, obscuring a true biological relationship. The close reciprocal relationship of circulating testosterone with central body fat is exemplified by experimental studies alternating caloric restriction with overfeeding. These studies reported among various measures of body fat, weight change-associated changes in circulating testosterone (increase with weight loss and decrease with weight gain) most closely tracked with reciprocal changes in visceral adipose tissue mass [12,13].

In men with prostate cancer receiving androgen deprivation therapy, abdominal fat mass accumulates within 3 months, in parallel with increased insulin resistance, likely responsible for the androgen deprivation therapy-associated increased risk of Type 2 diabetes [14]. Furthermore, reduction in fat mass is one of the most consistently reported effects of testosterone treatment in clinical trials, not only in frankly hypogonadal young men, but also in older men with age-related reductions in circulating testosterone, irrespective of whether they have Type 2 diabetes or not [15]. In most prospective studies, men with low testosterone have an approximately twofold increased risk of a future diagnosis of metabolic syndrome and/or Type 2 diabetes [16]. Conversely, however, men with metabolic syndrome are at higher risk of experiencing a low testosterone level during follow-up [17]. Overall, the data suggest that the relationship between low testosterone and insulin resistance is bidirectional, with increased visceral adiposity representing an important mediator.

<H1>Mechanism of testosterone deficiency in men with Type 2 diabetes

The biological mechanisms responsible for the complex associations among low testosterone, adiposity and insulin resistance are not fully understood but are likely to operate at all levels of the hypothalamic–pituitary–testicular axis (see Fig. 1). Luteinizing hormone levels are rarely elevated in men with Type 2 diabetes and low testosterone levels, especially if they are obese [1], suggesting that the dominant level of effect is central. Furthermore, a hypothalamic defect is suggested by the observation that men have a normal increase in gonadotropins following gonadotropin-releasing hormone stimulation [1] and that obese men have reduced luteinizing hormone pulse amplitudes [19].

Given that circulating oestradiol is produced by aromatization from testosterone, it is not surprising that, in men with Type 2 diabetes, low circulating testosterone is paralleled by low oestradiol [20]. Moreover, men with Type 2 diabetes and low testosterone express lower amounts of aromatase in adipose tissue compared with men with diabetes but whose testosterone level is within the normal range [21]. Although the current evidence does not support a major role of increased oestradiol in central gonadal axis suppression, the studies are largely based on circulating oestradiol, and local (intracrine) effects cannot be fully excluded.

People who are obese have evidence of insulin resistance at the level of the central nervous system (CNS) [22] and CNS-directed insulin delivery has been reported to decrease body weight in men [23]. Mice with genetically inhibited signalling targeted

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to the CNS develop obesity and insulin resistance [24], associated with significant reductions in circulating testosterone and luteinizing hormone concentrations, but normal response to gonadotropin-releasing hormone challenge. Therefore, central insulin resistance could be one mechanism linking obesity and hypogonadotropic hypogonadism.

In preclinical studies, pro-inflammatory cytokines (e.g. tumour necrosis factor α , interleukin-1 β) have been reported to inhibit gonadotropin-releasing hormone secretion and hence decrease circulating luteinizing hormone levels *in vitro* and *in vivo* [25]. Men with Type 2 diabetes and low testosterone levels commonly have elevated C-reactive protein levels [2], suggesting that a low-grade pro-inflammatory state may contribute to the central suppression of the male gonadal axis.

The adipokine leptin plays an important role in body weight regulation and absence of the leptin gene or leptin signalling in humans results in hypogonadotropic hypogonadism and rare forms of obesity. It is hypothesized that leptin resistance common to most forms of obesity may mediate the hypogonadotropic hypogonadism seen in obese men with Type 2 diabetes. Functional leptin receptors are present in rodent Leydig cells and leptin inhibits human chorionic gonadotropin-stimulated testosterone secretion from rat Leydig cells at concentrations similar to that seen in obese men [26]. Human chorionic gonadotropin-stimulated testosterone secretion is lower in obese men and those with impaired glucose tolerance compared with normal glucose tolerance [27]. The molecular mechanism has not been elucidated but it has been hypothesized that Leydig cell steroidogenesis is impaired because of local resistance to insulin action and/or production of hormones including leptin.

<H1>Impact of testosterone treatment on glucose metabolism in men with Type 2 diabetes

Preclinical evidence suggests that testosterone may mediate changes in insulin resistance and body composition through a number of mechanisms. First, testosterone treatment is associated with a reduction in pro-inflammatory, insulin resistance increasing, cytokines [28]. In adipose tissue, testosterone treatment stimulates the expression of insulin receptor β , insulin receptor substrate-1, Akt-2 and GLUT-4 in humans and mice [29], and of β 3 adrenergic receptors on rat adipose precursor cells, leading to increased catecholamine-induced lipolysis [30]. In men, circulating testosterone correlates with mitochondrial markers of insulin sensitivity in skeletal

muscle, suggesting that some of the insulin-sensitizing effects of testosterone could be mediated by modulating signalling pathways in muscle tissue [27]. Finally, there is evidence from male mice with a deletion of the androgen receptor targeted to pancreatic β -cells that androgenic signalling augments glucose-stimulated insulin secretion in β -cells via amplifying the incretin effect of glucagon-like peptide 1 (GLP-1) [31].

In RCTs of testosterone treatment in men with Type 2 diabetes and low testosterone, treatment may improve insulin resistance but has not been shown to consistently improve diabetes control. Most trials have involved a relatively small number of men over a short period (<12 months) and have not controlled for changes in other diabetic therapies that might affect findings. There is significant heterogeneity in cohorts in terms of age, weight, baseline testosterone level, duration of diabetes and methods used to measure insulin resistance. A summary of RCTs of testosterone treatment in men with Type 2 diabetes with glycaemic outcomes is provided in Table 1 [32–42].

Reduced insulin resistance as measured by hyperinsulinaemic–euglycaemic clamp was seen with intramuscular testosterone cypionate treatment in a 24-week RCT of 44 obese men with Type 2 diabetes and hypogonadotropic hypogonadism [35]. Hyperinsulinaemic–euglycaemic clamp is considered the gold standard in assessment of insulin resistance but is expensive, laborious and unsuitable for larger scale trials. Homeostatic model assessment of insulin resistance (HOMA-IR) is more commonly used in clinical trials to calculate insulin resistance. Positive effects of testosterone treatment on insulin resistance as measured by HOMA-IR was shown in a RCT of transdermal gel in 220 men with metabolic syndrome, two-thirds of whom had Type 2 diabetes; testosterone treatment was associated with a significant reduction in HOMA-IR at 6 months (-15.2% , CI 3, 26; $P = 0.018$) [41]. Testosterone treatment did not decrease total body fat or HbA_{1c} at 6 months, during which time no changes in either glycaemic or lipid-lowering treatments were allowed. After changes in other diabetes therapies were permitted, a significant decrease in HbA_{1c} was shown at 9 months, which did not persist at 12 months. A 30-week RCT of intramuscular testosterone undecanoate involving 184 obese men with metabolic syndrome, one-third of whom had Type 2 diabetes, found a 31% reduction in HOMA-IR and significant weight loss (-4.3 kg) in the testosterone-treated group [34]. Additionally,

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significant reductions in HOMA-IR, HbA_{1c}, waist circumference and fat mass, and elevations in fat free mass were observed with testosterone treatment in a small RCT of intramuscular testosterone undecanoate in 50 obese men with metabolic syndrome, half of whom had Type 2 diabetes [40]. In a 12-month RCT of intramuscular testosterone undecanoate in 55 obese hypogonadal men with Type 2 diabetes, testosterone treatment was shown to decrease HOMA-IR and HbA_{1c} despite no significant between group difference in weight and BMI [36].

However, a number of RCTs show that testosterone treatment has a neutral effect on insulin resistance in men with Type 2 diabetes. In the BLAST study, a 30-week RCT of intramuscular testosterone undecanoate in 199 men with Type 2 diabetes [39], testosterone treatment was not associated with a change in insulin resistance as measured by homeostatic model assessment of insulin resistance model 2 (HOMA2-IR) or in body weight. A decrease in HbA_{1c} at 6 weeks with testosterone treatment was seen and maintained at 18 weeks but was not persistent at study end (estimated mean difference between groups compared to baseline -0.11%, CI -0.34, 0.13; $P = 0.36$). In a 40-week RCT of intramuscular testosterone undecanoate in 88 men with Type 2 diabetes, testosterone treatment did not reduce HOMA2-IR or HbA_{1c} despite a reduction in total fat mass [38]. An unpublished, industry-supported 26-week RCT of transdermal testosterone gel in 180 men with Type 2 diabetes did not find any reduction in HOMA-IR or HbA_{1c}, despite significant increase in lean body mass [42]. Additionally, in a 24-week RCT of transdermal testosterone gel in 43 men with Type 2 diabetes, no change was seen in insulin resistance or HbA_{1c} favouring testosterone treatment, despite a decrease in total body fat mass [37]. Finally, in a 3-year placebo controlled trial in older men without diabetes and serum testosterone < 13.9 nmol/l, testosterone treatment did not improve insulin sensitivity, as estimated by steady-state plasma glucose concentration at equilibrium during octreotide and insulin administration [43].

These conflicting results may, at least in part, be related to the different methods used to measure insulin resistance. The original HOMA-IR model used in earlier studies was calibrated to an insulin assay used in the 1970s, which showed poor specificity to insulin, and is not validated for the use of contemporary insulin assays. HOMA2-IR is the updated version of the HOMA model that is computer based and has been recalibrated for use with contemporaneous insulin assays [44]. The HOMA2-IR model accounts for variations in hepatic and peripheral glucose resistance,

incorporates renal glucose losses in the model and hence allows for its use in hyperglycaemic subjects. Calculated values and proposed normative ranges of HOMA2-IR are lower than those calculated by original HOMA-IR model [45]. A meta-analysis of seven RCTs involving 833 men with Type 2 diabetes and/or metabolic syndrome reported that testosterone treatment modestly improved insulin resistance in studies using the simple linear equation to calculate HOMA-IR but the treatment effect was not significant for RCTs using the modern HOMA2-IR model to define insulin resistance [46]. It also found that testosterone treatment did not improve HbA_{1c}.

RCTs of testosterone treatment in men with Type 2 diabetes performed to date have involved small numbers of men and were of short duration. It is not known if men with Type 2 diabetes and more marked reductions in circulating testosterone will experience greater glycaemic benefits from testosterone treatment. However, substantial reductions in circulating testosterone levels are infrequently reported in men with Type 2 diabetes; for example, in a cohort of 580 men attending diabetes clinics, only 5% had a serum testosterone < 5.2 nmol/l [2]. Therefore, markedly reduced testosterone concentrations should prompt evaluation for organic causes of hypogonadism [47]. Most RCTs have been performed in men with good to intermediate diabetes control, hence evidence is lacking as to whether men with less well-controlled Type 2 diabetes or men with prediabetes may derive more glycaemic benefit from testosterone treatment.

<H1>Impact of testosterone treatment on weight and body composition in men with Type 2 diabetes

It is well established that testosterone treatment decreases total body fat mass and increases total fat free mass in men with hypogonadism [48]. Moreover, in obese men subjected to a rigorous weight loss programme, testosterone treatment not only increased the loss of fat mass over and above the effects of caloric restriction alone, but also prevented the diet-associated loss of lean mass [49]. This positive effect on body composition is also commonly seen in RCTs of testosterone treatment in men with Type 2 diabetes (see Table 1) [32–42].

Although testosterone treatment can decrease fat mass it does not appear to substantially affect visceral adiposity in men with Type 2 diabetes. In a 40-week RCT of intramuscular testosterone undecanoate in 88 men with Type 2 diabetes, testosterone treatment resulted in a decrease in total body fat mass and abdominal

subcutaneous adipose tissue volume with no change in abdominal visceral adipose tissue volume, insulin resistance or diabetes control [38]. This finding has been confirmed in a subsequent 24-week RCT of transdermal testosterone gel in 43 men with Type 2 diabetes [50]. Similarly, in a 24-week trial of intramuscular testosterone cypionate in 44 men with Type 2 diabetes and hypogonadotropic hypogonadism [35], men randomized to testosterone treatment had a significant decrease in subcutaneous fat mass with no change in visceral fat mass compared with the placebo group, although in this study a reduction in insulin resistance was noted. Experimental castration studies in men showed that testosterone replacement prevented gain of subcutaneous but not visceral fat, although no data on glucose metabolism were provided [51]. These observations may explain in part why despite testosterone treatment being associated with what would be expected to be metabolically favourable effects on total fat mass and lean mass, treatment may not be associated with improved insulin resistance or glycaemic control. However, not all data are consistent; in the aforementioned RCT in obese men [49], testosterone treatment reduced visceral adiposity above and beyond the effects of weight loss alone.

<H1>Impact of testosterone treatment on sexual function in men with Type 2 diabetes

Erectile dysfunction and low libido are common but non-specific complaints in men with lowered testosterone. A cross-sectional study of 355 men with Type 2 diabetes and lowered testosterone levels documented that 64% had self-reported low libido, and 74% erectile dysfunction. Interestingly, men with normal testosterone concentrations had similarly high levels of low libido (48%) and erectile dysfunction (65%), and sexual symptoms tracked more closely with increasing age rather than lower testosterone level [52].

A meta-analysis of 41 RCTs of testosterone treatment (involving 1930 men) reporting on sexual function [53] found that treatment was associated with an improvement in overall erectile function (effect size 0.82; CI 0.47, 1.17; $P < 0.0001$) in men with hypogonadism. Testosterone treatment was also associated with significant improvement in sexual-related erectile function, libido, orgasm, nocturnal erection, frequency of intercourse, overall sexual satisfaction and overall sexual function in hypogonadal men. Six of the trials involved in this meta-analysis included men with a diagnosis of Type 2 diabetes. Meta-regression analysis found that the effect size of testosterone treatment on erectile function was attenuated by prevalent Type 2

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diabetes, whereas the improvement in libido and orgasm was not lessened in men with diabetes. A subsequent meta-analysis of six RCTs of testosterone treatment in 587 men with Type 2 diabetes confirmed an improvement with treatment in sexual desire (random effects pooled effect size 0.314; 95% CI 0.082–0.546) and erectile function (effect size 0.203; 95% CI 0.007–0.399) [54]. Significant heterogeneity exists in trials conducted in relation to baseline and treatment testosterone levels; formulation and dose of testosterone treatment, and sexual function were investigated with different tools.

Phosphodiesterase 5 inhibitors have benefits on erectile function irrespective of gonadal status [55]. In the aforementioned meta-analysis, 12 of the trials evaluated the effect of testosterone add-on treatment to phosphodiesterase inhibitor therapy with a positive effect of testosterone treatment seen in uncontrolled studies but not in placebo controlled trials [53].

Testosterone treatment may be a useful therapy in hypogonadal men with Type 2 diabetes and sexual dysfunction, although the treatment effect may be attenuated compared with men without diabetes. This is possibly because, especially in men with long-standing diabetes, the contribution of neurovascular disease to erectile dysfunction becomes more significant. Moreover, testosterone's utility as an adjunctive treatment to phosphodiesterase 5 inhibitor therapy remains insufficiently understood.

<H1>Impact of testosterone treatment on constitutional symptoms in men with Type 2 diabetes

Androgen deficiency is accompanied by a multitude of non-specific symptoms. Ageing and obese men with Type 2 diabetes often report similar symptoms. In a cross-sectional study of 350 men with Type 2 diabetes, up to 70% of men with lowered total testosterone (< 8 nmol/l) reported symptoms compatible with androgen deficiency; however, up to 55% of men with a normal total testosterone level (> 12 nmol/l) also had such symptoms [52]. Similarly, in a retrospective cohort study of 329 men (115 with Type 2 diabetes), the weak inverse association between testosterone concentrations and androgen deficiency-like symptoms was nullified after adjustment for age and central obesity [56]. Therefore, it is unknown in men with Type 2 diabetes whether reported constitutional symptoms are causally related to the modest hypotestosteronaemia or are a consequence of age-related comorbidities.

RCTs have reported inconsistent effects of testosterone treatment on androgen

deficiency-like symptoms in men with Type 2 diabetes. In the Testosterone Trials, testosterone treatment in older men with hypogonadism (of whom one-third had diabetes) did not improve fatigue or increase vitality [57]. A meta-analysis of seven RCTs involving 833 men with Type 2 diabetes and/or metabolic syndrome reported no change in symptoms as measured by ageing male symptom score with testosterone treatment [46].

<H1>Adverse effects of testosterone treatment

Common adverse events due to testosterone treatment include acne, oily skin, breast tenderness, decrease in high-density lipoprotein cholesterol, injection pain and/or skin irritation [47]. An increase in haematocrit is the most common adverse event reported in RCTs of testosterone treatment and is more frequently observed in older men. Reported neuro-occlusive events with treatment are very low [47].

<H2>Prostate

Testosterone treatment is contraindicated in men with prostate cancer and it is recommended that assessment of prostate cancer risk be made in all men aged ≥ 40 years before initiating treatment [47]. Although endogenous testosterone concentrations are not associated with prostate cancer risk in observational studies [58], testosterone treatment induces an increase in prostate-specific antigen levels. In some men, this may prompt prostatic biopsy and increased detection of subclinical prostate cancer. Many older men have subclinical prostate cancer [59] and it is likely that some men receiving testosterone treatment and having prostate screening will face greater risks associated with biopsy and cancer treatment despite many not destined to develop progressive or symptomatic malignancy. For men who choose prostate monitoring, digital rectal exam and prostate-specific antigen measurement should be performed at baseline, 3–12 months after initiation of testosterone treatment and thereafter individualized, taking into account the man's prostate cancer risk [47].

<H2>Cardiovascular

Whether testosterone treatment in men is beneficial, harmful or neutral with regards to cardiac health is unknown. The US Food and Drug Administration (FDA) conducted an extensive review examining the potential cardiovascular dangers of testosterone treatment and concluded that the studies examined have 'significant limitations that weaken their evidentiary value for confirming a causal relationship between testosterone treatment and cardiovascular outcomes' [60]. However, the

FDA stipulated that labelling information about a possible increased risk of cardiovascular events must be added to testosterone products. The European Medicines Agency, however, concluded that there is no consistent evidence of an increased risk of cardiovascular disease with testosterone treatment [61].

Early publications suggested positive cardiac effects; pharmacological doses of testosterone have been shown to produce coronary artery vasodilation during coronary angiography or exercise stress testing [62], and were associated with reduced angina frequency in elderly men [63]. Testosterone can modulate the lipid transport mechanisms of macrophages, increase *ex vivo* platelet aggregation, and decrease fibrinogen, lipoprotein A, low-density lipoprotein and triglycerides [64] which may be important in atherosclerosis development.

Androgen deprivation therapy-induced hypogonadism in men with prostate cancer is associated with increased cardiovascular events [65], as is anabolic androgen abuse. A trial of testosterone gel in 200 elderly frail men at high risk of cardiovascular disease [66] was terminated prematurely due to a greater frequency of cardiovascular adverse events with treatment. A subsequent RCT in a similar study cohort did not confirm these findings [67]. More recently in the Testosterone Trials involving 170 older men with hypogonadism (one-third of whom had Type 2 diabetes) testosterone treatment was associated with a significantly greater increase in coronary artery non-calcified plaque volume [68], the clinical implications of which are unknown. In contrast a 3-year RCT in older men did not find a difference in atherosclerosis progression (quantified by common carotid artery intima media thickness and computerized tomography) between men receiving testosterone and placebo [69]. Meta-analyses have failed to show consistent results and have inadequate power to detect an association between treatment and major adverse cardiac events [70–72]. Retrospective analyses of databases are also inconclusive, variously limited by lack of randomization, failure to adjudicate cardiovascular events prospectively, healthy user effects and heterogeneity with respect to clinical characteristics of participants, as well as testosterone treatment, including dosing and intervention duration.

Given that cardiovascular disease is the leading cause of death of men in the western world, even small increases in the incidence of cardiovascular disease with testosterone treatment would likely outweigh any benefits of treatment. Men with Type 2 diabetes are at high risk of cardiovascular disease and hence there is need for caution.

Several observational studies have reported that, in men with Type 2 diabetes, low testosterone is a strong independent risk factor of mortality, after adjustment for multiple confounders [73]. Similar associations of low testosterone with increased mortality have also been reported in men with other chronic conditions, such as cardiovascular, respiratory or renal disease, or cancer [74]. In two retrospective studies of men with low testosterone with [73] and without diabetes [75], testosterone treatment was associated with reduced mortality. The retrospective observational design of such studies, however, carries a risk of selection bias due to the non-random assignment of testosterone treatment and, by design, observational studies cannot confirm a causal relationship.

<H1>Impact of standard treatments for Type 2 diabetes on testosterone levels

Treatment with standard anti-hyperglycaemic therapies in men with Type 2 diabetes may produce changes in serum testosterone levels. In a multicentre, 12-week observational study of 176 obese men with poorly controlled Type 2 diabetes, exenatide and metformin treatment resulted in significant increases in testosterone levels compared with glimepiride and metformin, despite similar improvements in glycaemic control [76]. Changes in testosterone levels with exenatide treatment were closely related to the reduction in waist circumference and were associated with improvement in sexual function. GLP-1 agonists such as exenatide are known to reduce body weight through a variety of mechanisms including induction of brown adipose tissue thermogenesis, browning in white adipose tissue, increasing satiety, reducing food intake and retarding gastric emptying. Exenatide may have a direct impact on GLP-1 receptors in the testis and GLP-1 may protect the function of endothelial cells in the corpus cavernosum and regulate the Akt/eNOS signalling pathway improving erectile function [77]. The effect of sulphonylureas [76] and metformin [78] on testosterone levels in men with Type 2 diabetes has been inconsistent, whereas pioglitazone treatment is associated with a reduction in testosterone level in men with Type 2 diabetes [79]. The clinical relevance of these changes in testosterone levels is unknown.

Weight reduction is a critical aspect of diabetes management. In prospective studies of obese men, 10% lifestyle-mediated weight loss increased total testosterone by ~3 nmol/l, whereas more marked weight loss (~30% by bariatric surgery) increased testosterone by >10 nmol/l; in addition to increases in free testosterone of 12% to 43% [80]. Even modest (5 kg) weight loss in only mildly overweight men has been

reported to significantly increase circulating testosterone [12]. However, not all data are consistent, in a recent RCT of testosterone treatment in combination with a rigorous weight loss programme in middle aged and older obese men, the increase in serum testosterone in men receiving placebo was relatively modest, 2.9 nmol/l despite a 11% loss of body weight, and not sustained at follow-up 18 months after trial completion [81].

<H1>Conclusion: clinical considerations in the management of men with low testosterone levels and Type 2 diabetes

Important considerations for the physician in the management of men with low testosterone levels and Type 2 diabetes are summarized in [Box 1](#).

Although men with Type 2 diabetes commonly have low testosterone levels, it remains unclear as to the appropriateness of long-term testosterone treatment in this population. Treatment effects in RCTs have been mixed (Table 1), however, long-term (> 5 years) registry studies [82] have reported more robust improvements in glycaemic control compared with clinical RCTs. Although some authorities posit that the better outcomes in these registry studies may be related to the longer duration of testosterone treatment, such studies were neither randomized nor blinded. The Testosterone for Type 2 Diabetes (T4DM) trial (ACTRN 12612000287831) is a large, multicentre 2-year RCT in progress [83] which will inform of the utility or otherwise of testosterone treatment in prevention of Type 2 diabetes in men with prediabetes.

Based, on current evidence, we recommend that asymptomatic men with Type 2 diabetes should not have testosterone levels checked routinely. If a man with Type 2 diabetes has sexual dysfunction or other symptoms of hypogonadism then a screen should be offered, as it would in a man irrespective of diabetes status. A low testosterone level should always be confirmed by a second measurement before testosterone deficiency is diagnosed [47].

It is likely that testosterone levels will decrease gradually with ageing and it is reasonable that men with Type 2 diabetes are screened for clinical evidence of testosterone deficiency on a periodic basis.

In obese/overweight men, weight loss is an important aspect of diabetes treatment and may increase testosterone levels in men with lowered levels. Weight loss and standard anti-hyperglycaemic treatments should be recommended to all men with Type 2 diabetes, irrespective of whether they have low testosterone levels or not. Consistent with international testosterone treatment guidelines [47], we recommend against the

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routine treatment with testosterone of asymptomatic men with Type 2 diabetes and low testosterone levels.

The situation in 'symptomatic' men is complex because symptoms are non-specific and especially in men with borderline low testosterone, which constitutes the vast majority of men with diabetes, may be caused by comorbidities rather than the lowered testosterone. In such men, optimization of comorbidities, stopping offending medications (e.g. opioids and glucocorticoids) where applicable, and weight loss should be the first line approach. As reviewed elsewhere [84], if successful this strategy can provide symptomatic (and other health benefits), and lead to increases in circulating testosterone. In addition, specific concerns such as sexual dysfunction, low mood and end organ deficits (e.g. osteoporosis) can be treated with targeted treatments (phosphodiesterase type 5 inhibitor, antidepressants, anti-resorptives).

However, in practice, these general interventions to reverse functional hypogonadism may not be successful, either because they cannot be implemented (e.g. cessation of opioids) or they are not sustained (e.g. weight loss). In others, symptoms and low testosterone levels may persist even despite successful implementation of these measures. Indeed, although the evidence is limited, the studies discussed above suggest that testosterone treatment may augment the benefits of successful lifestyle interventions [49,85].

International guidelines (not specifically directed at men with Type 2 diabetes) on testosterone treatment in older men with low testosterone show some differences in recommendations. Australian guidelines [86] recommend against treatment for indications other than organic hypogonadism, whereas American guidelines give an option in carefully selected older men, in the context of a shared decision between clinicians and men with low testosterone provided they are fully informed as to the benefits and risks [87]. British guidelines [88] state that symptomatic men with a confirmed testosterone of < 8 nmol/l 'usually require testosterone treatment', whereas those with a level between 8 and 12 nmol/l 'might require a trial' of treatment. Finally, European Association of Urology Guidelines [89] emphasize that obesity and poor general health are the main causes of late-onset male hypogonadism, however, it 'may' be treated with testosterone therapy, noting that the indications and risks for testosterone treatment are yet to be fully defined.

In appropriately selected men, e.g. those with significant symptoms and low testosterone, testosterone treatment could be started concomitantly to initial general

interventions discussed above, or after these measures fail. It is our practice to inform men with functional hypogonadism about the absence of high-level evidence regarding long-term benefits and risks [82]. We also recommend that clear individual-specific goals should be identified, and, if these goals are not achieved after a sufficient course of effective treatment, testosterone treatment should be stopped. Based on some evidence, men can be reassured that the risk of sustained iatrogenic gonadal axis suppression if testosterone treatment is ceased after 12 months is likely low [81]. Contraindications to testosterone treatment include planning fertility in the near term, a personal history of breast or prostate cancer, presence of a palpable prostate nodule or induration, prostate-specific antigen > 4 ng/ml (without further urological evaluation), elevated haematocrit, untreated severe obstructive sleep apnoea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia [87]. In men in whom low serum testosterone contributes to clinical manifestations, symptoms should generally improve within 3–6 months after initiation of testosterone treatment, provided that adequate circulating testosterone concentrations, targeted to the mid-normal range for healthy young men, are achieved and maintained [87]. However, with respect to improvements in other manifestations, such as sarcopaenia or osteoporosis, a longer duration of testosterone treatment may be required. During testosterone treatment, monitoring for adverse effects includes, within 3–6 and then 12 months after initiation, and subsequently at least annually, clinical assessment, haematocrit monitoring and individualized prostate health monitoring, as further outlined in the US Endocrine Society guidelines [87]. Reassuringly, in the 12-month Testosterone trials [57], which included carefully selected symptomatic men with a confirmed low testosterone and followed US Endocrine Society guidelines with respect to both contraindications to and monitoring during treatment, adverse events were similar between testosterone- and placebo-treated men.

In conclusion, although in recent years, progress has been made to better understand mechanistic and clinical aspects of the low testosterone–diabetes relationship, many questions remain. For example, the extent to which low testosterone is a pathogenic mediator of dysglycaemia, rather than primarily a marker of poor health, remains unknown. Moreover, the long-term benefit–risk ratio of testosterone therapy with respect to clinically important outcomes in older men without organic hypogonadism due to medical disease of the hypothalamic–pituitary–testicular axis, whether diabetic

or not is also not known, due to the lack of adequately powered long-term trials. As such, this area remains a fertile ground for further research.

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FIGURE 1 Schematic demonstrating relationship between visceral fat and testosterone: a self-perpetuating cycle promoting insulin resistance [89]. CNS, central nervous system; SHBG, sex hormone-binding globulin; HPT, hypothalamic–pituitary–testicular.

Table 1. Randomized controlled trials of testosterone therapy in men with Type 2 diabetes or the metabolic syndrome with glycemic outcomes

Lead author	n	Age (years)	BMI (kg/m ²)	HOMA-IR baseline ^h	HbA _{1c} baseline [mmol/ mol (%)]	Duration (weeks)	Drop- out (%)	Total testost erone baseli ne	HOMA-IR (% change) ^d	HbA _{1c} (%) ^d	Body composition ^d
Kapoor [32]	24	64	33	4.8	56 (7.3)	12	0	8.6	−39* ^j	−0.37* ^j	Waist circumference: −1.6 cm* ^j BMI: No change Body fat: No change ^e
Gopal [33]	22	44	24	5.5	53 (7.0)	12	0	10.1	NC	NC	Waist circumference: No change BMI: No change
Kalinchenko [34]	184 ^a	52	35	5.4	NR	30	7	6.7	NC	NR	Waist circumference: −6 cm* BMI: −1.32* Weight: −4.3 kg*
Dhindsa [35]	44 ^g	55	39	4.1	53 (7.0)	24	23	8.8	−34*	NC	Waist circumference: No change BMI : No change Increased lean mass: +2.6 kg* ⁱ Decreased subcutaneous fat mass: −2.4 kg* ⁱ Abdominal visceral adipose tissue volume: No change ⁱ
Groti [36]	55	60	33	11.5	65 (8.1) ^h	52	0	7.6	−41*	−0.94*	Waist circumference: −1.58 cm* BMI: −0.80*

Magnussen [37]	43	61 ^h	31	3.7	48 (6.5) ^h	24	9	7.1	NC	NC	Waist circumference: No change BMI: No change Decreased total body fat mass: −1.2 kg ^{*i} Increased lean mass: +1.9 kg ^{*i} Decreased abdominal subcutaneous adipose tissue volume ^{*i} Abdominal visceral adipose tissue volume: No change
Gianatti [38]	88	62	31.5 ^h	2.1 [†]	51 (6.8) ^h	40	15	8.7	NC	NC	Waist circumference: No change BMI: No change Decreased total body fat mass: −2.4 kg ^{*ij} Increased total lean mass: +2.1 kg ^{*ij} Decreased abdominal subcutaneous adipose tissue volume ^{*ij} Abdominal visceral adipose tissue volume: No change ⁱ
Hackett [39]	199	62	33	4.1 [†]	61 (7.7) ^h	30	4.5	9.2	NC	NC	Waist circumference: −2.5 cm [*] BMI: No change
Aversa [40]	50	57	30.2 ^h	4.3	49 (6.6) ^h	52	8	8.3	−49 [*]	−0.2 [*]	Waist circumference: −8.5 cm [*] Decreased total body fat mass: ^{*i} Increased free fat mass: +4.8 kg ^{*i}

Jones [41]				5.9							Waist circumference: No change
	220 ^b	60	33 ^h		55 (7.2) ^c	26	29	9.4	-15 ^{*j}	NC	BMI: No change
											Body fat: No change ^e
Solvay				NR							Increased total lean mass:
Pharmaceuticals [42]	180	NR	NR		53-80 (7-9.5)	26	11	<13	NC	NC	+1.4 kg ^{*f}

^aMen had a diagnosis of metabolic syndrome: n = 111 (60%) also had diabetes.

^bMen had either diabetes (n = 137) and or metabolic syndrome.

^cMen with diabetes subgroup.

^dPer cent change relative to baseline.

^eMeasured by bioelectrical impedance.

^fMethodology not reported.

^gData only for men who completed.

^hData for testosterone group.

ⁱMeasured by DXA+MRI abdomen.

^jChange from baseline compared to placebo.

*P<0.05.

Testosterone was measured by immunoassay in these studies, and body composition changes were inferred from anthropometric, DXA or bioelectrical impedance measurements as indicated.

NR, not reported; NC, no change (P > 0.05). Adapted and updated from Giannatti et al. [38]. HOMA-IR refers to reported values calculated using the original HOMA-IR equation (fasting insulin in mU/l × fasting glucose in mM)/22.5.

†Two trials [38,39] employed the computer-based HOMA2-IR model as indicated.

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