Role of testosterone in men with type 2 diabetes

SABASHINI K. RAMCHAND BMedSci, MB BS
MATHIS GROSSMANN MD, PhD, FRACP

Older, obese men with type 2 diabetes commonly present with nonspecific symptoms consistent with androgen deficiency and modestly reduced testosterone levels. Lifestyle measures, especially weight loss and optimisation of diabetes control and comorbidities such as sleep apnoea, can increase and sometimes even normalise testosterone levels in such men. Recent randomised clinical trials of testosterone therapy in men with diabetes and low testosterone levels without organic hypogonadism have failed to show a consistent benefit in symptoms or glycaemic control.

Up to 50% of ageing, obese men presenting to the diabetes clinic have lowered testosterone levels relative to reference ranges that are established in healthy young men. Many of these older, obese men have symptoms consistent with androgen deficiency such as fatigue and sexual dysfunction. However, such symptoms are nonspecific and may well be due to comorbidities rather than being caused by what are typically only modest reductions in serum testosterone levels.

A large study in men with type 2 diabetes showed that 50 to 75% of men who had a serum total testosterone level of less than 8 nmol/L reported low libido, erectile dysfunction and fatigue.[1] However, 50 to 55% of men with clearly normal testosterone levels (above 12 nmol/L) also reported these symptoms. Symptoms were more closely linked to increasing age than to testosterone levels suggesting that these nonspecific symptoms may be a consequence of ill health due to age-related accumulation of comorbidities.[1]

Key points

- **Measurement of testosterone levels in men with type 2 diabetes should not be performed routinely, but instead be targeted to men in whom significant androgen deficiency is suspected clinically.**
- **Men with unequivocally low testosterone levels should be evaluated for an underlying pathological cause. It should not be assumed that hypogonadism is a consequence of type 2 diabetes.**
- **First-line management in the older, obese man with type 2 diabetes and low-normal testosterone levels should be the optimisation of lifestyle measures and glycaemic control, using established antidiabetic medications.**

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Dr Ramchand is an Endocrine Advanced Trainee, Endocrine Unit, Austin Health, Melbourne. Associate Professor Grossmann is a Consultant Endocrinologist and Head of Clinical Andrology, Endocrine Unit, Austin Health, Melbourne, and Associate Professor, Department of Medicine Austin Health, The University of Melbourne, Melbourne, Vic.

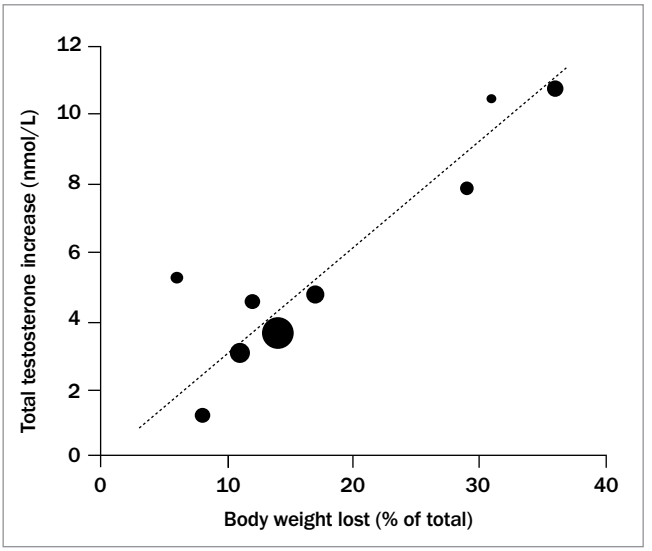


Figure. Effect of weight loss on testosterone levels. Each data point refers to an individual weight loss study, and the size of the data point is proportional to the size of the study, ranging from 10 to 58 men. For individual references see reference 3.

Most of the evidence suggests that low testosterone levels is a biomarker of poor health, and that the reduced testosterone level is primarily a consequence of insulin resistance and obesity.[2] Furthermore, randomised controlled clinical trials of testosterone therapy, discussed in more detail below, have so far not demonstrated consistent symptomatic or glycaemic benefits in men with diabetes and low testosterone levels without organic hypogonadism.

It is important to note that only a very small proportion of men with diabetes and low testosterone levels will have classic hypogonadism due to organic hypothalamic–pituitary–testicular axis pathology; however, this is an important diagnosis not to be missed.

Diagnostic assessment

If androgen deficiency is suspected, clinical assessment should look for specific features such as gynaecomastia, loss of sexual hair and small testes. Fatigue, sexual dysfunction and reduced muscle bulk are nonspecific and can be caused by almost any chronic disease.

Testosterone levels should be measured only if there is clinical suspicion of androgen deficiency. The initial diagnostic test is a fasting total testosterone level drawn before 10 am in a medically stable patient. This is because food intake (due to unknown mechanisms), acute illness (due to gonadal axis suppression) or a blood test later in the day (due to circadian rhythmicity) can give a misleadingly lower result.

Population-based studies have shown that men with diabetes have total testosterone levels 2 to 3 nmol/L lower than age- and BMI-matched men without diabetes.[3] The average total testosterone level in older, obese men with type 2 diabetes is about 10 nmol/L.[3] Therefore, a total testosterone level of more than 8 to 10 nmol/L generally rules out significant androgen deficiency and these men are very unlikely to have underlying organic hypothalamic–pituitary–gonadal axis pathology. However, there is variability between different testosterone assay, and 8 to 10 nmol/L is to be understood as a general guide only, rather than a dogmatic cut-off. In addition, testosterone levels must be interpreted in light of the clinical picture, including the man's age, BMI and comorbidities. Indeed, obesity is one of the strongest correlates of low testosterone levels, especially in younger men.[2,3] Modest overweight predominantly decreases total testosterone levels secondary to decreases in sex hormone binding globulin (see Figure), but marked obesity may lead to functional hypogonadism due to pituitary suppression by adipose tissue-derived factors.

Although a normal testosterone level does not need to be repeated, a low total testosterone level should be confirmed, because about 30% of men with an initially low level have normal levels on repeat testing. Modest reductions in total testosterone are usually due to a reduction in sex hormone binding globulin, consequent to insulin resistance. If total testosterone levels are borderline, a normal calculated free testosterone (which takes sex hormone binding globulin into account) can therefore be reassuring that such men do not have androgen deficiency. However, given that the age-related decline of free testosterone is steeper than that of total testosterone, a low free testosterone level should be used with caution to confirm hypogonadism in older men because the risk of overdiagnosis is substantial.

Markedly reduced total testosterone levels are uncommon in men with diabetes. In a large Australian cohort of men with diabetes, levels of less than 5.2 nmol/L were seen in only 5% of patients.[4] Unequivocally low testosterone levels require a tailored, individualised work up to exclude defined causes of primary or secondary testicular failure (so called organic hypogonadism). This may include measurement of gonadotrophins, iron studies and, in the setting of low gonadotrophin levels, measurement of prolactin levels and pituitary imaging.

In general, a low testosterone level is more suggestive of hypogonadism the younger, healthier and leaner the man is, but is much less predictive in older, obese men with chronic disease (such as diabetes) and nonspecific symptoms.

First-line management

The key response to the ageing, obese man with type 2 diabetes and lowered testosterone levels but without organic hypogonadism should be implementation of lifestyle measures, especially weight loss, and optimisation of glycaemic control and other comorbidities. In these men, the hypothalamic–pituitary–gonadal axis suppression is functional and in principle reversible. If successful, these measures can increase testosterone levels and result in other health benefits. In obese men, loss of 10% of body weight increases total testosterone levels by 3 nmol/L, which may be sufficient to normalise the modest reductions in testosterone levels commonly seen in these men.[3] Similarly, improvement of glycaemic control,

especially in men with poorly controlled type 2 diabetes, treatment of obstructive sleep apnoea or cessation of certain medications (e.g. opioids or glucocorticoids) can increase the circulating testosterone levels. In addition, there is evidence that weight loss can improve sexual function, the most common reason why men seek testosterone treatment.[5] An approach to the management of men with diabetes with suspected androgen deficiency is summarised in the flowchart.

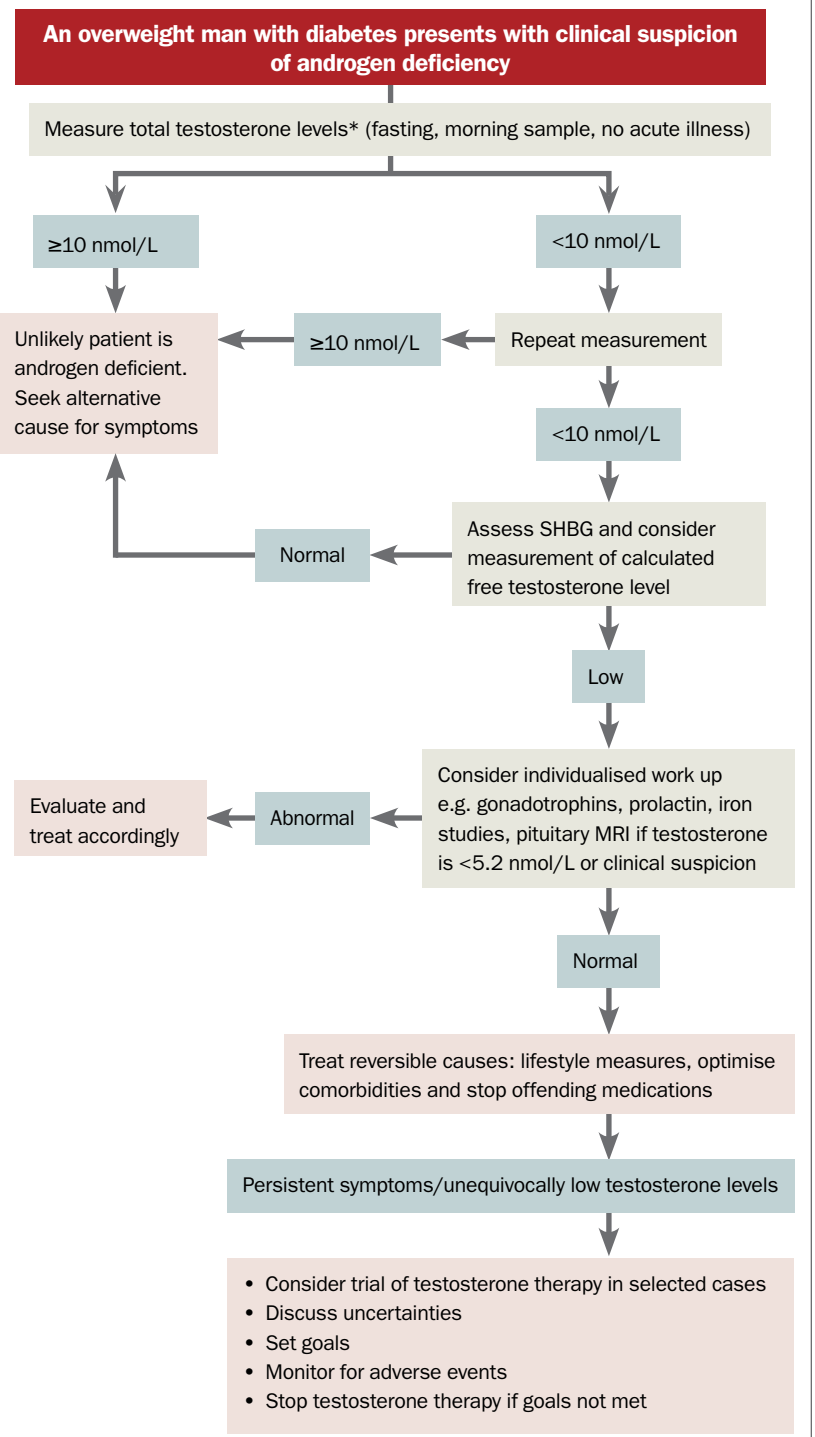
Considerations regarding testosterone treatment

It is widely agreed that men with organic hypogonadism due to established pituitary or testicular disease should be treated with testosterone replacement irrespective of whether they have type 2 diabetes or not. Contraindications to therapy (e.g. prostate cancer) are well known but less so is the desire for paternity; this must be considered before initiation of treatment because testosterone therapy can decrease fertility.

By contrast, the risk-to-benefit ratio of testosterone treatment in men without organic hypogonadism is not known. A recent Australian randomised controlled trial has shown that testosterone treatment, given to older (average age 62 years) obese (average BMI 32.5 kg/m^2) men with type 2 diabetes did not improve measures of insulin resistance or glycaemic control (assessed by HbA_{1c}).[6] This was despite modest changes in body composition – a 2 kg gain of muscle mass and 2 kg loss of fat mass – that might have been expected to be metabolically favourable. In addition, testosterone treatment did not improve constitutional symptoms (such as fatigue, well-being or poor sleep) or sexual dysfunction in these men.[7] At baseline, symptoms correlated with comorbidities, but not with testosterone levels, suggesting that symptoms are driven by comorbidities rather than low testosterone levels, providing a potential explanation why testosterone treatment did not provide a symptomatic benefit.[7]

A recent meta-analysis of all published randomised controlled trials in men with type 2 diabetes without classic hypogonadism found no evidence that testosterone treatment improves HbA_{1c} or constitutional symptoms.[8] Although

Approach to suspected androgen deficiency in men with type 2 diabetes



* The testosterone level below which work up and treatment should be considered needs to be individualised according to the clinical picture and patient characteristics. For a given testosterone level, obese older men with multiple comorbidities are less likely to have significant organic pathology, and less likely to respond to testosterone treatment than younger, leaner men with fewer comorbidities.

Abbreviation: SHBG = sex hormone binding globulin.

there was a modest improvement in insulin resistance with testosterone therapy, the clinical significance remains unclear. Overall, existing randomised controlled trials have been relatively small and short term.

Large, well-designed, randomised controlled trials are required to clarify whether testosterone treatment has clinical benefits in men without classic hypogonadism. One such important trial is the Testosterone for the prevention of Diabetes Mellitus (T4DM), which is an Australian multicentre NHMRC-funded study, and is the largest worldwide. This randomised controlled trial investigates whether testosterone therapy, in addition to a lifestyle program (administered by weight watchers), can prevent the development of type 2 diabetes in high-risk men. This trial is currently open for recruitment in all Australian capital cities, and can be accessed at www.t4dm.org.au.

Given the paucity of clinical trials in older men, the potential harms of testosterone treatment in these men are not well characterised. Older men with type 2 diabetes commonly have significant comorbidities and may be at higher risk of adverse outcomes of testosterone therapy compared with younger men receiving testosterone replacement for pathological androgen deficiency. In particular, cardiovascular events (such as myocardial infarction or stroke) and prostate events (such as prostate cancer or hypertrophy) remain a concern, and their true risk is not known.[9]

Therefore, in men with diabetes without organic hypogonadism, testosterone treatment should only be considered in carefully selected cases, when first-line measures fail, after explicit discussion of the uncertainty regarding the risk-to-benefit ratio of testosterone therapy. Outside clinical trials, indications for testosterone therapy in men with type 2 diabetes should be no different from those in men without type 2 diabetes. Treatment, if considered, should be targeted to men with persistent symptoms and persistently low testosterone levels.

In response to the marked increase in testosterone prescribing to older men, and given uncertainty regarding the risk-to-benefit ratio of testosterone therapy,[10] the recently updated PBS guidelines for subsidised testosterone treatment in men without organic hypogonadism have been tightened. This now applies to men older than 40 years and a total testosterone level of less than 6 nmol/L (documented on more than one occasion, OR testosterone level between 6 and 15 nmol/L with a high luteinising hormone level). Treatment can only be prescribed by, or in conjunction with, a specialist endocrinologist, urologist or registered member of the Australian Chapter of Sexual Health Medicine.

If a trial of testosterone treatment is considered, clear patient-specific goals agreed on by the practitioner and the patient should be determined at the onset. The patient should be informed that if the goals are not met, testosterone treatment will be stopped. Given that symptoms improve within one to three months, a three- to six-month trial is usually of sufficient duration to determine benefit. During treatment, risk should be minimised by following a standardised monitoring plan.[11] In cases of uncertainty, referral of the patient to an endocrinologist may be useful.

Conclusion

A low testosterone level in men with diabetes is a risk marker of poor health and should prompt the assiduous care of comorbidities.

Clinical trials of testosterone treatment in men with diabetes without organic hypogonadism have not provided evidence that testosterone treatment leads to clinically important benefits. More trials are needed to better evaluate the risks and benefits of testosterone treatment. Until better evidence is available, testosterone treatment should be individualised and be preferentially selected for men with symptoms and unequivocally low testosterone levels that persist after a trial of lifestyle measures and after optimisation of comorbidities. **ET**

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