A practical guide to the assessment and management of testosterone deficiency in adult men

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Testosterone deficiency is increasingly common and has significant health implications, but it can be challenging to diagnose and treat. Here the authors present a summary of a recent update to the British Society for Sexual Medicine (BSSM) guidelines on male adult testosterone deficiency.

Testosterone deficiency is an increasingly common problem with significant health implications, but its diagnosis and management can be challenging. A multidisciplinary panel from the BSSM reviewed the available literature on testosterone deficiency and have provided evidence-based statements for clinical practice, as an update to the previous 2017 version.[1]

This search revealed 1714 articles, including 52 clinical trials and 32 placebo-controlled randomised controlled trials. In the full version, a total of 25 statements are provided, relating to five key areas: screening; diagnosis; initiating testosterone therapy; benefits and risks of testosterone therapy, and follow-up. Seven statements are supported by level 1 evidence, eight by level 2, five by level 3, and five by level 4.

Recent studies have demonstrated that low levels of testosterone in men are associated with increased risk of incident type 2 diabetes mellitus, worse outcomes in chronic kidney disease and COVID-19 infection with increased all-cause mortality, along with significant quality of life implications. The BSSM guidelines should help practitioners to effectively diagnose and manage primary and age-related testosterone deficiency. This short version was developed to make the information more easily accessible, and contains all the key points.

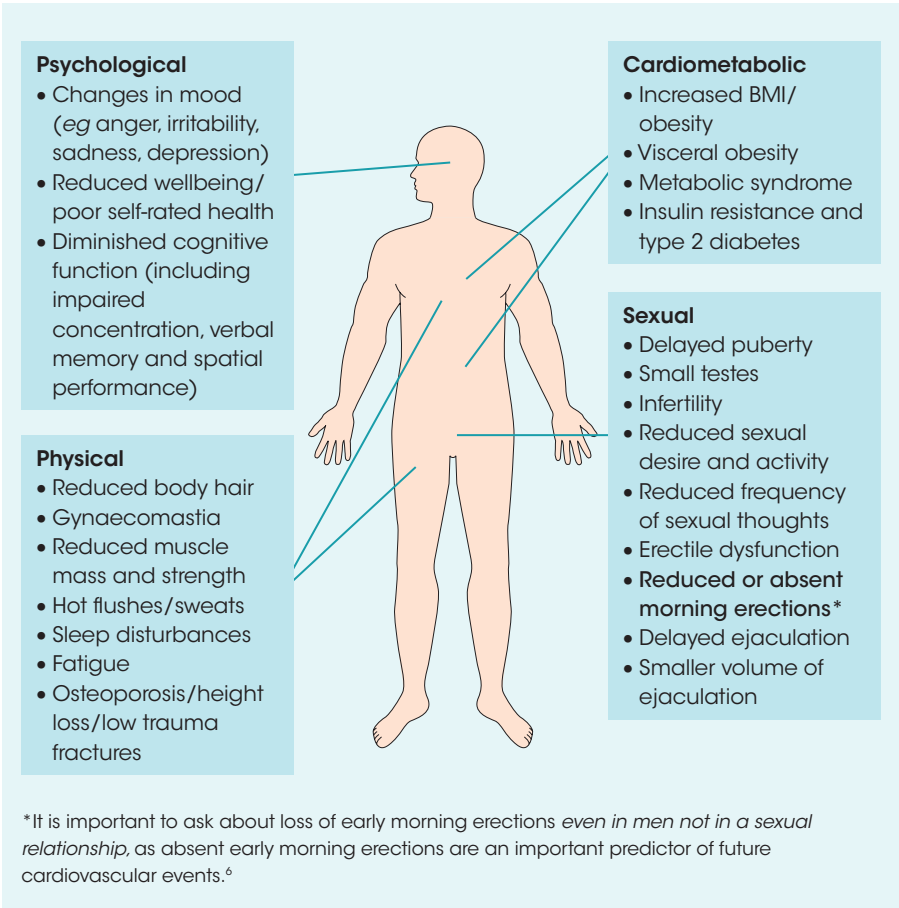


Figure 1. Clinical signs and symptoms suggestive of testosterone deficiency[2,5–8]

Why does it occur?

Testosterone deficiency, also known as hypogonadism, may result from:[2–4]

- Problems with the testes (primary hypergonadotropic testosterone deficiency)
- Problems with the hypothalamus and pituitary gland (secondary hypogonadatropic testosterone deficiency)
- Problems with the hypothalamus/ pituitary and testes (combined primary and secondary testosterone deficiency)
- Impaired action/suppression of testosterone, especially with medication such as opiates.

How is it diagnosed?

The diagnosis of symptomatic testosterone deficiency requires the presence of characteristic signs and symptoms (Figure 1) PLUS reduced

serum concentrations of total testosterone or free testosterone.[5]

The three most common symptoms of testosterone deficiency are erectile dysfunction, loss of early morning erections and low sexual desire. Men often present with sexual dysfunction and a desire for treatment. It is important to ask about loss of early morning erections, *even in men not in a sexual relationship*, as absent early morning erections are an important predictor of future cardiovascular events.[6]

Who should be screened?

Screening for testosterone deficiency should be undertaken in all men:

- With consistent and multiple signs of testosterone deficiency
- Presenting with erectile dysfunction/ loss of spontaneous erections or reduced sexual desire (even without a sexual partner)
- With type 2 diabetes, chronic kidney disease and body mass index (BMI) >30/m^2 and/or waist circumference >102cm
- On long-term opiate, antipsychotic or anticonvulsant medication.

History taking

When taking a medical history:

- Enquire about previous and current prescription and non-prescription drug use.[3,4,7]
- Assess and exclude systemic illness, ongoing acute disease, COVID-19 infection, malabsorption and malnutrition.[7]
- Consider the use of validated questionnaires, such as the Androgen Deficiency in the Ageing Male (ADAM) questionnaire or the Ageing Males' Symptoms (AMS) scale (www.issam.ch/AMS_English.pdf). The AMS scale provides a quantitative assessment of baseline symptoms and helps to evaluate the clinical response to treatment.[9]

Physical examination

Physical examination should include the following:

- Measure height, weight, BMI and waist circumference.[5]
- Assess the degree of body hair (including facial and pubic).[5]
- Examine for the presence and degree of breast enlargement, abnormalities of the penis, testicles[5,7] and scrotum.[5]
- Check the prostate via digital rectal examination (DRE).[7]
- Arrange blood investigations, including prostate specific antigen (PSA), haematocrit and appropriate tests according to physical findings.

Laboratory diagnosis

Serum testosterone

Measure serum testosterone between 7am and 11am,[5,7] with a reliable method, on at least two occasions,[7] preferably four weeks apart. Luteinising hormone (LH) and follicle-stimulating hormone (FSH) are required to distinguish between primary and secondary hypogonadism. An initial prolactin is required to exclude hyperprolactinaemia and full blood count (FBC) should be measured as anaemia is a frequent finding in hypogonadism. Fasting levels should be obtained where possible, as recommended by the European Association of Urology.[7]

Sex-hormone-binding globulin and free testosterone

These are closely related to increased cardiovascular risk and mortality according to long-term European Male Ageing (EMA) data.[6] An online free testosterone calculator can be found at www.pctag.uk/testosterone-calculator or http://www.issam.ch/freetesto.htm.

Contraindications

The main contraindications to testosterone therapy are:[7]

- Prostate cancer (locally advanced or metastatic)
- Male breast cancer
- An active desire to have children, currently or possibly in the future
- Haematocrit >54%
- Severe chronic heart failure – New York Heart Association (NYHA) class IV.

Testosterone therapy and erectile dysfunction

Testosterone therapy is appropriate for treating erectile dysfunction,[1,2,5] particularly at total testosterone levels <8nmol/L,[1] and for salvaging erectile dysfunction treatment failures with oral medication, particularly at total testosterone levels <10.4nmol/L.[10]

A daily phosphodiesterase type 5 inhibitor (PDE5i) (tadalafil licensed) recommended as testosterone therapy only modestly increased the erectile function score by 1–2 points in clinical trials.[11] Low libido is likely to reduce motivation for on-demand medication

Testosterone therapy reduces the need for more invasive and expensive, second- and third-line erectile dysfunction treatments.[1,12–14]

In men with secondary hypogonadism, with low or low normal LH, who desire fertility, human chorionic gonadotropin (hCG) or clomiphene (off label) are the preferred options.[15,16]

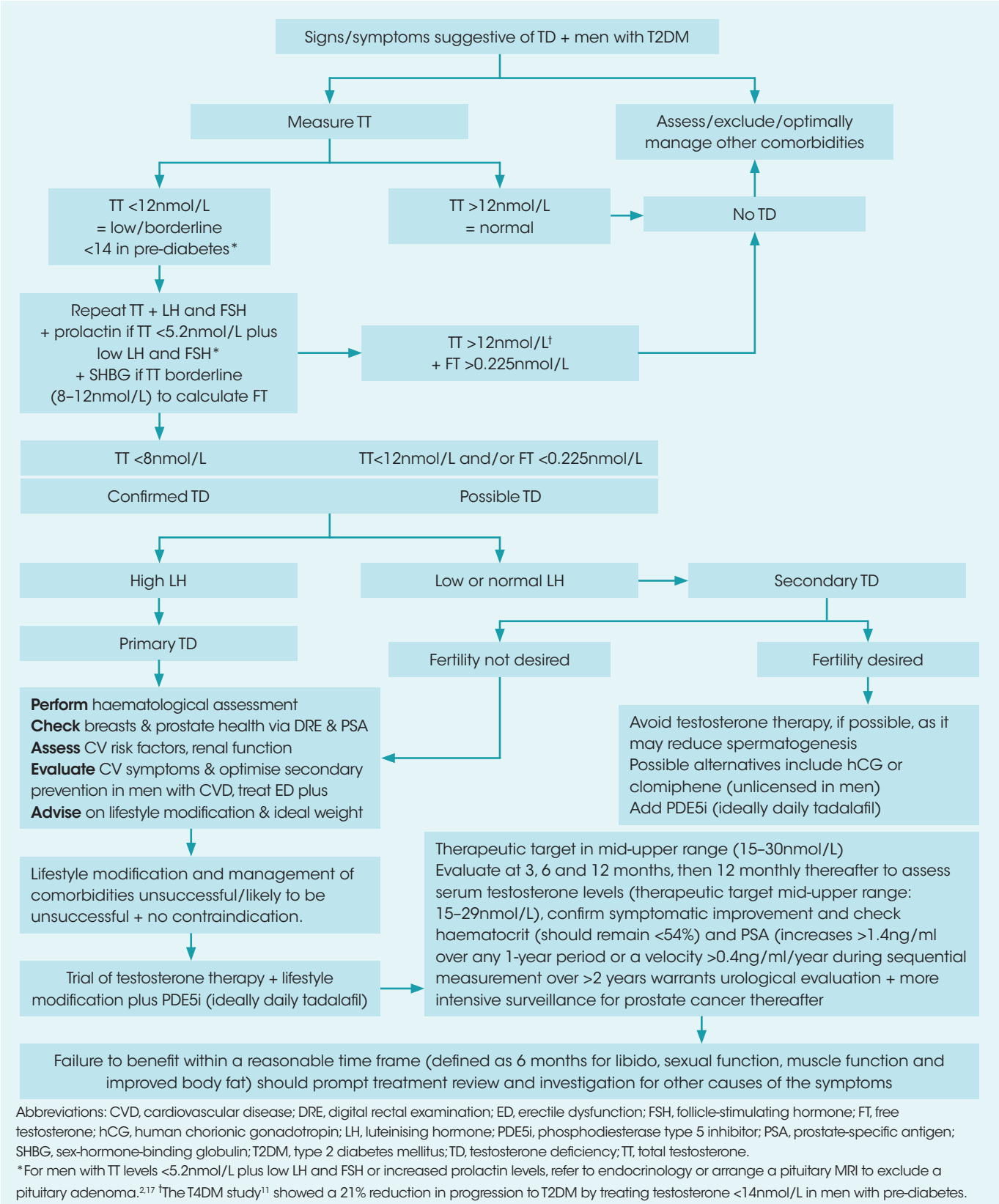
Therapy options and treatment outcomes

Patients should be fully informed about the expected benefits and side-effects of testosterone therapy to facilitate a joint decision on treatment choice. Short-acting preparations are recommended initially, so treatment can be adjusted or discontinued in the event of adverse side-effects. A full flowchart is show in Figure 2. Current testosterone therapy options are shown in Table 1.[1,17,18]

Patients with defined low testosterone should be *accurately* counselled about the benefits and risks of testosterone therapy to facilitate an informed decision.[8,19]

Testosterone therapy, especially to achieve normal levels, improves sexual and erectile function, bone mineral density, corrects unexplained anaemia, improves skeletal muscle mass, physical function, renal function, depressed mood, cognitive function,[19] and reduces progression from pre-diabetes to overt type 2 diabetes by 41%.[10]

There is no evidence that testosterone therapy is associated with increased risk of prostate cancer or cardiovascular risk.[19] Current evidence suggests likely benefit in cardiovascular outcomes,[19] especially in men with chronic kidney disease and atrial fibrillation,[20,21] and after previous myocardial infarction.[22] Further long-term studies are expected to clarify these issues. Recent studies suggest that testosterone therapy (and additionally metformin) significantly reduces the incidence of prostate and colorectal cancer.[23]



Abbreviations: CVD, cardiovascular disease; DRE, digital rectal examination; ED, erectile dysfunction; FSH, follicle-stimulating hormone; FT, free testosterone; hCG, human chorionic gonadotropin; LH, luteinising hormone; PDE5i, phosphodiesterase type 5 inhibitor; PSA, prostate-specific antigen; SHBG, sex-hormone-binding globulin; T2DM, type 2 diabetes mellitus; TD, testosterone deficiency; TT, total testosterone.
*For men with TT levels <5.2nmol/L plus low LH and FSH or increased prolactin levels, refer to endocrinology or arrange a pituitary MRI to exclude a pituitary adenoma.[2,17] †The T4DM study[11] showed a 21% reduction in progression to T2DM by treating testosterone <14nmol/L in men with pre-diabetes.

Figure 2. BSSM Guidelines 2023. Diagnosing and managing testosterone deficiency in adult men.[1] Reproduced from Hackett G, Kirby M, Rees R, *et al.* The British Society for Sexual Medicine Guidelines on Male Adult Testosterone Deficiency, with Statements for Practice. *World J Mens Health* 2023;41:e33.

Formulation	Route of administration	Frequency of administration	Advantages	Disadvantages
Testosterone 1% and 2% (5% scrotal cream licensed in Australia and for import)	Transdermal gel	Once daily	– Fast onset – Provides uniform and normal serum levels for 24 hours – Short duration of action[18] allows drug withdrawal in the event of side-effects	– Skin irritation at application site – Potential for interpersonal transfer – Adherence may be an issue long term
Testosterone undecanoate	Intramuscular injection	Every 10–14 weeks, adjusted to maintain trough testosterone >12nmol/L	– Steady state levels – Reduced frequency of administration improves compliance	– Possible injection site pain – Long duration of action delays drug withdrawal in the event of adverse side-effects
Testosterone enanthate/ propionate	Intramuscular injection	Every 2–3 weeks	– Short duration of action allows drug withdrawal in the event of side-effects	– Levels fluctuate from high to low – Testosterone enanthate is associated with increased rates of erythrocytosis

Adapted from Hackett *et al*, 2023[1] and Dohle *et al*, 2017.[17]

Table 1. Current testosterone therapy options[1]

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