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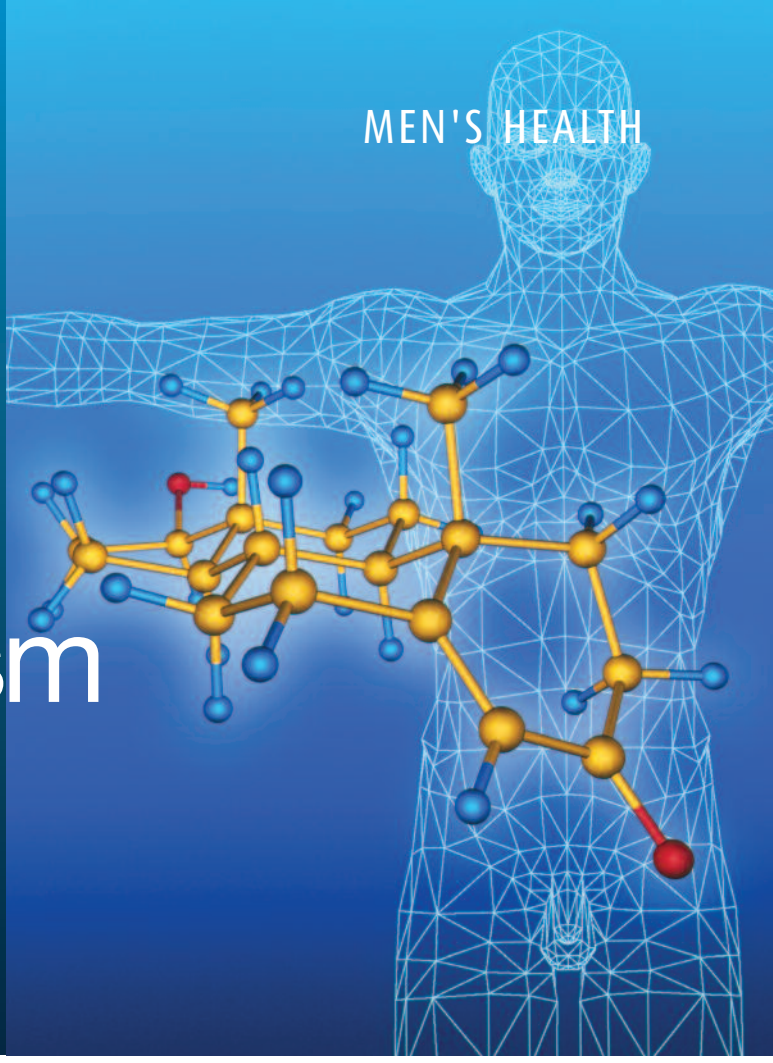

Hypogonadism in men: how to evaluate and when to treat

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Low testosterone levels may be due to underlying disease or lifestyle factors and these need to be addressed before testosterone supplementation is considered.

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Over the past two decades, there has been a marked increase in the number of testosterone prescriptions in Australia. For the most part, low serum testosterone levels are the consequence of concomitant disease and lifestyle factors and require treatment of the underlying disorder rather than the administration of testosterone supplements. In some circumstances, a lowering of testosterone levels may even be an adaptive biological process.

Increasingly, men are inappropriately treated with testosterone supplementation rather than having other causative health problems addressed. Only in a few cases might testosterone therapy be legitimately considered. This article provides a guide to the evaluation of suspected hypogonadism or the finding of a low serum testosterone level in men and the causes thereof. It also describes the appropriate use of testosterone supplements.

DEFINITION AND CLINICAL FEATURES OF HYPOGONADISM

Male hypogonadism is a clinical syndrome resulting from failure of the testes to produce physiological levels of testosterone, usually in association with abnormal spermatogenesis. The testosterone level below which symptoms occur, variation in the testosterone levels at which particular symptoms occur and whether there is any level associated with adverse health

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CAUSES OF HYPOGONADISM

Primary hypogonadism

- Klinefelter's syndrome
- Disorders of testicular descent
- Cancer chemotherapy
- Radiation therapy to testes
- Testicular trauma
- Infections – e.g. mumps orchitis, HIV infection
- Orchiectomy

Secondary hypogonadism

- Pituitary neoplasms
- Radiation therapy to the hypothalamic-pituitary region
- Hyperprolactinaemia
- Haemochromatosis
- Infiltrative disorders
- Idiopathic hypogonadotropic hypogonadism with or without anosmia
- Genetic disorders of pituitary development
- Eating disorders
- Anabolic steroid abuse
- Opioid use

outcomes remain unclear.[1,2] The abnormality may be at one or more levels of the hypothalamic-pituitary-testicular axis.[1,3,4]

In primary hypogonadism, the abnormality is in the testis and the serum levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH), secreted from the gonadotrophs of the anterior pituitary, are increased. Secondary hypogonadism results from disorders of the hypothalamus and pituitary gland, and LH and FSH levels are inappropriately normal or low. The causes of primary and secondary hypogonadism are shown in the box on this page. Under some circumstances both situations occur – for example, in response to glucocorticoid administration or in patients with haemochromatosis.

The onset of testosterone deficiency before the completion of pubertal development leads to delayed or incomplete sexual development, and body proportions become eunuchoidal – the arm span exceeds the patient's height by more than 2 cm.[1,4] The development of testosterone deficiency after the completion of pubertal maturation is associated with reduced sexual desire and activity, erectile dysfunction with notably decreased spontaneous erections, reduced frequency of shaving, reduced muscle mass and strength, hot flushes and sweats. Testicular size decreases and breast tenderness may occur. Other, nonspecific symptoms, such as decreased energy motivation and initiative, dysthymia, poor concentration and memory, sleep disturbance, increased body fat and diminished physical or work capacity, may also occur.[5] The symptoms of testosterone deficiency may be extremely difficult to distinguish from an underlying disease process, and the probability of being able to make a diagnosis of hypogonadism from a screening questionnaire alone is about 50%.[1,4]

PREVALENCE

Data from the Massachusetts Male Aging Study (MMAS) indicate that in the greater Boston area of the USA the prevalence of men with symptomatic hypogonadism is about 9% based on a testosterone level of 8 nmol/L and the presence of three or more symptoms.[6] More recent data from the European Male Aging Study (EMAS) estimate the overall prevalence of hypogonadism in European men to be 2.1%, increasing with age from 0.1% for men aged 40 to 49 years to 5.1% for those aged 70 to 79 years.[7] A similar overall prevalence of 2.2% has been found in a study of men from north-west Adelaide (unpublished data). The higher prevalence from the MMAS most likely reflects the effect of a range of disease processes that increase with age and result secondarily in dysfunction of the hypothalamic-pituitary-gonadal axis. In these instances, targeting treatment to the primary disease process usually results in an increase in androgen levels and, importantly, resolution of symptoms.

DIAGNOSIS OF TESTOSTERONE DEFICIENCY

The symptoms and signs of testosterone deficiency vary depending on the age of onset, the severity and duration of the deficiency, comorbid conditions, testosterone sensitivity and previous testosterone therapy. In Australia, the diagnosis of testosterone deficiency (for reimbursement through the PBS) requires the presence of a compatible clinical syndrome and a morning serum testosterone level of 8 nmol/L or less on at least two occasions, or up to 11 nmol/L when the LH and FSH are elevated by 1.5 times above the upper limit of normal.

The total testosterone level should be measured in the morning after an overnight fast because levels tend to be highest on waking.[8,9] Low testosterone levels should be confirmed by a repeat measurement on another day. The necessity for repeating measurements of testosterone at a subsequent time point is based on data showing that about 30% of men with an initial testosterone level of 11 nmol/L had a higher level on repeat testing. In men with an initial testosterone level of 8 nmol/L, 20% had an average testosterone level of more than 11 nmol/L over six months. When repeat samples were 8 nmol/L or less, no men had a testosterone level above 11 nmol/L over the subsequent six months.[6,10,11] Total testosterone levels reflect both albumin- and sex hormone binding globulin (SHBG)-bound testosterone. SHBG, produced in the liver, is regulated by a number of factors (see the box on page 51) and variations in levels may be reflected by commensurately higher or lower levels of testosterone in standard total testosterone assays. Therefore, SHBG levels must also be measured and taken

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CAUSES OF ALTERED SEX HORMONE BINDING GLOBULIN (SHBG) LEVELS

Increased SHBG

- Hyperthyroidism
- Cirrhosis
- Oestrogens
- Increasing age
- Use of anticonvulsants
- Inadequate nutrient intake
- Anorexia nervosa
- HIV infection

Decreased SHBG

- Obesity and insulin resistance
- Impaired glucose tolerance and type 2 diabetes
- Hypothyroidism
- Polycystic ovary syndrome
- Use of glucocorticoids
- Nephrotic syndrome
- Androgens

into account when interpreting the results of total testosterone measurements.[12]

Although liquid chromatography tandem mass spectrometry is now considered to be the method with the highest precision for measuring sex steroids,[8,9,13] for clinical purposes a standard platform assay, as offered by commercial laboratories in Australia, is quite sufficient. The calculation of free testosterone by equations using the law of mass action does not provide any additional information of clinical relevance. The free androgen index in which the total testosterone level is divided by the SHBG level is of no use in men.

A thorough evaluation for the causes of hypogonadism, both primary and secondary (see the box on page 50), together with evaluation of general health to exclude systemic illness, eating disorders and abuse of drugs such as alcohol, marijuana and opiates must be undertaken. Any acute illness, nutritional deficiency, stress, depression, obesity (particularly when visceral), type 2 diabetes or a sleep disorder can lower testosterone levels. Heavy alcohol consumption may have a marked effect on lowering testosterone levels. It is important to recognise that cigarette smokers have testosterone levels 5 to 15% higher than nonsmokers; however, the reason for this is not entirely clear.

In men with testosterone deficiency, the measurement of LH and FSH levels helps to determine whether the defect resides at the testicular or hypothalamic-pituitary level.[1,4] A karyotype analysis should be obtained in men with primary testicular failure to exclude Klinefelter's syndrome (47XXY), which occurs in between about one in 500 and one in 1000 men.[14] Men with secondary hypogonadism need additional evaluation, including measurements of prolactin levels, other pituitary hormones, serum iron and transferrin saturation, and an MRI scan, to exclude haemochromatosis, prolactinoma and space-occupying or destructive lesions of the hypothalamus and pituitary. The extent of this additional evaluation should be individualised.

TESTOSTERONE THERAPY

Currently, testosterone therapy is recommended for symptomatic men with classical testosterone deficiency syndromes and low serum testosterone levels, and in whom benefit in terms of induction and or maintenance of secondary sex characteristics and body composition, improved sexual function, mood and sense of well-being occurs.[3] Other indications include short-term adjuvant therapy in men with HIV infection, low testosterone levels or weight loss, and men treated with glucocorticoids or opioids who have low testosterone levels and require supplementation to preserve lean body mass and bone mineral density.[3] Contraindications to testosterone supplementation must be excluded in the initial work up (see the box on this page).

CONTRAINDICATIONS TO TESTOSTERONE THERAPY

- Prostate cancer
- Breast cancer
- Haematocrit level above 50%
- Severe obstructive urinary tract symptoms
- Poorly controlled congestive heart failure
- Myocardial infarction, acute coronary event, unstable angina or coronary revascularisation procedure in the preceding six months
- Untreated severe obstructive sleep apnoea

Testosterone injections

Testosterone enanthate is administered by intramuscular injection at a dose of 200 mg. The patient's serum testosterone level subsequently rises into the supraphysiological range within 24 to 48 hours, and then gradually declines to the hypogonadal range over the next two weeks.[15,16] This produces a 'surge and wane' effect that many recipients find unpleasant.

A mix of four testosterone esters (testosterone isocaproate, testosterone phenylpropionate, testosterone propionate and testosterone decanoate) at a dose of 250 mg is administered similarly, every three weeks. It has similar problems with a surge and wane effect.

Testosterone undecanoate at a dose of 1000 mg is administered as a 4 mL oily suspension, by deep intramuscular injection. It maintains serum testos terone levels in the normal range for 10 to 14 weeks.[1] An initial loading dose is followed six weeks later by a further dose and then regular doses are given. The dose interval varies between patients, and in some cases 16 weeks between doses may suffice. Accordingly, monitoring of testosterone levels predose is advisable.

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Testosterone implants

In patients treated with testosterone implants, three pellets, each slowly releasing 200 mg of testosterone, are implanted deep below the subcutaneous abdominal fat, using a trochar and cannula technique. This provides stable physiological levels for five to six months.

Topical testosterone

Transdermal testosterone gel is available in 5 g sachets. It is applied once daily,[3] and provides stable and physiological testosterone levels. There is a potential for transfer of testosterone to a sexual partner or to children who come in close contact with the patient. Case reports of precocious puberty in children due to gel transfer have prompted the US Food and Drug Administration to issue a black box warning for this product.

Testosterone patches are applied to the skin of the upper arms and torso. The 24.3 mg patch delivers 5 mg testosterone over 24 hours in a continuous manner and provides stable physiological testosterone levels. A patch half that strength is also available. About one-third of patients using these patches develop significant skin reactions.

Other topical testosterone preparations include a cream that is currently in clinical trials to compare its pharmacokinetics with the testosterone gel, and a formulation for application to the axilla, which is not currently available in Australia.

Oral testosterone

Oral testosterone undecanoate is absorbed preferentially through the lymphatics into the systemic circulation. Doses of 40 to 80 mg given two or three times daily with a fatty meal are typically used. The clinical responses are variable and generally suboptimal.[17] It may be useful in the very elderly, for the induction of puberty or as a slow introduction of testosterone therapy in men with longstanding deficiency.

ADVERSE EFFECTS OF TESTOSTERONE THERAPY

Testosterone is generally well tolerated and safe, particularly in otherwise healthy men.[18,19] Specific concerns relating to testosterone therapy are described below.

Erythrocytosis

Testosterone therapy increases red cell mass in a dose-dependent manner. The increase in haematocrit levels during testosterone administration is greater in older men,[20,21] men who smoke and those who have obstructive sleep apnoea. Although it had been postulated that testosterone stimulates erythropoiesis through its effects on erythropoietin and stem cell proliferation, it has recently been demonstrated that testosterone increases red cell mass by inhibiting hepcidin and thereby increasing iron availability for erythropoiesis.[20]

Testosterone supplements should not be administered to men with baseline haematocrit levels of 50% or more without appropriate evaluation and treatment of erythrocytosis. Testosterone therapy should be discontinued when haematocrit levels increase above 54%, and therapy should be withheld until haematocrit levels have fallen to less than 50%, at which time testosterone therapy may be reinitiated at a lower dose.[3] Regular venesection can be instituted if necessary.

Cardiovascular events

The long-term effects of testosterone therapy on the risk of cardiovascular events remain unknown. A recent trial reported an increased cardiovascular mortality in frail old men already at high risk for cardiovascular disease who received testosterone therapy.[22] The significance of this is uncertain. Until adequately powered trials have been undertaken, testosterone should be used with caution in frail men with significant active cardiac disease.

Prostate cancer

There is general agreement that testosterone therapy does not cause prostate cancer.[3,23] A meta-analysis of randomised testosterone trials has reported a higher rate of prostate biopsy and all-cause prostate-related events in the testosterone arms than in the placebo arms.[23] Serum prostate specific antigen (PSA) levels are lower in testosterone-deficient men and are restored to normal after testosterone therapy, but this increase in PSA levels is within normal ranges and generally less than 0.5 ng/mL. The major concern in men over the age of 40 years relates to the risk of promoting the growth of pre-existing prostate cancer. This should be excluded with a PSA test and digital rectal examination before the commencement of testosterone treatment and then at three and six months, followed by annual reviews. A prostate biopsy should be considered if:

- the PSA is more than 4 ng/mL
- the PSA increases by 1.4 ng/mL at 12 months
- the PSA velocity is 0.4 ng/mL/year
- the digital rectal examination reveals any abnormality.

Benign prostatic hypertrophy

Testosterone replacement can be administered safely to men with benign prostatic hypertrophy who have mild to moderate lower urinary tract symptoms.[3] A urology evaluation is recommended if there is an increase in lower urinary tract symptoms – for example urgency, frequency, after dribble, difficulty initiating urination or deteriorating stream.

MONITORING OF TESTOSTERONE REPLACEMENT

Testosterone therapy should aim to raise testosterone levels into the mid-normal range for young adult men.[3] Total testosterone levels should be measured:

- midway between injections for testosterone enanthate and testosterone ester mix

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- three to 12 hours after application for testosterone patches
- after one week for testosterone gels
- prior to each subsequent injection for testosterone undecanoate
- prior to each implantation of testosterone pellet.

With testosterone undecanoate, the trough level of testosterone should be in the low-normal range, not the mid-normal range, to minimise the risk of erythrocytosis. At three to six months after the initiation of treatment, the patient should be assessed for improvement in sexual function, libido, muscle strength and body composition, as well as mood and overall well-being. In borderline cases, treatment should be discontinued if there is no symptomatic improvement.

Urological, haematocrit and cardiac monitoring are described above. Bone mineral density measurement needs to be repeated only one to two years after treatment if testosterone supplementation was started for low bone mineral density.

CONCLUSIONS

True hypogonadism is uncommon, but when present testosterone replacement is beneficial. With secondary hypogonadism, a correctable or at least modifiable underlying disorder should be considered and treated. Similarly, a significant lowering of testosterone levels with advancing age is an indication of the presence of underlying disease. Where a significantly low testosterone level persists with a compatible clinical syndrome, supplementation to achieve physiological levels may be warranted with monitoring for a symptomatic response. Induction of supra-therapeutic levels confers no particular clinical benefit. MT

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A list of references is available on request to the editorial office.

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