Lifelong Learning

Hypogonadism in Men: How to Evaluate and When to Treat

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

Low serum testosterone levels are mostly the consequence of concomitant disease and lifestyle factors. Treatment of the underlying disorder is needed, rather than 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. It is only in a few cases that testosterone therapy might be legitimately considered. This article provides a guide to evaluating suspected hypogonadism or finding of a low serum testosterone level in men and it's causes. 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 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 hypgonadism 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. 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 2cm.[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]

Key points

- True hypogonadism is uncommon, but when it is 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.

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Causes of hypogonadism

Primary hypogonadism

- Klinefelter's syndrome
- Disorders of testicular descent
- Cancer chemotherapy
- Radiation therapy to testes
- Infections - eg, mumps, orchitis, HIV infection
- Orchiectomy

Secondary hypogonadism

- Pituitary neoplasms
- Radiation therapy to the hypothalmic - pituitary region
- Hyperproclactinaemia
- Haemochromatosis
- Infiltrative disorders
- Idiopathic hypogonadotropic hypogonadism with or without anosmia
- Genetic disorders of pituitary development
- Eating disorders
- Anabolic steroid use
- Opoid use

Prevalence

Data from the Massachusetts Male Aging Study (MMAS) indicate that in the Boston area of the USA the prevalence of men with symptomatic hypogonadism is about 9% based on a testosterone level of 8nmol/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 Adelaide, Australia (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. The diagnosis of testosterone deficiency requires the presence of a compatible clinical syndrome and a morning serum testosterone level of 8nmol/L or less on at least two occasions, or up to 11nmol/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 is based on data showing that about 30% of men with an initial testosterone level of 11nmol/L had a higher level on repeat testing. In men with an initial testosterone level of 8nmol/L, 20% had an average testosterone level of more than 11nmol/L over six months. When repeat samples were 8nmol/L or less, no men had a testosterone level above 11nmol/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) and variations in levels may be reflected by commensurately higher or lower levels of testosterone in standard total testosterone assays. Therefore SHBG levels, too, must be measured and taken 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 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.

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

A thorough evaluation must be made for the causes of hypogonadism, both primary and secondary (see the box), in addition to evaluating general health to exclude systemic illness, eating disorders and abuse of drugs such as alcohol, marijuana and opiates. 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 also reduce testosterone levels. It is important to recognise that cigarette smokers have testosterone levels 5% to 15% higher than nonsmokers, although 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 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 who show benefit in terms of induction and/or maintenance of secondary sex characteristics and body composition, improved sexual function, mood and sense of well-being.[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).

Testosterone injections

When testosterone enanthate is administered by intramuscular injection at a dose of 200mg, 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.

Testosterone undecanoate at a dose of 1000mg is administered as a 4 mL oily suspension, by deep intramuscular injection. It maintains serum testosterone 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 pre-dose is advisable.

Testosterone implants

In patients treated with testosterone implants, three pellets, each slowly releasing 200mg 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.

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

Topical testosterone

Transdermal testosterone gel is available in 5g 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 24.3mg patch delivers 5mg testosterone over 24 hours continuously 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, currently in clinical trials to compare its pharmaco-kinetics with the testosterone gel, and a formulation for application to the axilla.

Oral testosterone

Oral testosterone undecanoate is absorbed preferentially through the lymphatics into the systemic circulation. Doses are typically 40mg to 80mg, given two or three times daily with a fatty meal. 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, 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

General agreement is 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 0.5ng/mL. The major concern in men older than 40 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 4ng/mL
- The PSA increases by 1.4ng/mL at 12 months
- The PSA velocity is 0.4ng/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 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 before each subsequent injection for testosterone undecanoate.

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.

References are available on request.

Food-based Compound Found to Kill Diseased Cells

A new class of food-based natural compounds, known as phytonutrients, has been found to cause the death of malfunctioning cells, such as cancer cells. The researchers who first discovered this in 1998 have called it "probably the most significant breakthrough in nutrition since the discovery of vitamins."

The phytonutrient responds to an enzyme called CYP1B1, which is over-expressed in malfunctioning cells and is not present in normal healthy cells. The metabolism of the nutrient by the CYP1B1 enzyme results in metabolites that suppress and cause the death of malfunctioning cells.

The active substance, piceatannol, is known to be highly toxic to cancer cells while being nontoxic to normal cells.

These phytonutrients were named 'salvestrols' by the cancer researchers who discovered them - Prof Gerry Potter from De Montfort University in Leicester, UK and Prof Dan Burke, a pharmacologist and former Dean of Science at that country's Sunderland University. The result is that they have now focussed all their cancer treatment research on salvestrols.

The initial research has been backed, and further studies conducted by other scientists. Positive outcomes with diseased patients have been published in respected journals. Among these:

- An article in *Journal of Orthomolecular Medicine* (Vol25, Number 1, 2010): 'Nutrition and Cancer: Salvestrol case studies'
- Evidence that CYP1B1 is a universal tumour marker (Prof Dan Burke, Sep 2007)
- A paper on nutrition and the prevention and treatment of cancer (*Integrated Cancer Therapy*, Dec 2009).

Salvestrols have been identified in parts of fruit, vegetables and herb plants. However, they have a sharp and bitter taste prompting people to remove it before cooking. It also does not survive pesticides.

Salvestrol is distributed in SA by Coyne Consultance. A company spokesperson says a number of SA doctors have worked with this nutrient and have had excellent results.