ARTICLE

Low testosterone in men

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SUMMARY

Male hypogonadism is a clinical syndrome of symptoms and signs confirmed by the presence of low testosterone.

Serum testosterone concentrations decline with age. The symptoms of hypogonadism are often mimicked by non-specific effects of other illness and ageing.

Low concentrations of serum testosterone should be confirmed by a reliable assay and laboratory. Some conditions alter sex hormone binding globulin, so calculating free testosterone is sometimes useful.

Treatment should not be based on serum testosterone alone. Primary and particularly secondary causes of hypogonadism should be identified. Reversible conditions and the adverse effects of other therapies should be excluded before prescribing testosterone.

The benefits and harms of testosterone should be discussed, with a defined plan to stop the drug if the response is unsatisfactory.

When indicated, testosterone therapy is relatively safe in the short term at recommended doses, but long-term placebo-controlled studies of efficacy and safety are required. Recent publications suggest increased cardiovascular events in older men treated with testosterone.

Introduction

Hypogonadism in men refers to decreased function of the testes, in either testosterone or sperm production. A deficiency of testosterone may be due to primary gonadal failure, or be secondary to hypothalamo-pituitary disease. Certain symptoms and signs suggest androgen deficiency in men (Box 1). Others are less specific and can be seen with many comorbidities and their therapies, and with ageing.[1]

Men with the classical clinical features of androgen deficiency and a confirmed low serum total testosterone concentration should be considered for testosterone therapy.[1] Prescribing testosterone for non-specific symptoms or the lower testosterone concentrations associated with ageing is poorly validated and may be harmful.[2-5] Over the last decade the steep rise in the amount of testosterone dispensed in Australia[6] and globally[7,8] suggests that testosterone is being used when true hypogonadism is not proven, and indeed misused for non-specific symptoms in older men.[7,8]

Testosterone physiology

Testosterone in plasma is bound to sex hormone binding globulin, and weakly to albumin. Only non-bound or free testosterone, representing 1–3% of the total concentration, is biologically available.

Testosterone production in the testes is stimulated by luteinising hormone. When total testosterone is low, an elevated luteinising hormone concentration is a sensitive indicator of primary Leydig cell failure. Low testosterone with inappropriately low, normal or minimally elevated luteinising hormone may indicate hypothalamo-pituitary disease that demands investigation. However, this pattern may be seen with ageing, illness and certain drugs (Box 2).[9]

There is a diurnal variation in serum testosterone with a morning peak and mid-afternoon nadir. Cross-sectional and longitudinal studies show declining concentrations[10-13] and a loss of the diurnal rhythm with ageing.[12] Sampling should therefore be done between 8 and 10 am. With ageing there is a significant rise in concentrations of sex hormone binding globulin and this causes a decline in free testosterone.

Measuring testosterone across populations of men produces a range of results depending on the population selected, sampling times, sample storage and assay methods.[10,12-14] The definition of 'normality' is held to be the serum testosterone range found in healthy 20–40-year-old men. Deficiency is a value lower than the 2.5 percentile in morning samples. One could argue that the decline in testosterone concentrations beyond the age of 60 years in healthy populations should lead to the development of age-specific reference ranges.

Assessment

Following a careful history including checking for specific symptoms of androgen deficiency, assess the patient's body hair distribution, testicular size, body habitus, breast size and ask if there is a history of low trauma fracture. If the history and examination suggest androgen deficiency (Box 1)[1] then consider measuring serum total testosterone. Samples are taken on two separate mornings (Fig.).[1]

Serum luteinising hormone and follicle stimulating hormone should be measured in one of the low total testosterone samples to discriminate primary from secondary gonadal failure. Seminal fluid examination will be required if fertility is a problem. A karyotype is indicated to exclude Klinefelter syndrome (47 XXY) if the testes are less than 5 mL in volume.

Secondary gonadal failure should be further evaluated by exclusion of reversible comorbidities including nutritional deficiency, obesity, severe sleep apnoea, diabetes mellitus, and certain drugs (Box 2).[9] Hypothalamo-pituitary disease can be evaluated by careful assessment for possible diabetes insipidus, intracranial mass effect and visual field assessment. If indicated, measure serum prolactin and other pituitary hormones and consider pituitary magnetic resonance imaging.

Certain syndromes causing 'idiopathic' hypogonadotrophic hypogonadism may be suggested by dysmorphic features. Examples are extreme obesity in Prader-Willi syndrome, polydactyly, renal anomalies and anosmia in Kallmann syndrome, and short stature in certain gene deletion syndromes.

Laboratory assays

While the gold standard for measurement of serum total testosterone is gas or liquid chromatography and mass spectrometry, these techniques are labour intensive and expensive. The need for a high volume output and lower costs has resulted in laboratories using automated immunoassays which have variable sensitivity, accuracy and reproducibility.[14,15] There is less accuracy and greater variability for results in the hypogonadal range, with some significant discrepancies. Reference standards and manufacturers' reference ranges are not always well defined.

Given these caveats, defining a reference range, particularly the lower limit of normal, is fraught with difficulty. American consensus statements say above 11.1 nmol/L is normal, below 6.9 nmol/L is diagnostic of hypogonadism, and 6.9–11.1 nmol/L is equivocal.[14] In Europe those figures are respectively 12, 8 and 8–12 nmol/L.[15]

Box 1 Symptoms and signs suggestive of androgen deficiency in men

More specific

- decreased spontaneous erections
- gynaecomastia
- hot flushes
- incomplete sexual development
- loss of body hair, reduced shaving
- low sperm count
- osteoporosis or fragility fracture
- reduced libido and sexual activity
- small (<5 mL) or shrinking testes

Less specific

- decreased energy and motivation
- dysthymia, depression
- increased body mass index and body fat
- normochromic anaemia
- poor concentration, lethargy
- reduced muscle bulk and strength
- reduced physical or mental performance
- sleep disturbance

Adapted from reference 1

Box 2 Drugs associated with low testosterone

Potent analgesics especially opioids

Systemic glucocorticoids

Gonadal steroids

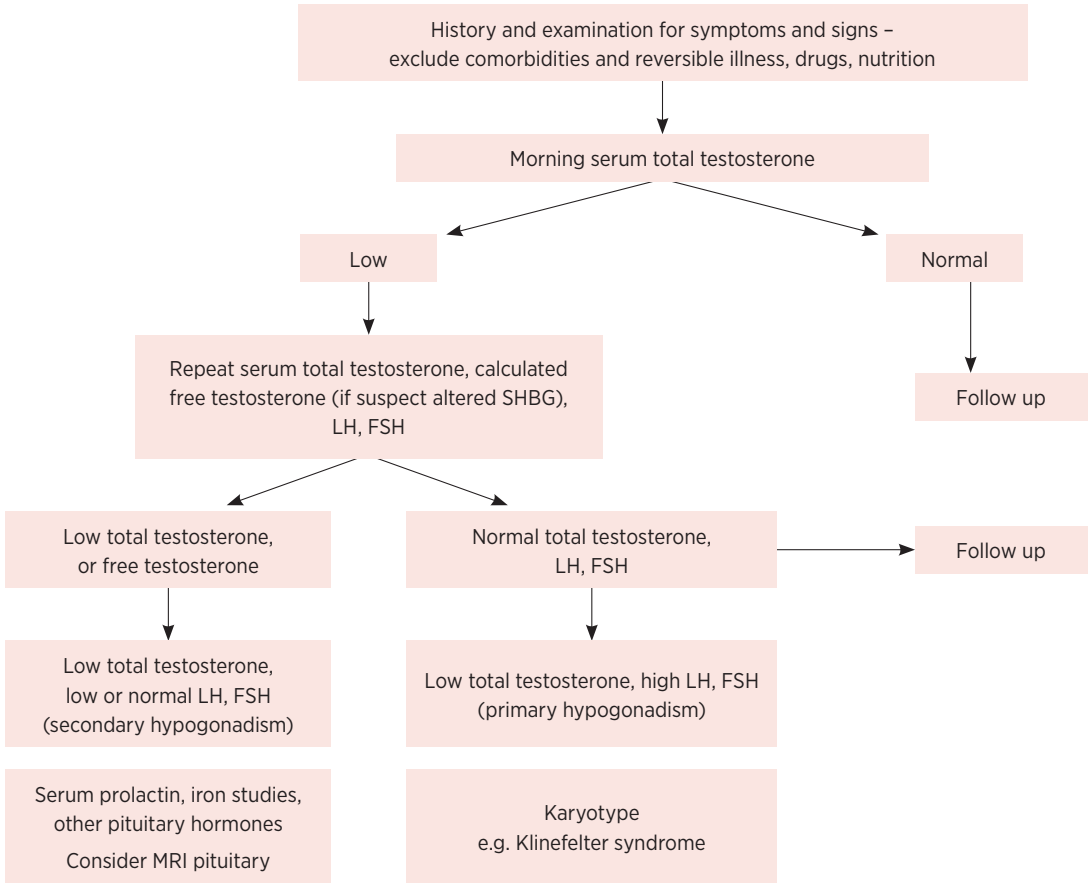
- anabolics
- oestrogenic compounds

Chemotherapy[9]

Gonadotrophin suppressors

A problem in defining a reference range is that most population studies include men with poorly defined health status. An Australian study, in 21–35-year-old men with clearly defined normal health and fertility, used gas chromatography mass spectrometry to measure total testosterone.[16] It reported a reference range of 9.7–34.3 nmol/L with a mean of 18.2 nmol/L. However, there were significant discrepancies between the seven immunoassays assessed. Lower reference values ranged from 6.1 to 11.5 nmol/L, and upper values ranged from 35.1 to 44.9 nmol/L, highlighting the dilemma of defining a normal range with individual assays.

Fig. **Algorithm for assessing adult men with suspected testosterone deficiency**



SHBG sex hormone binding globulin
FSH follicular stimulating hormone
LH luteinising hormone
MRI magnetic resonance imaging
Adapted from reference 1

Measurement of free testosterone, while attractive, is troubled by the poor reliability of such assays and should be abandoned.[1,14,15,17] Calculated free testosterone which depends on measurement of total testosterone, albumin and sex hormone binding globulin bears a close resemblance to the estimate of free testosterone by equilibrium dialysis, but should still be interpreted with caution.[14,15,17,18] These calculations may be useful where variations in sex hormone binding globulin are suspected (Box 3),[1] particularly when total testosterone is low or the patient is old or obese.

Testosterone therapy

There is no argument about testosterone therapy for male hypogonadism due to established testicular disorders, or pituitary disease.[19]

When serum total testosterone is less than 6.9 nmol/L in repeat samples, there is little doubt that true hypogonadism exists. If the results are in the range 6.9–11.1 nmol/L, therapy might be considered if there are symptoms and signs of androgen deficiency.

In Australia, the Pharmaceutical Benefits Scheme subsidises testosterone (Box 4) 'on authority' for males with established pituitary or testicular disease. For men over 40 years old without such disorders the serum total testosterone must be below 8 nmol/L, or below 15 nmol/L in association with concentrations of serum luteinising hormone more than 1.5 times the upper limit of normal. To qualify for subsidised treatment, the patient must have a low testosterone on at least two occasions.

Therapy aims to restore serum testosterone to the mid–normal range and correct symptoms and signs of androgen deficiency.

The amount of circulating testosterone (and indeed oestradiol by aromatisation) that confers physiological effects on body composition, strength and sexual function in males is uncertain. A dose-finding study found that both testosterone and oestradiol are important, and that doses of at least 5 g of testosterone gel or equivalent are required.[20]

The choice of preparation and goals of therapy should be discussed with the patient before starting therapy. Dosing needs to be mindful of the peaks and troughs of plasma concentrations. With the testosterone enanthate product the peak concentrations are often supra-normal at 7–10 days, sometimes with evident behavioural changes such as increased libido and aggression, with a trough 2–3 weeks after the injection.

Monitoring

Monitor the patient by careful clinical review and measuring serum total testosterone. Initial sampling is reasonably performed after two months of therapy (two months after the third injection if testosterone undecanoate is used) then annually.

When defined pituitary or testicular disease is not present, it is important to assess the clinical and symptomatic benefit of therapy after 3–6 months. Withdraw therapy if there is no benefit.

Benefits of therapy

Testosterone therapy for hypogonadal men may improve muscle bulk and strength, libido, sexual function and mood,[21,22] but the evidence is poor, with lack of large placebo-controlled trials.[1,23] Bone density improves[24,25] but there is no current evidence regarding fracture reduction.[24] There is some evidence of improvement in body composition.[25]

For older men with low testosterone, the influences of the age-related decline in testosterone versus effects of other illness are difficult to define.[1,26-28] After correction of any reversible illness or interfering drug therapy and after weight reduction in the obese, it is reasonable to consider a trial of testosterone therapy on a case-by-case basis if the patient has symptoms of androgen deficiency and low testosterone.

Safety and adverse effects

Testosterone should not be given to men with prostate or breast cancer, a haematocrit more than 50%, severe untreated obstructive sleep apnoea or prostatic symptoms. These conditions may be exacerbated by testosterone, so pre-existing prostatic disease, significant obstructive sleep apnoea, and elevated haematocrit should be excluded. A digital rectal examination should be performed and prostate specific antigen measured. In men above age 40 years a prostate specific antigen more than 6 microgram/L should be followed by closer clinical monitoring of the prostate and repeat measurements of prostate specific antigen during therapy.[1,29] In young males with secondary hypogonadism who need fertility, testosterone therapy will suppress spermatogenesis. Gonadotrophin therapy would be the temporary alternative.

Meta-analyses of placebo-controlled trials suggest that testosterone therapy in physiological doses is significantly associated with increased haematocrit, reduced high-density lipoprotein cholesterol and prostatic symptoms.[29,30] If prostate cancer has been excluded, there appears to be no increased risk of induction by testosterone therapy. There is inconsistent evidence regarding the risk of cardiovascular events.[29-31] A recent meta-analysis suggested increased cardiovascular risk and reported publication biases.[32] Long-term safety data are lacking, but recent

Box 3 Variations in sex hormone binding globulin

Causes of increased sex hormone binding globulin

- ageing
- anticonvulsant therapy
- hepatitis and hepatic cirrhosis
- HIV disease
- hyperthyroidism
- oestrogen therapy

Causes of decreased sex hormone binding globulin

- acromegaly
- diabetes mellitus
- glucocorticoids, progestins, androgens
- hypothyroidism
- nephrotic syndrome
- obesity

Adapted from reference 1

Box 4 Testosterone preparations currently subsidised in Australia (2014)

Topical

- testosterone 1% gel 50 mg per 5 g sachet
- testosterone patch either 2.5 mg or 5 mg release in 24 hours
- testosterone 2% axillary dermal spray 30 mg per actuation

Injectable

- testosterone pellets 100 or 200 mg each for deep subcutaneous insertion usually 600–800 mg approximately 6 monthly
- testosterone enanthate 250 mg intramuscular injection every 2–3 weeks
- testosterone undecanoate 1000 mg intramuscular injection every 3 months after initial loading

Oral

- testosterone undecanoate capsule 40 mg (this is a poorly bioavailable androgen and only really suitable for inducing puberty in boys)

Caution is required with some topical preparations to avoid transfer to sexual partners

Other testosterone preparations are available including dermal creams and buccal tablets, but these are not well standardised for absorption and safety

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reports more strongly suggest an increased risk of cardiovascular events in older men.[3,4] This has prompted the Endocrine Society to issue a warning statement.[5] The results and safety of long-term prospective controlled trials of testosterone therapy are awaited.

Conclusion and recommendations

If a man has symptomatic hypogonadism and proven testosterone deficiency the cause needs to be explored, especially if there is secondary hypogonadism. Serum testosterone is reduced by comorbidities and treatments, which need to be corrected as far as possible before testosterone therapy is considered. Testosterone should not be prescribed for non-specific symptoms.

While a confirmed serum total testosterone less than 8 nmol/L reliably suggests androgen deficiency, values in the range 8–12 nmol/L create uncertainty because of variability in testosterone assays. There is need for standardisation and quality control in testosterone assays.

Short-term studies show benefit with testosterone therapy for androgen deficiency. There are improvements in lean body mass, bone mineral density and strength. Adverse events are erythrocytosis, reduced high-density lipoprotein cholesterol, and some increase in prostatic symptoms. Recent data show a risk of cardiovascular events in men with or at risk of vascular disease. Long-term studies of efficacy and safety are required. <

Conflict of interest: none declared

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