Testosterone therapy in men
Ongoing management and surveillance

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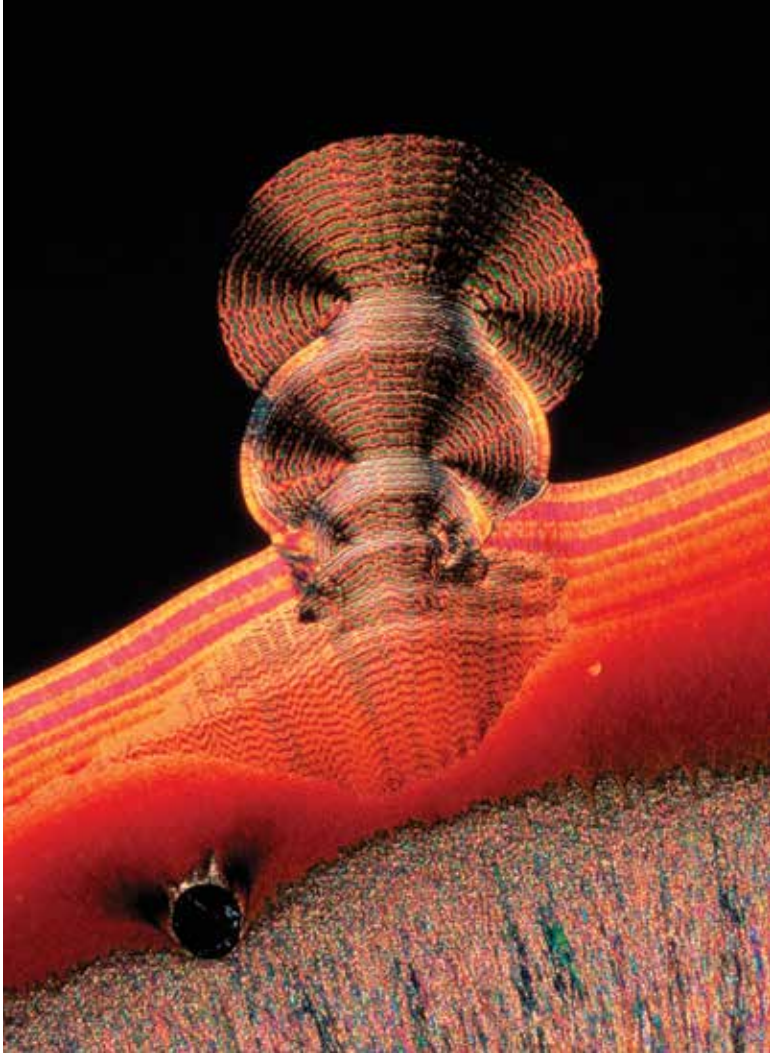
Men with testicular or hypothalamo–pituitary disease who are taking testosterone replacement therapy can expect to remain on treatment lifelong. Appropriate surveillance protocols therefore need to be established to ensure the reversal of existing manifestations of androgen deficiency and to monitor for potential adverse effects of treatment.



TESTOSTERONE CRYSTALS (LIGHT MICROGRAPH). © GETTY IMAGES/SPL/SIDNEY MOULDS

Key points

- **Men with proven testosterone deficiency can expect to remain on therapy lifelong.**
- **Assessment of men receiving testosterone therapy includes digital rectal examination; full blood exam; dual-energy x-ray absorptiometry; measurement of prostate-specific antigen, lipids and fasting blood glucose levels; and a sleep assessment. These should occur at baseline and then according to consensus protocols and individual risk profiles.**
- **Measurement of serum testosterone levels in men treated with testosterone should be interpreted in the context of the mode of testosterone administration.**
- **Testosterone therapy should not be administered to men who desire fertility.**

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Notwithstanding the uncertainties about the role of testosterone supplementation in men with age-related declines in serum testosterone levels, androgen deficiency remains the most common hormonal disorder in men, occurring in approximately one in 200 adult men. Men with proven testicular or hypothalamo–pituitary disease who are commenced on testosterone replacement therapy can expect to remain on treatment lifelong. It is therefore important that appropriate surveillance protocols are established to ensure the reversal of existing manifestations of androgen deficiency and to monitor for potential adverse effects of treatment with exogenous androgens (see Table).[1-3]

Testosterone levels

Serum testosterone levels in men treated with testosterone replacement therapy must be interpreted in the context of the mode of the androgen delivery. Target levels will depend on the man's age, body mass index, comorbidities, clinical response to treatment, and the duration and severity of the androgen deficiency.[4]

Testosterone levels should be measured periodically (one to two times per year in men stable on testosterone replacement therapy). Transdermal preparations (patches, gels [applied either to nonscrotal skin or to the axillae] and creams) are applied daily and testosterone levels are measured several hours post application. The usual aim is for a level in the mid-normal young adult range,

Table. Monitoring of men receiving long-term testosterone replacement therapy[1]

Parameter	Monitoring tool	Frequency
Clinical	Clinical assessment: side effects of specific testosterone preparation, quality of life, sleep, fertility	Baseline, at 3 to 6 months then once or twice per year
Testosterone levels	Measurement of serum testosterone level	Baseline, at 3 to 6 months then once or twice per year*
Erythrocytosis	Full blood exam, haematocrit	Baseline, at 3 to 6 months then annually
Bone density	Dual-energy x-ray absorptiometry	Baseline, then after 1 to 2 years
Prostate	Digital rectal examination, measurement of prostate-specific antigen	Baseline, at 3 to 6 months then as per guidelines for prostate cancer screening
Cardiovascular	Measurement of blood pressure, lipids, glucose and weight and smoking cessation	Baseline, at 3 to 6 months then as per predicted cardiovascular risk

* Protocol for measuring serum testosterone levels will be determined by choice of testosterone preparation.

although lower levels may be more appropriate in some older or elderly men (there are no age-specific reference ranges and recent data suggest that age per se does not lower serum testosterone in men who maintain optimal health as they age.[5] Short-acting intramuscular preparations lead to peaks and troughs, which limit the interpretation of serum testosterone levels. Long-acting intramuscular preparations are assessed by measuring testosterone levels before administration of the next dose to determine the optimal dose interval once the loading regimen is completed – the target range is typically 10 to 15 nmol/L.

Once stable testosterone levels are achieved monitoring should occur on a six- to 12-month basis. In men with primary hypogonadism, luteinising hormone levels can be measured (injectable therapies tend to lead to a greater suppression than transdermal or oral therapies). Dose adjustments are, however, routinely made on the basis of adequacy of the serum testosterone level. Oestrogen levels are not routinely measured. As testosterone is partly aromatised, oestradiol levels are expected to increase proportionally. Oestrogen is the most important determinant of bone density in men.

Specific considerations to treatment modality

Following initiation of testosterone therapy, men should be monitored for potential adverse effects relevant to the mode of androgen administration.[1,2] Transdermal therapies may cause local skin reactions and this most commonly occurs with the patch preparations. Intramuscular preparations may lead to bruising; therefore, use of anticoagulants or presence of a bleeding diathesis are usually considered to be contraindications to using this form of testosterone replacement.

Bone health

All men should undergo a baseline bone density study,[1] particularly if it is suspected that they may have had longstanding androgen deficiency. Further bone density testing will depend on the baseline result and/or the presence of low trauma fractures. Men with osteoporosis should undergo repeat testing 12 months after the initiation of testosterone therapy. All men should be advised about the importance of smoking cessation and the need to ensure adequate calcium and vitamin D intake, with supplements added if required.

Cardiovascular health

The relation between androgen status and cardiovascular health remains controversial. Epidemiological data have linked excess cardiovascular risk to low serum testosterone levels;[6] however, recent observational studies have suggested that exogenous testosterone may increase ischaemic events in older men.[7] Importantly, these data do not differentiate between men with testicular or pituitary disorders (and hypogonadal baseline testosterone levels) and those with age-related partial androgen deficiency, many of whom have adverse cardiometabolic profiles at baseline. Men with Klinefelter's syndrome have a slightly increased cardiovascular risk but it is not clear if this is specifically related to androgen status.

It is recommended that screening of blood pressure, lipids and fasting blood glucose be undertaken as per national guidelines (National Health and Medical Research Council and National Heart Foundation). Men should be counselled about the importance of maintaining a healthy body mass index and smoking cessation.

Erythrocytosis

Erythrocytosis is an important adverse effect of testosterone replacement that must routinely be monitored for.[1,2] It is seen more commonly in men taking intramuscular forms of testosterone, and men who are smokers and/or have a history of cardiorespiratory disease are at increased risk. Haemoglobin and haematocrit levels should be measured before commencement of treatment and after three months, and then six- to 12-monthly. A haematocrit level above 50% is a contraindication to testosterone therapy. Men with elevated haematocrit levels require dose adjustment and consideration of alternative modes of administration (e.g. transdermal rather than intramuscular) with reassessment of the haematocrit level after two to three months. Ongoing elevation of the haematocrit level in parallel with testosterone levels in the lower part of the target range requires further investigation and may necessitate periodic venesection.

Prostate health

Men with androgen deficiency who are supplemented with testosterone return to a risk of prostate cancer akin to that of their age-matched peers. Although there is no consensus about screening for prostate cancer for the general male population, the US Endocrine Society clinical practice guidelines on testosterone therapy in hypogonadal men recommend digital rectal examination and measurement of serum prostate-specific antigen levels before initiating testosterone replacement in men over 50 years of age, or over 40 years if the man has a family history of prostate cancer.[1] Repeat testing should be undertaken three and six months after treatment has commenced.

As prostate-specific antigen levels and prostate volumes increase in response to testosterone levels returning to approximately eugonadal levels, men receiving long-term testosterone therapy should be monitored as per guidelines for eugonadal men. Men with abnormal findings should be referred for urological assessment.

Moderate to severe benign prostatic hyperplasia and/or lower urinary tract symptoms, if present, should be addressed before men are commenced on testosterone treatment. Clinical surveillance for worsening of symptoms while taking treatment can be supported with the use of questionnaires such as the International Prostate Symptom Score.

Sleep apnoea

A baseline assessment for the presence of sleep apnoea should occur before commencing testosterone treatment, especially in obese men.[1] Although the literature is not consistent, sleep apnoea may be worsened by testosterone administration and enquiry about symptoms, including reported apnoea and excessive daytime sleepiness, should form part of routine clinical follow up. Men stable using continuous positive airway pressure therapy can take testosterone replacement therapy to age-appropriate levels.

Spermatogenesis

Fertility is an important consideration for men who are commencing or are established on testosterone replacement therapy. As the administration of exogenous testosterone impairs the function of the hypothalamo–pituitary–testicular axis, potentially for extended periods of time, plans for reproduction should be discussed well in advance. Men with secondary hypogonadism can be treated with gonadotrophins (luteinising hormone and follicle-stimulating hormone), which will optimise both spermatogenesis and testosterone production. The time to response depends on several factors, including the onset of hypogonadism (pre- or post-pubertal), prior treatment with testosterone and previous exposure to gonadotrophins. Reproductive options for men with primary hypogonadism should be assessed on an individual basis. Successful sperm retrieval is possible for men with primary testicular dysfunction, including those with Klinefelter's syndrome. As this may delay initiation of testosterone treatment or may require prolonged withdrawal of therapy, it is recommended that advice is sought from an endocrinologist/andrologist or fertility specialist.

Conclusion

The aim of testosterone replacement therapy is to return men with established hypothalamo–pituitary or testicular disease to a eugonadal state. Once an appropriate therapeutic regimen is established, clinical and biochemical surveillance protocols can usually be co-ordinated with testosterone administration (long-acting intramuscular preparations) or biannual (usually) provision of a prescription for other modalities (short-acting intramuscular, transdermal, oral preparations) and form part of a general healthcare program. **ET**

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