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Current concepts of low testosterone levels in ageing men

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Low testosterone levels are associated with increased risk of cardiovascular disease and increased mortality in ageing men. Men with pathologically based hypogonadism should be considered for testosterone supplementation. For older men suspected of being androgen deficient in the absence of pituitary or testicular disease, controversy exists because symptoms can be nonspecific, the definition of low testosterone levels is under debate and the risks of extended treatment are uncertain.

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Testosterone is the primary male sex hormone or androgen in men. Hypothalamic secretion of gonadotrophin-releasing hormone (GnRH) regulates pituitary secretion of luteinising hormone (LH), which in turn stimulates testicular secretion of testosterone (see Figure). Testosterone regulates male sexual development, virilisation and body composition. There is considerable interest in the putative relation of low endogenous testosterone levels to risk of cardiovascular disease and increased mortality in ageing men.

Men with an identifiable lesion within the hypothalamo-pituitary-gonadal axis, such as a pituitary tumour (or previous surgery or radiotherapy to the pituitary) or a primary testicular disorder, such as Klinefelter's syndrome, trauma, cytotoxic chemotherapy or orchitis, may exhibit pathologically based hypogonadism with a sound rationale for consideration of testosterone supplementation. Controversy arises over the definition of low testosterone levels in older men without pituitary or testicular disease, particularly in the context of nonspecific symptoms and limited outcome data from randomised controlled trials.

Assessment of hypogonadal men

Symptoms and signs of androgen deficiency include reduced libido, decreased spontaneous erections, loss of body hair and reduced need

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for shaving, gynaecomastia and increased risk of osteoporosis or fracture.[1] Less specific symptoms and signs include decreased energy, motivation and self-confidence, lower mood, mild anaemia, reduced muscle bulk and increased body fat.

Testicular volumes can be assessed using an orchidometer. Men with hypothalamic or pituitary disease have normal or low LH and low testosterone levels (secondary hypogonadism), whereas those with testicular disease have elevated LH and low testosterone levels (primary hypogonadism). Therefore, biochemical evaluation should include measurement of circulating testosterone and LH levels. Sex hormone-binding globulin (SHBG) levels can also be measured because testosterone levels may be influenced by very low or very high SHBG levels. Obesity is associated with decreased SHBG concentrations,[1] and calculated free testosterone levels can be normal when total testosterone levels are low in the setting of low SHBG levels. Hyperprolactinaemia results in secondary hypogonadism responsive to dopamine agonist therapy.

Measurement of testosterone levels should be made using early morning blood samples to minimise confounding from circadian variation, preferably with a testosterone assay using mass spectrometry rather than the less accurate immunoassay.[2] Men with pathologically based hypogonadism who have an identifiable disruption of the hypothalamo-pituitary-gonadal axis and symptoms and signs strongly suggestive of androgen

Key points

- Men who have an identifiable lesion of the hypothalamo-pituitary-gonadal axis or a primary testicular disorder may exhibit pathologically based hypogonadism. These men should be considered for testosterone supplementation.
- Symptoms and signs of androgen deficiency include reduced libido, decreased spontaneous erections, loss of body hair and reduced need for shaving, gynaecomastia, and increased risk of osteoporosis or fracture.
- Biochemical evaluation should include measurement of circulating testosterone and luteinising hormone levels.
- Low testosterone levels are associated with increased risk of cardiovascular disease and increased mortality in ageing men. In this context, it remains unclear whether a reduced testosterone level is a causal factor or a biomarker for ill health.
- Adequately powered randomised clinical trials investigating testosterone therapy in older men with hard clinical endpoints are needed.
- Consensus clinical guidelines currently recommend making a diagnosis of androgen deficiency only in symptomatic men with unequivocally low testosterone levels, with a careful discussion of the risks versus benefits of any intervention.

Figure. The hypothalamo-pituitary-gonadal axis and actions of testosterone.
ABBREVIATIONS: FSH = follicle-stimulating hormone; GnRH = gonadotrophin-releasing hormone; LH = luteinising hormone; SHBG = sex hormone-binding globulin.
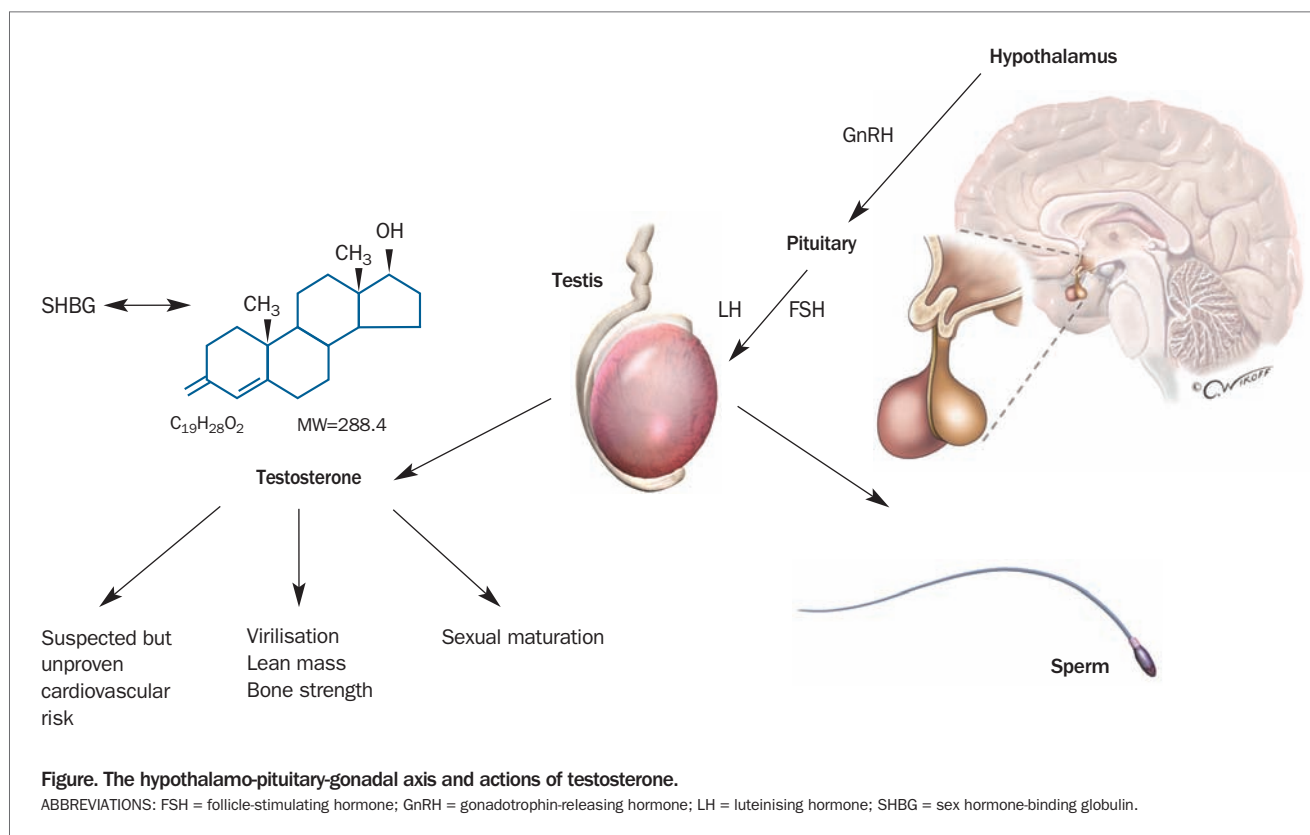
deficiency, qualify for subsidised therapy via the PBS under the authority 'androgen deficiency in males with established pituitary or testicular disorders' (see below for more details).

Declining testosterone levels and increasing ill health in ageing men

As men grow older, testosterone levels decline.[3] The difference has been estimated as 1% lower per year of age. Therefore, the older the sample of men examined the greater the proportion at or below any given threshold of testosterone.

There is ongoing debate over whether lower testosterone levels are a consequence of ageing or result from the cumulative effect of behavioural, lifestyle or health-related factors.[4] A higher body mass index is associated with lower free and total testosterone levels.[5,6] In older men testosterone levels in the low-normal range are associated with poorer health outcomes.[3,7]

In the Western Australian Health In Men Study (HIMS) involving 3638 community-dwelling men aged 70 years or older, testosterone levels in the lowest quartile were associated with increased incidence of stroke or transient ischaemic attack independently of conventional risk factors for cardiovascular disease.[8] A lower testosterone level was also associated with the presence of abdominal aortic aneurysm, a predictor of mortality from rupture or cardiovascular disease.[9] The HIMS and other studies have shown associations of low testosterone levels with increased risk of mortality.[10,11] However, there are no randomised controlled clinical trials of testosterone with the endpoint of incident cardiovascular events or mortality.[12] Such studies are difficult logistically because large numbers of men would need to be randomised and followed for an extended period of time to accumulate sufficient outcome events. Until such evidence is available, prescribing of testosterone therapy should be limited to men with proven androgen deficiency.[1,12]

Defining low testosterone levels

Currently the PBS allows consideration of testosterone therapy for 'androgen deficiency in males 40 years and older who do not have established pituitary or testicular disorders other than aging', with androgen deficiency confirmed by at least two testosterone levels of less than 8 nmol/L from blood samples taken on different mornings (see the full Schedule). Under these criteria therapy can also be considered for men with intermediate testosterone levels and high LH levels.

In community-dwelling older men serum testosterone is a continuous variable approximating the normal distribution.[5] It is therefore difficult to define a specific threshold as demarcating with sensitivity and specificity for 'low' testosterone levels in ageing men. Thresholds of 6.9, 9.8 or 10.4 nmol/L have been suggested, the latter two based on results in healthy younger men.[1,12,13] If the PBS threshold of less than 8 nmol/L is followed, then 5.2% of the 3638 men aged 70 to 89 years in HIMS would have had early morning testosterone levels below this level, albeit measured by immunoassay.[5] By comparison, 4.1% of 3369 men aged 40 to 79 years from the European Male Aging Study (EMAS) had testosterone levels below 8 nmol/L, measured using mass spectrometry.[14] However, fewer men in EMAS had symptoms consistent with androgen deficiency, as well as reduced testosterone levels.[14] Therefore, in the absence of pathologically based hypogonadism, only a minority of middle-aged and older men in the community would have testosterone levels low enough to warrant consideration of therapy. Recent Australian data suggest that the threshold for 'low' testosterone in men aged 70 years and above should be 6.4 nmol/L using mass spectrometry.[15]

Benefits of testosterone therapy

A meta-analysis of 29 randomised controlled trials involving 1083 men with a mean age of 64.5 years and baseline testosterone levels of 10.9 nmol/L indicated that the effects of testosterone therapy reduced total body fat (-1.6 kg), increased fat free mass (+1.6 kg) and increased bone mineral density (approximately 3% at lumbar spine) compared with placebo.[16]

A meta-analysis of 17 randomised placebo-controlled trials including 656 men aged 57.5 years with average testosterone levels at baseline of less than 12 nmol/L showed modestly improved sexual thoughts and motivation, frequency of successful intercourse and overall sexual satisfaction.[17] However, testosterone is less likely to improve symptoms of erectile dysfunction in men with predominantly neurovascular pathology.[18]

A placebo-controlled randomised trial of transdermal testosterone (50 mg/day) in 274 men aged 65 years or above with total testosterone levels of 12 nmol/L or less who were intermediate-frail or frail demonstrated an improvement in lower limb muscle strength over six months.[19] However, the benefit was not maintained at six months after cessation of therapy.[20]

Controversy following the TOM trial

Of note, the Testosterone in Older Men with Mobility Limitations (TOM) trial was a randomised, placebo-controlled trial investigating transdermal testosterone in men aged 65 years or above with a total testosterone level of 3.5 to 12.1 nmol/L and evidence of mobility limitation.[21] Therapy was started at a dose of 100 mg/day and titrated to maintain total testosterone levels in the range of 17.4 to 34.7 nmol/L. The trial was discontinued early because of a significantly higher incidence of adverse cardiovascular events in the testosterone group compared with placebo.[21] Therefore, caution is needed when considering more frail older men for testosterone therapy, and high doses of testosterone therapy are best avoided. This debate has been fuelled by retrospective analyses of patient databases examining outcomes in men prescribed testosterone. In different studies men prescribed testosterone have been reported to have lower mortality, a debatable increase in cardiovascular events, or possibly increased nonfatal myocardial infarction.[22-24] These studies have important limitations including nonrandom allocation to testosterone, the selective nature of data retrieved, and challenges related to the statistical analyses. Randomised clinical trials are needed to clarify the benefits and risks of testosterone in older men.

Screening and monitoring of patients on testosterone therapy

Consensus guidelines recommend pre-treatment screening of patients for prostate neoplasia, polycythaemia and obstructive sleep apnoea, and on-treatment monitoring of prostate-specific antigen, haematocrit and lipid profiles.[1] A review of 51 interventional studies reported that testosterone therapy was associated with an increase in haemoglobin and haematocrit levels, and a decrease in HDL-cholesterol levels, with no significant effect reported for incidence of prostate cancer, cardiovascular outcomes or mortality.[25] A recent meta-analysis found no definite evidence of increased cardiovascular adverse events associated with testosterone therapy.[26]

Efficacy of testosterone therapy can be gauged by symptomatic improvement, alterations in body composition and bone mineral density, and monitoring testosterone levels. However, long-term outcomes, optimal duration of treatment and risks of sustained therapy require clarification in adequately powered randomised controlled trials of extended duration.

Role of the GP

GPs play an important role in the initial assessment of patients with hypogonadism. Men presenting with symptoms suggestive of androgen deficiency should be carefully assessed because symptoms can be nonspecific.[1,12] Chronic disease, systemic illness or other factors known to be associated with low testosterone levels, such as obesity and use of alcohol, glucocorticoids, opiates or recreational drugs, need to be identified. Blood sampling for testosterone should be conducted early in the morning with use of an accurate assay.

Treatment should be directed at any underlying illness or condition predisposing to low testosterone levels. Men with testosterone levels in the normal range can be reassured that supplementation is not warranted. If pathologically based hypogonadism is present, testosterone supplementation can be considered. In older men without pituitary or testicular disease who have convincing symptoms and signs of androgen deficiency, the PBS criteria can be used as a threshold for classifying 'low' testosterone levels. The benefits versus risks of testosterone therapy need to be considered and discussed in an individual context for an informed decision to be made. Referral of patients to an endocrinologist is justifiable if there is doubt over the diagnosis of androgen deficiency or uncertainty regarding the optimal management plan.

Conclusion

Men with pathologically based hypogonadism merit evaluation for testosterone therapy. In the absence of pituitary or testicular disease, older men with symptoms and signs of androgen deficiency and confirmed low testosterone levels may be considered for testosterone supplementation. However, any decision to treat must be based on informed consent following careful discussion of benefits and risks of testosterone supplementation, acknowledging the incomplete evidence base. Men with normal testosterone levels should be discouraged from seeking hormonal therapy.   **ET**

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Hypogonadism in men:
diagnosis and treatment

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Low testosterone levels may be due to underlying disease or lifestyle factors 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. In and of itself, ageing results in a very small decrease in testosterone levels (0.1 nmol/year at most) from middle age onward. 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.

Outside of a research setting testosterone therapy is appropriate only for disorders of the hypothalamo-pituitary gonadal axis where a low serum testosterone level and a consequent clinical syndrome are present. 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 varies with the particular symptom and also varies between individuals, although is quite reproducible within an individual.[1,2] The abnormality in testosterone production may be the result of

1. 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

pathology 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 gonadotropic cells 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 Box 1 on this page. Under some circumstances, for example in response to glucocorticoid administration or in patients with haemochromatosis, the effects occur both at the levels of the hypothalamus and pituitary as well as the testis.

The clinical features of testosterone deficiency depend on the age of onset. During embryogenesis the abnormality depends on the degree of testosterone deficiency and timing, ranging from varying degrees of hypospadias, micropenis, and in the cases of complete androgen insensitivity where the defect is the receptor for androgens a female phenotype results. Testosterone deficiency occurring before the completion of pubertal development leads to delayed or incomplete sexual development, and body proportions become eunuchoidal where 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.[8] The higher prevalence from the MMAS most likely reflects secondary dysfunction of the hypothalamic-pituitary-gonadal axis resulting from a range of disease processes that increase with age. In these instances, targeting treatment to the primary disease process usually results in an increase in testosterone 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 less than 8 nmol/L on at least two occasions, or 8 to 15 nmol/L when LH is greater than 1.5 times above the upper limit of the eugonadal reference range for young men.

The total testosterone level should be measured in the morning after an overnight fast because levels tend to be highest on waking.[9,10] 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 single 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 11 nmol/L or above over the subsequent six months.[6,11,12]

Total testosterone levels reflect both albumin- and sex hormone binding

2. 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

3. 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

globulin (SHBG)-bound testosterone. SHBG, produced in the liver, is regulated by a number of factors (see Box 1) and variations in levels may be reflected by commensurately higher or lower levels of testosterone in standard total testosterone assays. Therefore, SHBG levels must be measured and taken into account when interpreting the results of total testosterone measurements.[13]

Although liquid chromatography tandem mass spectrometry is now considered to be the method with the highest precision for measuring sex steroids,[9,10,14] 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 Box 1), 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, cardiovascular disease, chronic liver disease, HIV infection, chronic obstructive airways disease and hypothyroidism can lower testosterone levels. It is important to recognise that cigarette smokers have testosterone levels 5 to 15% higher than nonsmokers; the reason for this is not entirely clear, but it is certainly no reason to start or continue smoking.

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 about one in 500 men.[15] Men with secondary hypogonadism need additional evaluation, including measurements of prolactin levels, other pituitary hormones, thyroxine, serum iron and transferrin saturation, and where indicated an MRI scan to exclude 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 wellbeing occurs.[3] Other indications include short-term adjuvant therapy in men with HIV infection and 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 Box 3).

Testosterone injections

Testosterone enanthate is administered by intramuscular injection at a dose of 250 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 to four weeks.[16,17] This 'surge and wane' effect is found unpleasant by many recipients.

A mix of four testosterone esters (testosterone isocaproate, testosterone phenylpropionate, testosterone propionate and testosterone decanoate) at a dose of 250 mg is administered by intramuscular injection 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.[1] An initial loading dose is followed six weeks later by a further dose and then regular doses are given approximately

every 12 weeks. The dose interval varies between patients, and in some cases 16 weeks between doses may suffice. Accordingly, monitoring of testosterone levels predose is advisable.

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.

A 2% testosterone solution containing 30 mg of testosterone per 1.5 mL of solution is available for topical use underarm. One application of 1.5 mL to each underarm once daily provides stable testosterone levels over 24 hours.

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.[18] 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.[19,20] Cough has been described after intramuscular injection of testosterone suspensions in oil, possibly due to pulmonary microemboli. It is recommended that these injections be administered very slowly. Topical applications, particularly patches, are associated with skin reactions. Specific concerns relating to testosterone therapy in general 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,[21,22] 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.[21]

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.[23] The adverse events occurred in those with the highest dose exposure and generally supraphysiological levels of testosterone. Two more recent studies, both based on retrospective assessment of large patient databases, have also raised concern about the cardiovascular safety of testosterone.[24,25] Both studies were, however, significantly flawed and other epidemiological studies are more reassuring.[26] Until adequately powered trials have been undertaken, testosterone should be used with caution in men with significant active cardiac disease.

Prostate cancer

There is general agreement that testosterone therapy does not cause prostate cancer.[3,27] 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.[27] 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 preexisting 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
- three to 12 hours after application for testosterone patches
- after one week for testosterone gels
- prior to 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.

CONCLUSIONS

True hypogonadism is not particularly common, 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 supratherapeutic levels confers no particular clinical benefit. MT

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An update on testosterone replacement therapies

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Effective treatments for testosterone deficiency are available for men at all ages. The choice of testosterone preparation depends on several factors, including length and severity of testosterone deficiency, pharmacokinetic profiles of the available preparations and the patient's age, comorbidities and personal preference.

Testosterone deficiency is one of the most common hormonal deficiencies in men, affecting approximately one in 200 men aged less than 60 years. It is categorised as primary (a consequence of intrinsic testicular damage or failure) or secondary (as a result of hypothalamic–pituitary disorders) and may be either congenital or acquired throughout a man's life.[1]

The role of testosterone replacement in men with established testosterone deficiency is of proven clinical efficacy and safety; however, its role in other clinical settings (e.g. male ageing, systemic illness) requires further study.[2]

Therapeutic options for testosterone prescribing

A number of modalities for testosterone replacement are currently approved for use in Australia (see Table). These include oral, transdermal, intramuscular and subdermal modalities. The available therapies have changed with the withdrawal of all testosterone implants and the delisting of an intramuscular preparation from the PBS. A new transdermal preparation with a novel mode of application has recently become available.

The PBS criteria for the prescription of testosterone in adult men are:
- androgen deficiency in men with established pituitary or testicular disorders
- androgen deficiency in men aged 40 years and older who do not have established pituitary or testicular disorders other than ageing, confirmed by at least two morning blood samples taken on different mornings. Androgen deficiency is confirmed by testosterone levels of less than 8 nmol/L, or 8 to 15 nmol/L with high levels of luteinising hormone (greater than 1.5 times the upper limit of the eugonadal reference range for young men).

The Figure demonstrates the changes in prescribing trends in Australia for androgen replacement therapy since 2000 according to PBS data.

Oral therapy

Testosterone undecanoate (Andriol Testocaps; 40 mg capsules) are absorbed via the intestinal lymphatic system and should be taken with a meal containing fat.[3] Daily doses vary from 160 to 240 mg in two to three divided doses. Gastrointestinal intolerances and frequent dosing limit clinical use, although it may be appropriate for initiating therapy when endogenous

Key points

- **Testosterone deficiency is common in the male population.**
- **Several therapeutic options are available to treat men with testosterone deficiency.**
- **There have been recent changes in testosterone products available on the PBS with the addition of a metered pump applicator and the withdrawal of subcutaneous pellets.**
- **The modality of testosterone replacement should be individualised according to patient convenience, compliance and side effect profile.**
- **Patients need to be assessed for contraindications before commencing testosterone therapy and monitored during therapy for the development of adverse effects.**

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Table. Summary of currently available testosterone preparations for use in men with testosterone deficiency

| Trade name	Generic name	Route of administration	Preparation	Typical dose regimen
Andriol Testocaps	Testosterone undecanoate	Oral	40 mg	80 to 160 mg in 2 to 3 divided doses daily
Androderm	Testosterone patches	Transdermal	2.5 mg per 24 hours 5.0 mg per 24 hours	2.5 to 5.0 mg daily
Testogel	Testosterone gel	Transdermal	1%, 50 mg per 24 hours (1 sachet)	2.5 to 5.0 g daily
AndroForte*	Testosterone cream	Transdermal	5%, 50 mg per mL 2%, 20 mg per mL	20 to 50 mg daily
Axiron	Testosterone transdermal solution	Transdermal	2%, 30 mg/1.5 mL (1 actuation)	30 to 60 mg daily
Sustanon*	Mixed testosterone esters	Intramuscular	250 mg per mL	250 mg every 2 to 3 weeks
Primoteston Depot	Testosterone enanthate	Intramuscular	250 mg per mL	250 mg every 2 to 3 weeks
Reandron 1000	Testosterone undecanoate	Intramuscular	1000 mg per 4 mL	1000 mg every 12 weeks (additional loading dose at 6 weeks)

*Not available on the PBS.
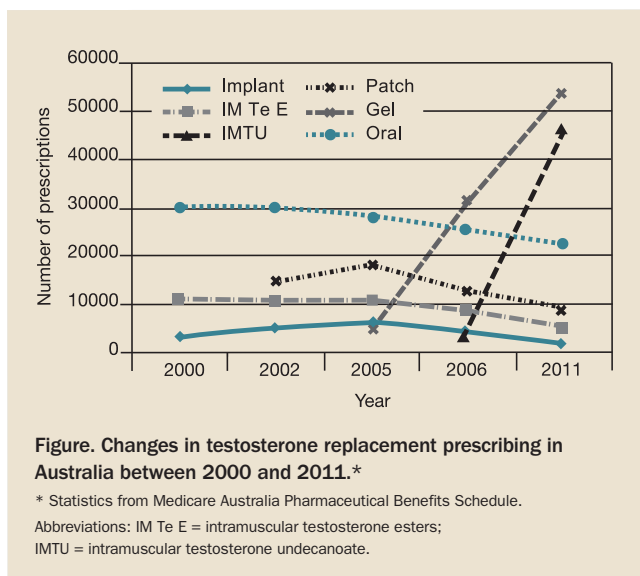
Figure. Changes in testosterone replacement prescribing in Australia between 2000 and 2011.*

* Statistics from Medicare Australia Pharmaceutical Benefits Schedule.

Abbreviations: IM Te E = intramuscular testosterone esters; IMTU = intramuscular testosterone undecanoate.

levels have been low for a prolonged period of time and/or when only modest elevations in serum testosterone levels are required (e.g. in elderly men). It is safe for use in men with bleeding disorders in whom injections or implants are not suitable.

Transdermal therapies

Nonscrotal testosterone patches (Androderm) are applied nightly to the back, stomach, thighs or upper arms. They mimic normal circadian rhythms of testosterone concentrations, peaking in the morning and declining slowly to a nadir in the evening. They achieve stable serum levels over a few days, resulting in maintenance of relatively stable energy levels, mood and libido.[4] These patches are available in two strengths, 12.2 mg (releasing 2.5 mg/24 hours) and 24.3 mg (releasing 5 mg/24 hours). Application sites should be rotated daily to reduce skin irritation, avoiding sites with excessive hair and oil to promote adhesion. Showering and recreational water

activities should not affect adherence; however, strenuous exercise and perspiration may result in loosening and detachment. Use of these patches may be limited by skin irritation due to the addition of permeation enhancers.[5] The skin irritation can be minimised by using corticosteroid creams on the skin beneath the patch.

A testosterone gel 1% preparation (Testogel) is also available and is formulated as 5 g sachets containing 50 mg testosterone. The gel is applied once daily to the shoulders and torso. Approximately 10% of the gel is absorbed into the skin where it remains in the stratum corneum as a reservoir that is slowly released over hours. Serum testosterone concentrations reach normal range within a month and remain in steady state throughout the 24-hour period.[6] The testosterone gel has been shown to have similar clinical efficacy to that achieved with the patches but produces less skin irritation.[7] For several hours after application, men using the gel need to avoid direct physical contact with others (to prevent interpersonal transfer) and to avoid washing.

A testosterone cream (AndroForte) is available from the manufacturer. This testosterone cream contains 50 mg testosterone per 1 mL and is applied via a dose measuring applicator once daily to clean, dry scrotal skin. It is massaged into the scrotum until the cream is absorbed (usually 30 to 60 seconds). An alternative formulation containing 20 mg/mL testosterone is also available (see: http://www.lawleypharm.com.au/pharm/products/androforte.html).

A 2% testosterone formulation (Axiron) presented in a metered dose pump with an applicator is now available for use in Australia. Dosing is based on the amount of liquid pumped into the applicator (each depressed pump of 1.5 mL yields 30 mg testosterone). The preparation is applied once daily to the underarms in a similar fashion to roll-on deodorant. It has similar efficacy to other transdermal preparations with normalisation of serum testosterone levels.[8] It was well tolerated in an open-label trial, with few subjects discontinuing use because of side effects, the most common of which was application-site irritation including erythema.[9] The use of deodorants and antiperspirants does not impede efficacy, but they

should be applied before the testosterone preparation. This preparation became available on the PBS on 1 March 2013.

Intramuscular therapies

Intramuscular injections (Sustanon and Primoteston Depot) use esterified testosterone. Esterification renders testosterone less polar and more lipid soluble, thereby prolonging its duration of action. Although the esterification of testosterone provides a sustained release, nonlinear and different esters provide varying half-lives. Sustanon contains a combination of four different testosterone esters whereas Primoteston Depot contains the single ester testosterone enanthate. The typical dose is 200 to 250 mg, which is administered as a depot every two to three weeks. The interval between injections may produce wide variations in testosterone levels over the weeks with initial supraphysiological levels followed by a gradual decline, which may result in fluctuations in energy, mood and libido in many patients.[10] A reduced dose of 100 mg administered more frequently, for example weekly, may ameliorate these fluctuations. This form of therapy requires a deep intramuscular injection; therefore, it is contraindicated in men who are taking anticoagulants and those with bleeding diatheses due to the risk of haematoma formation. Sustanon is no longer available on the PBS but is available on private prescription.

More recently, a longer-acting intramuscular injection (Reandron 1000) has become available.[11] This is administered initially at 0, 6, 18 and 30 weeks with the ongoing dosage interval determined by preinjection serum testosterone levels (commonly 10 to 14 weeks). Dependent on the patient's age, symptoms of androgen deficiency and comorbidities, a nadir serum testosterone level between 10 and 15 nmol/L is usually considered appropriate. Administered as a 4 mL injection with a castor oil vehicle into the buttock, it is usually well tolerated, requiring little analgesia and causing minimal interference in daily activities.[12] Although the extended dosing interval is appropriate in younger men, because of the long duration of action it should be used with caution in older men who may be at risk of developing clinically significant prostate disease, including carcinoma of the prostate. It is contraindicated in men who are taking anticoagulants or who have a bleeding diathesis.

Subdermal therapies

Subcutaneous testosterone pellets, which were available in 100 mg and 200 mg strengths, were withdrawn from the Australian market at the end of 2012. When used, testosterone pellets (usual dose 600 to 800 mg) were inserted into the subdermal fat of the buttocks, abdomen or thigh under local anaesthetic every four to six months.[13] The infrequent administration of the implants was often suited to younger patients who were unlikely to need to terminate their therapy. Stable physiological levels of testosterone were achieved with a slow decline over four to six months. Dosing intervals were individualised according to serum testosterone levels and symptoms of androgen deficiency.[14] Pellet extrusion (5 to 10%), infection and fibrosis were potential adverse events.

Contraindications to prescribing testosterone[2]

- Hormonally-dependent malignancies (prostate or breast)
- Abnormal prostate examination or an elevated prostate-specific antigen level (before urological review)
- Haematocrit value above 50%
- Untreated severe obstructive sleep apnoea
- Severe lower urinary tract symptoms
- Uncontrolled or poorly controlled heart failure
- Desire for fertility

Contraindications to prescribing testosterone

Clinical assessment and relevant laboratory testing should be undertaken before prescribing testosterone. The box on this page lists the accepted contraindications to testosterone therapy.[2]

Conclusion

Testosterone deficiency is important to recognise in men of all ages as treatments are available with long-term efficacy and safety that improve the clinical features of androgen deficiency.

The choice of testosterone preparation for an individual man depends on several factors, including duration and severity of testosterone deficiency, pharmacokinetic profiles of the available preparations and the patient's age, comorbidities and personal preference. **ET**

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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.

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.**

TESTOSTERONE CRYSTALS (LIGHT MICROGRAPH). © GETTY IMAGES/SPL/SIDNEY MOULDS
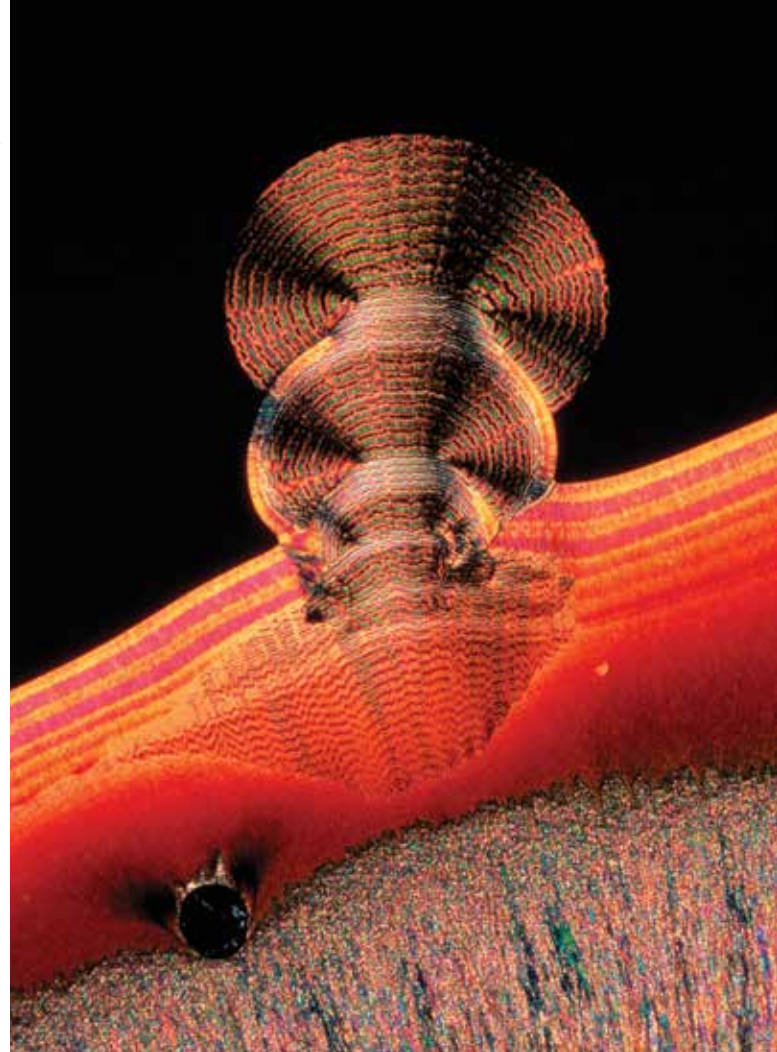
Notwithstanding the uncertainties about the role of testosterone supplementation in men with age-related declines in serum testosterone levels, androgen deficiency remains the most common hormonal disorder in men, occurring in approximately one in 200 adult men. Men with proven testicular or hypothalamo–pituitary 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,

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

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

* 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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Obesity
A growing issue for male fertility

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Obesity in men has been associated with reduced fertility. The impact of paternal body mass index on fertility is multifactorial, with increased weight associated with endocrine dysregulation and impaired sexual desire and function. Weight loss may improve fertility outcomes as well as conferring longer-term health benefits.

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Obesity is a growing health issue that causes substantial morbidity and mortality. Epidemiological data suggest an association between increasing body mass index (BMI) and reduced fertility in men, with one study suggesting that a gain of 10 kg decreases male fertility by approximately 10%.[1] The effect of BMI on male fertility is multifactorial, with increased weight associated with changes in sex hormone profile and impaired sexual desire and function. Some studies also suggest poorer semen parameters in overweight men.

Despite the prevalence and costs of male subfertility, there are few data regarding the fertility benefits of weight loss in men. Although weight reduction may normalise the hormone profile, the extent that this improves fertility and the time course of any improvement are unclear.

FACTORS CONTRIBUTING TO SUBFERTILITY IN OBESE MEN

Increased BMI is strongly associated with both hormonal dysregulation and poorer sexual function in men, which can impair fertility, as outlined in the flowchart on page 21.
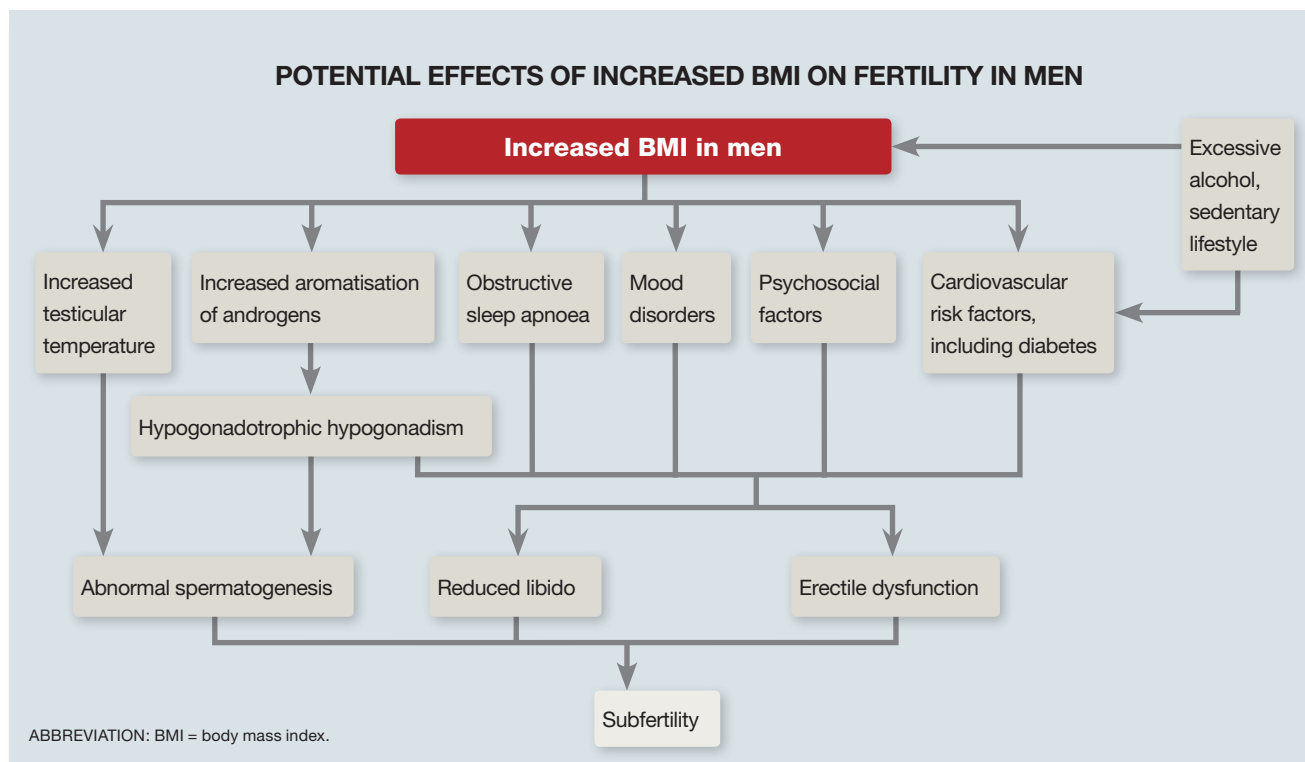
Hormonal dysregulation

Excess body weight has numerous effects on the reproductive hormone profile in men, leading to:

- a relative excess of oestrogen
- resultant suppression of hypothalamic secretion of gonadotrophin-releasing hormone (GnRH)
- reduced serum levels of gonadotrophins (luteinising hormone and follicle stimulating hormone)
- reduced serum testosterone levels.

© GETTY IMAGES/OF SCIENCE EYE. SPERM FERTILISING AN OVUM

POTENTIAL EFFECTS OF INCREASED BMI ON FERTILITY IN MEN

ABBREVIATION: BMI = body mass index.

Furthermore, there may be a feedback effect as there is a well-recognised association between hypogonadism and the metabolic syndrome, which itself is associated with increased weight.

Effects on testosterone
BMI is a strong predictor of low serum total testosterone concentrations in men, with a clear inverse correlation shown in many studies. BMI is also inversely proportional to free testosterone concentrations, suggesting an association even after accounting for lower sex hormone binding globulin levels due to insulin resistance.[2]

Effects on other reproductive hormones
Low serum testosterone in overweight men is associated with inappropriately low-to-normal levels of gonadotrophins. This reversible hypogonadotrophic hypogonadism includes hyperoestrogenism as a significant component. Androgens are converted to oestrone and oestradiol by the aromatase enzyme in adipose tissue.

In overweight men, the increased adipose tissue mass and upregulation of aromatase activity lead to excess peripheral aromatisation of androgens. The resulting hyperoestrogenism exerts a negative feedback effect on hypothalamic GnRH pulses, reducing stimulation of gonadotrophin secretion. Circulating oestrogens may also have a direct adverse effect on testicular function. In addition, circulating endogenous opioids are likely to have a pathophysiological role in the development of hypogonadotrophic hypogonadism in overweight men.

Reduced libido and erectile dysfunction
Although hormonal dysregulation may affect semen quality, as described below, the primary reasons for the reduced fertility rate observed in obese men may be decreased sexual desire and impaired sexual function. Potential contributing factors include androgen deficiency, organic causes of erectile dysfunction (ED) and psychosocial factors.

Obese men report poorer sexual desire and satisfaction compared with control subjects, which may contribute to avoidance of sexual encounters.[3] Overweight individuals are more likely to have chronic medical comorbidities and to be of lower socioeconomic class with resulting financial or domestic problems that can reduce libido. Depressive illness is also more common, and correlates with both low libido and ED. Low libido ultimately results in reduced coital frequency, lowering fertility rates.

In addition, sexual dysfunction is an important contributor to subfertility, with the presence of ED being correlated with lower fertility rates in men. ED is more prevalent in men with higher BMI. Its aetiology in this setting is multifactorial, including androgen deficiency and vasculogenic dysfunction.

Medical comorbidities such as the metabolic syndrome are significantly associated with ED. Both diabetes and hypertension are associated with vascular dysfunction, and diabetes may also lead to neuropathic

TABLE. FERTILITY ASSESSMENT OF OVERWEIGHT MEN

History

Risk factors for male infertility	• Previous history of infertility • Family history of infertility • Genital trauma or infection (e.g. orchitis) • Cryptorchidism, testicular tumours • Previous inguinal or pelvic surgery • Previous chemotherapy or radiotherapy • Occupational or environmental toxin exposure • Current medications • Tobacco, alcohol, anabolic steroid use
Symptoms of androgen deficiency	• Decreased sexual desire • Decreased sexual function • Reduced sense of wellbeing, energy, mood
Comorbidities	• History of cardiovascular disease, stroke • Diabetes mellitus, dyslipidaemia, hypertension • Obstructive sleep apnoea

Physical examination

General examination	• Height, weight, waist circumference • Blood pressure
Genital examination	• Testicular volume • Epididymis, vas deferens • Signs of androgen deficiency • Secondary sexual characteristics • Gynaecomastia • Hair distribution

Investigations

Reproductive and other hormones	• Total and calculated free testosterone and SHBG levels • FSH, LH and prolactin levels; thyroid function tests
Semen analysis	• Sperm concentration, motility, morphology
Cardiovascular risk	• Diabetes screen • Lipid profile
Other	• Liver function tests (to exclude nonalcoholic fatty liver disease) • Sleep study (if symptoms of obstructive sleep apnoea)

ABBREVIATIONS: FSH = follicle stimulating hormone; LH = luteinising hormone; SHBG = sex hormone binding globulin.

complications. Furthermore, obstructive sleep apnoea (OSA) is more common in obese men and is strongly independently linked with both ED and androgen deficiency.

Reduced sperm quality

Effect of BMI on semen parameters

The relationship between BMI and subfertility is not completely explained by obesity-associated sexual dysfunction and reduced frequency of intercourse. Changes with increased BMI, including hormonal imbalance and increased testicular temperature, may impair semen parameters. Some recent studies have attributed decreased spermatozoa concentration, reduced motility and increased sperm DNA fragmentation to obesity.[4,5]

However, data are conflicting, and the relationship between BMI and reduced sperm concentration was not confirmed by a recent systematic review.[6] Furthermore, the effects of increased BMI on qualitative parameters are more contentious. Although the data increasingly suggest a modest decrease in progressive sperm motility, no difference in sperm morphology has been clearly demonstrated between obese and normal weight men.

Recent studies have reported an association between increased BMI and higher levels of sperm DNA fragmentation, with the effect being most pronounced in obese men.[4] DNA fragmentation may correlate with poorer sperm quality and integrity, and consequently be associated with reduced fertility and an increased incidence of subsequent miscarriage. Additionally, mouse models suggest that paternal obesity may have metabolic sequelae and lead to subfertility in offspring through epigenetic effects.

Effect of BMI on assisted reproductive technology outcomes

With the increasing use of assisted reproductive technology, the impact of paternal BMI on their outcomes is pertinent. Increased paternal BMI has been associated with reduced chemical and clinical pregnancy rates, as well as lower live-birth rates.[7] This may be a result of sperm dysfunction that is not detectable by standard analysis. In addition to effects on implantation and pregnancy rates, there have also been suggestions that paternal obesity may have an impact on blastocyst development, possibly as a consequence of sperm DNA damage.

Lifestyle and environmental factors

A range of potentially remediable lifestyle factors can affect fertility and should be

addressed in all men with subfertility. Some of these factors, such as a sedentary lifestyle, are associated with obesity.

Sedentary lifestyle. Prolonged sitting, in combination with increased lower abdominal and scrotal fat deposition, might adversely affect sperm production by increasing testicular temperature.

Tobacco. Tobacco use has a modest dose-dependent effect on sperm quality, with lower sperm concentration and poorer sperm motility seen in smokers.[8] Furthermore, smoking may decrease the success rate of assisted reproductive technologies, including in vitro fertilisation and intracytoplasmic sperm injection. Sperm isolated from smokers have poorer function and higher DNA fragmentation, suggesting a direct detrimental effect of tobacco on sperm DNA. These outcomes may be reversible within a year of tobacco cessation.

Alcohol. Heavy alcohol use may be associated with hypogonadism, poorer sperm quality and sexual dysfunction.

Cannabis. Although human data regarding the effects of cannabis on male fertility are limited, it has been suggested that cannabis may activate cannabinoid receptors located on sperm. These receptors are believed to be responsible for regulating sperm motility. Furthermore, cannabis use has been linked with abnormal sperm motility and impaired fertility in male mice.[9]

MANAGEMENT OF OVERWEIGHT MEN WITH SUBFERTILITY

Patient assessment

Assessment of overweight men with subfertility should include a basic fertility assessment to ensure that other causes of male subfertility are not overlooked.[10] The potential contribution of female factors must also be considered. A male fertility assessment tool developed by Andrology Australia is available for free download at www.andrologyaustralia.org/patient-assessment-tools. Points to cover in a fertility assessment of overweight men are summarised in the Table.

In addition to the basic fertility assessment, evaluation of overweight men should focus on identifying obesity-associated comorbidities and lifestyle factors that may play a significant role in the aetiology of subfertility as well as confer significant cardiovascular risk. Cardiovascular assessment should include inquiring about erectile dysfunction, measuring blood pressure and screening for diabetes and dyslipidaemia. The importance of ED as an independent risk factor for metabolic syndrome and cardiovascular disease is increasingly being recognised, with ED representing a surrogate biomarker for endothelial dysfunction and atherosclerosis. OSA and depression should also be considered in all overweight men.

The initial assessment of a couple with subfertility by a GP can expedite their evaluation and ensure they are referred to an appropriate specialist, such as an endocrinologist and/or a gynaecologist specialising in assisted reproductive technology.

Treatment

There are limited data regarding the fertility outcomes of interventions in obese men. Nevertheless, a patient consultation about fertility is an opportunity for a GP to establish a therapeutic relationship with the patient and to promote lifestyle modifications and weight loss that will have

long-term cardiovascular benefits. These include tobacco cessation, avoidance of excessive alcohol and promotion of moderate exercise. Identified comorbidities, such as diabetes, dyslipidaemia and OSA, should also be treated. Treatment of OSA with continuous positive airway pressure (CPAP) has been shown to increase testosterone levels.

Weight loss

Weight loss can reverse the hormonal abnormalities seen in overweight men, while also improving comorbidities such as OSA.[11] Biochemical changes that correlate with weight loss include increases in serum testosterone and sex hormone binding globulin levels and decreases in oestradiol levels. Nonsurgical approaches to weight loss include low-calorie diets, increased physical exercise and sometimes pharmacological therapy to help maintenance of weight loss. Bariatric surgery allows greater and more sustained weight loss. Reduced BMI in men after bariatric surgery has been shown to improve their sexual desire and satisfaction, as well as erectile function.[12]

There are limited data demonstrating a direct impact of weight loss on semen parameters. Furthermore, the effects of paternal obesity on spermatogenesis are likely to be at most modest, with most male subfertility and significant sperm defects

being a result of intrinsic disorders of spermatogenesis rather than solely attributable to BMI. It would thus be remiss to overstate the effects of overweight on fertility and to rely exclusively on weight loss as a cure for subfertility in obese men.

Other treatments

Although weight loss improves the hormone profile, there are few data regarding therapies that directly target endocrine abnormalities in obese men. Aromatase inhibitors might potentially correct oestrogen excess and ameliorate hypogonadotrophic hypogonadism, but this intervention has not been well studied in obese men, and these drugs are not approved for this indication. Notably, even in the presence of hypogonadism, exogenous androgens should not be prescribed in obese men seeking fertility because of their contraceptive action.

Other potential therapies include the use of phosphodiesterase inhibitors to improve erectile function. Scrotal lipectomy to remove accumulated fat has been advocated to reduce scrotal temperature.

CONCLUSION

Male obesity is a significant health issue and is associated with decreased fertility. The association is likely to involve multiple factors, including endocrine dysregulation, reduced sexual desire and function, comorbidities such as OSA, and suboptimal semen parameters. Although there are limited data demonstrating the direct benefits of weight loss on semen parameters and sperm quality, weight loss has been shown to improve the hormone profile and is linked with improved sexual function. Importantly, a consultation about fertility provides a rare opportunity for GPs to engage with obese men about their weight, lifestyle choices and cardiovascular health. Practice points regarding male obesity and fertility are summarised in the Box. MT

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