ANDROLOGY AUSTRALIA

Androgen deficiency in men

Presentations of androgen deficiency may be subtle, therefore it is important that the diagnosis is actively considered. Testosterone therapy is highly effective for younger men with established androgen deficiency, but its role in older men is less clear.

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Androgen deficiency (also termed testosterone deficiency or hypoandrogenism) is the most common hormonal disorder in men, affecting approximately one in 200 men under 60 years of age.[1] However, its clinical presentation may be subtle and the diagnosis overlooked unless it is actively considered. This article describes the presentation, diagnosis and management of androgen deficiency in men. The controversial area of androgen deficiency in ageing men is also discussed.

Androgen physiology

The predominant androgen in males is testosterone, 95% of which is secreted by testicular Leydig cells. Testosterone production is under the influence of luteinising hormone (LH), which is released from the pituitary gland. Most circulating testosterone is bound to carrier proteins – 44% to sex hormone binding globulin (SHBG) and 54% to albumin. The majority of testosterone that is produced daily (6 mg) is inactivated in the liver.[2] A small amount of testosterone is converted to

IN SUMMARY

- **The presentation of androgen deficiency may be subtle, therefore the diagnosis needs to be actively considered in the appropriate clinical context.**
- **Klinefelter's syndrome is the most common cause of primary hypogonadism. Secondary hypogonadism is caused by hypothalamo-pituitary disorders such as pituitary tumours (especially prolactinoma) and iron overload disorders such as haemochromatosis and thalassaemia.**
- **Serum total testosterone is the best method for assessing androgenic status. Calculated free testosterone values correlate well with actual free testosterone, but no published population-based reference ranges exist. Therefore calculated free testosterone levels must be interpreted with caution.**
- **A low serum LH in the presence of low testosterone raises the possibility of secondary hypogonadism. Investigation may involve assessment of prolactin, anterior pituitary hormones and iron levels.**
- **The benefits of treatment in testosterone-deficient men are well established. Clinical responses to treatment are important in determining the dose and frequency of testosterone replacement therapy.**
- **The treatment of symptomatic ageing men with borderline serum testosterone levels remains controversial, with the benefits and risks of testosterone therapy largely unknown.**

Table 1. Causes of androgen deficiency

Testicular (primary)

Chromosomal – Klinefelter's syndrome (most common cause of primary hypogonadism)
Undescended testes (cryptorchidism)
Surgery – bilateral orchidectomy
Trauma
Infection – mumps orchitis
Radiotherapy, chemotherapy, drugs (e.g. spironolactone, ketoconazole)
Systemic disease (e.g. haemochromatosis, thalassaemia, myotonic dystrophy)

Hypothalamo-pituitary (secondary)

Idiopathic hypogonadotrophic hypogonadism – Kallmann's syndrome
Pituitary disease:
- microadenoma: prolactinoma
- macroadenoma: nonfunctional
- panhypopituitarism – after surgery or radiotherapy

Haemochromatosis, thalassaemia

Important clinical features of Klinefelter's syndrome

Reproductive

Germ cell failure: small firm testes (<4 mL in volume), infertility
Leydig cell failure: failure to progress through puberty, gynaecomastia, eunuchoidal proportions, diminished body hair, decreased muscle mass

Nonreproductive*

Impaired glucose tolerance, diabetes mellitus, hypo- or hyperthyroidism
Mitral valve prolapse, ischaemic heart disease, venous thromboembolism
Mediastinal, breast cancer
Learning difficulties and behavioural problems, particularly in adolescents

* Except for cognitive and behavioural features, the absolute risk of these recognised disease associations is low.

bioactive metabolites – 4% to dihydrotestosterone and 0.2% to oestradiol.[1] Oestrogens play an important role in bone health in men.[3]

Aetiology

Common causes of androgen deficiency are listed in Table 1. Klinefelter's syndrome is the most common cause of primary hypogonadism (prevalence of one in 650 male births).[4] Patients who are diagnosed with Klinefelter's syndrome usually present during puberty or in association with infertility, but a recent study has suggested that 75% of cases remain undiagnosed.[5] The clinical features are listed in the box on this page – the presence of small firm testes (<4 mL in volume in early adulthood) is highly suggestive. A diagnosis of Klinefelter's syndrome can be confirmed with karyotyping (47 XXY).

Primary testicular disease may be associated with impaired spermatogenesis, so the coexistence of androgen deficiency needs to be considered in the infertile man. A minority of patients presenting with male infertility have androgen deficiency requiring immediate testosterone treatment. The remainder require long term follow up of their androgen status because testicular dysfunction may leave them at greater risk of subsequent androgen deficiency.

Secondary hypogonadism is caused by hypothalamo-pituitary disorders such as pituitary tumours (especially prolactinoma) and iron overload disorders such as haemochromatosis and thalassaemia. In these settings, low testosterone and gonadotrophin levels may be accompanied by other pituitary hormone deficiencies. Iron overload disorders may also affect the testes directly.

Assessment

History and examination

The features of androgen deficiency depend on its time of onset and severity. The following information should be sought specifically when the medical history is taken:

- undescended testes
- surgery of the testes
- pubertal development
- previous fertility
- genitourinary infection
- coexistent medical illness (such as pituitary disease, thalassaemia, haemochromatosis)
- changes in general wellbeing or sexual function (androgen deficiency is an uncommon cause of erectile dysfunction, but all men presenting with erectile dysfunction should be evaluated for androgen deficiency)
- degree of virilisation
- use of prescribed or recreational drugs.

The clinical features of androgen deficiency are listed in Table 2. In adolescence, androgen deficiency manifests as small testes, delayed or incomplete puberty, eunuchoid proportions and gynaecomastia (Figures 1a and b). Adult onset of androgen deficiency produces a number of features, but the clinical scenario may vary, depending on the rate and extent of the fall in testosterone levels.

Low testicular volume is an important indicator of underlying pituitary or testicular pathology. Normal testicular volumes, assessed using an orchidometer (Figure 2a), are:

- childhood, less than 3 mL
- puberty, 4 to 14 mL
- adulthood, 15 to 35 mL (Figure 2b).

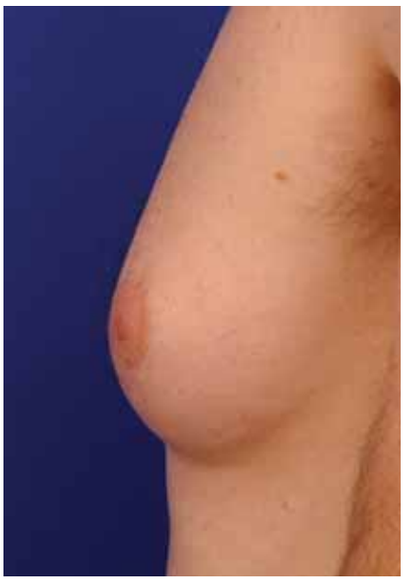
Table 2. Clinical features of androgen deficiency

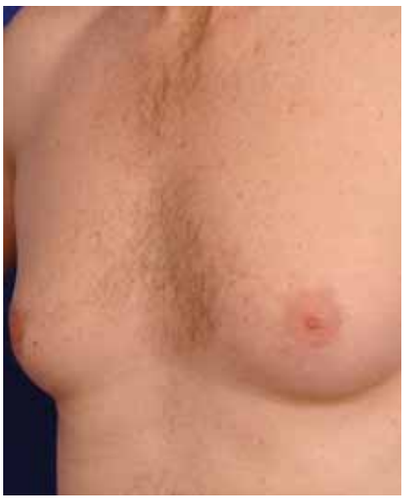
In adolescence

- Late or incomplete sexual and somatic maturation
- Small testes
- Failure of growth of the larynx
- Genital (failure of enlarged phallus and skin of scrotum becoming thickened and pigmented)
- Eunuchoid proportions (arm span exceeding height by ≥5 cm)
- Poor muscle development
- Poor facial, body and pubic hair (later onset of shaving)
- Gynaecomastia

In adulthood

- Regression of some features of virilisation
- Mood changes (low mood and irritability)
- Poor concentration
- Low energy (lethargy and lack of stamina)
- Reduced muscle strength
- Decreased libido
- Hot flushes and sweats
- Gynaecomastia
- Osteoporosis
- Low semen volume
- Reduced beard or body growth
- Erectile dysfunction (uncommon)





Figures 1a and b. Gynaecomastia.

IMAGES COURTESY OF MR G. SOUTHWICK, MELBOURNE INSTITUTE OF PLASTIC SURGERY, VIC.

Endocrine laboratory assessment

Serum total testosterone is the best measure of assessing androgenic status. Because of the circadian nature of testosterone production, blood samples should be taken in the morning,[6] and all abnormal values need to be confirmed with a second test on a different day.

Reference ranges for total testosterone in males depend on the assay employed. In a study of healthy fertile young men supported by Andrology Australia, considerable variability in total testosterone reference intervals was demonstrated for a number of immunoassay platforms that are used across the country when compared with mass spectroscopy – a gold standard.[7] This finding indicates a need for improvement in testosterone measurement and reporting.

Other measures of testosterone status include bioavailable testosterone (measurement of which is not widely available) and direct measurement of free testosterone by equilibrium dialysis (a technique that is impractical for routine use) or commercial kits (which are technically flawed and should not be used). Most often, free testosterone is estimated by either the free androgen index (FAI) or calculated free testosterone. However, the FAI (total testosterone/SHBG x 100%), although validated for use in women, is not reliable in men.[8] Calculated free total testosterone, which is based on levels of total testosterone, SHBG and albumin,[9] provides values which correlate well with actual free testosterone, but no published population-based reference ranges exist and therefore these levels must be interpreted with caution.

Serum LH levels are elevated in response to declining negative testosterone feedback and may be used in the diagnosis of primary androgen deficiency. In the presence of low testosterone, a low serum LH raises the possibility of secondary hypogonadism. The investigation of possible secondary hypogonadism includes prolactin levels (micro- or macroprolactinoma), anterior pituitary hormone levels (hypopituitarism) and iron levels (iron overload disorders – haemochromatosis, thalassaemia).

It should be noted that older men with age-related androgen deficiency may not exhibit a compensatory rise in LH levels.

Other investigations

Other relevant investigations may include chromosome analysis and pituitary imaging.[10] A DEXA study will determine the presence of osteopenia or osteoporosis. Semen analysis will document impaired spermatogenesis.

Treatment

Treatment of androgen deficiency should be an important goal for GPs because therapy is highly effective in restoring normal sexual function and libido, optimising bone and muscle health, improving aspects of mood and cognition, and enhancing overall quality of life. It may

Figures 2a and b. An orchidometer (a, left) shown being used to measure testes size (b, right) in a normal adult male with 30 mL testes.

also reduce cardiovascular disease risk. Androgen replacement therapy is usually lifelong and should only be started after androgen deficiency has been proven by hormone assays.

The testosterone preparations currently available are reviewed in Table 3.[11-16] Approved indications for subsidised testosterone therapy via the PBS, which are based on the consensus guidelines established by the Endocrine Society of Australia,[10] are summarised in the box on this page. Absolute contraindications to androgen replacement therapy are known or suspected hormone-dependent malignancies (prostate or breast), and hematocrit greater than 55%. Certain adverse effects, including polycythaemia and sleep apnoea must be sought prospectively – especially in older men – but the testosterone preparations discussed in Table 3 do not cause abnormal liver function. Older men treated outside of these guidelines should be informed that the long term risk–benefit profile of testosterone therapy is not yet documented.

It should be noted that exogenous testosterone results in suppression of spermatogenesis in eugonadal men. In men with secondary causes of androgen deficiency in whom fertility is desired, testosterone therapy should be withdrawn and gonadotrophin therapy instituted.

Monitoring

The goals of androgen replacement therapy are to:

- restore sexual function, libido, wellbeing and behaviour
- produce and maintain virilisation
- optimise bone density and prevent osteoporosis
- increase muscle and decrease fat mass.

The benefits of treatment in men who are testosterone deficient are well established.[17] Clinical responses to treatment are important in determining the dose and frequency of testosterone replacement therapy.

Androgen levels

Measurements of serum testosterone levels taken to monitor androgen replacement therapy must be interpreted in the context of the mode of the therapy being administered. They are best measured at the following times:

- standard injections – levels will vary widely because of peak and trough effects
- long acting injections – prior to the fourth injection (at 30 weeks) to determine optimal dosage interval
- subcutaneous implants – when symptoms recur (i.e. prior to next implant insertion) to determine optimum implant interval (this is usually four to six months but will depend on the number of pellets implanted)
- transdermal patches – in the morning (after application of patch in previous evening)

PBS approved indications for androgen replacement therapy

Approved indications for prescribing testosterone therapy via the PBS (authority required) are:

- micropenis, pubertal induction, or constitutional delay of growth or puberty in males under 18 years of age
- androgen deficiency in males with established pituitary or testicular disorders
- androgen deficiency in males 40 years and older who do not have established pituitary or testicular disorders other than ageing, confirmed by a testosterone level under 8 nmol/L or by a testosterone level between 8 and 15 nmol/L together with high LH (greater than 1.5 times the upper limit of the eugonadal reference range for young men).*

* Based on at least two blood samples taken on different mornings.

- transdermal gels – six to eight hours after administration
- oral – levels are difficult to interpret because of variable absorption.

In all cases, clinical symptoms should be monitored to assess the effectiveness of treatment. In cases of primary hypogonadism, LH levels may assist in assessing the efficacy of testosterone replacement.

Other

Prostate disease

Androgen deficient men are relatively protected from prostate disease, and restoring their testosterone levels to the normal range will return their risk to that of their eugonadal peers; their PSA levels may increase in a similar manner. Exclusion of significant prostate pathology is essential for men who are over 40 years of age at the commencement of therapy. Men receiving testosterone replacement therapy are subject to the same guidelines for prostate cancer screening as their peers with normal testosterone levels.

Cardiovascular risk factors

Monitoring of cardiovascular risk factors (blood pressure, diabetes and lipids) in androgen deficient men aligns with that

Table 3. Characteristics of testosterone products for androgen replacement therapy available in Australia*

Formulations	Usual dosage	Comments
Injectable (intramuscular)		
Mixed testosterone esters (Sustanon), testosterone enanthate (Primoteston Depot)	250 mg every two to three weeks; a smaller dose (100 mg) may be appropriate initially, particularly for younger and older patients	*Advantages:* Cost effective; extensive clinical experience *Disadvantages:* Wide fluctuation in testosterone levels that may produce symptoms or discomfort; contraindicated in men with bleeding disorders (including those using anticoagulant therapy)
Testosterone undecanoate, long acting (Reandron 1000)†	1000 mg every 12 weeks (4 mL injection into buttock), with an additional loading dose six weeks after initiating therapy	*Advantages:* Convenient (long dosing interval); well tolerated; pharmacokinetic profile is similar to that of pellets *Disadvantages:* Discomfort; contraindicated in men with bleeding disorders (including those using anticoagulant therapy); use with caution in older men‡
Subcutaneous		
Testosterone pellets (Testosterone Implants)†	Three or four 200 mg pellets every four to six months implanted subcutaneously in the buttock or abdomen (iliac fossa)[11]	*Advantages:* Convenient (long dosing interval suits younger men, with high patient satisfaction in this group[12]); pellets can be implanted under local anaesthesia in an office setting *Disadvantages:* Application site complications include pellet extrusion (5 to 10% of pellets) and, less commonly, infection and bleeding[12]; not usually suitable for older men‡; contraindicated in men with bleeding disorders (including those using anticoagulant therapy) or proneness to keloid formation

* Older men treated with androgen replacement therapy outside of guidelines should be informed that the long term risk–benefit profile has not yet been documented.
† In men with known or suspected prolonged, severe hypoandrogenism it may be appropriate to titrate therapy with a short acting testosterone preparation and then transfer to a long acting preparation.
‡ Older men are at increased risk of an intercurrent diagnosis of prostate cancer. In particular, pellets may need to be surgically removed.

of men of similar age in the general population.[10]

Osteopenia and osteoporosis

The presence of osteopenia and osteoporosis should be determined by monitoring bone mineral density (BMD). This should generally be conducted at baseline and after two years (but repeated after the first 12 months if osteopenia or osteoporosis is present at baseline) by dual x-ray absorptiometry (DEXA).

Polycythaemia

Haemoglobin and haematocrit levels should be measured before commencing treatment, and then at three and six months, and annually thereafter. This monitoring may need to be performed more frequently in older men.

Androgen deficiency in ageing men

Beginning late in the third decade, serum testosterone levels decline by 1% per year.[18,19] As SHBG levels also fall with age, the decline in free testosterone is more marked (2 to 3% per year).[18] The prevalence of age-associated androgen deficiency depends on the defined testosterone threshold (generally the lower

Formulations	Usual dosage	Comments
Transdermal		
Testosterone nonscrotal reservoir patch (Androderm, 2.5 and 5 mg)[13]	5 mg patch applied nightly to the back, abdomen, upper arms or thighs and worn continuously for 24 hours	*Advantages*: Suitable as initial therapy; convenient to apply; suitable in men with bleeding disorders; half usual dosage is suitable as initial therapy (e.g. in older men in whom only modest increases in serum testosterone are desired or in men with prolonged profound hypoandrogenism) *Disadvantages*: Must be applied daily, skin irritation due to the alcohol-based reservoir – some men may discontinue therapy because of skin irritation, whereas in other men the irritation will be transient[14] (these reactions may be ameliorated by pretreating the application site with a mild corticosteroid cream)
Clear, hydroalcoholic testosterone gel (Testogel)	50 mg (5 g gel sachet) applied daily across the shoulders and torso	*Advantages:* Suitable as initial therapy; convenient to apply; suitable in men with bleeding disorders; associated with less skin irritation than patches[15]; half usual dosage is suitable as initial therapy (e.g. in older men in whom only modest increases in serum testosterone are desired or in men with prolonged profound hypoandrogenism) *Disadvantages:* Must be applied daily; men must avoid washing, swimming and direct physical contact with women for several hours after applying the gel
Testosterone cream (Andromen Cream 2%, Andromen Forte Cream 5%)	2 to 6 cm of cream applied daily to nonscrotal skin	Available in Western Australia only; not approved by the TGA for national sales *Advantages:* Half usual dosage is suitable as initial therapy (e.g. in older men in whom only modest increases in serum testosterone are desired or in men with prolonged profound hypoandrogenism) *Disadvantages:* Must be applied daily
Oral		
Testosterone undecanoate capsules (Andriol Testocaps)	160 to 240 mg/day in two or three divided doses; starting dose may be as low as 40 mg/day (absorption occurs via the lymphatic system and is maximised by ingestion with fat-containing food)	*Advantages:* Suitable as initial therapy (e.g. in older men in whom only modest increases in serum testosterone are desired or in men with prolonged profound hypoandrogenism) *Disadvantages:* Serum testosterone levels cannot be used to monitor dosing;[16] not usually chosen as first line therapy because of dosing frequency and gastrointestinal intolerance[10]

limit of the normal young-male reference range) – a prevalence of 8% has been reported when androgen deficiency is defined by a total testosterone value of less than 8.7 nmol/L.[20] It remains uncertain, however, whether this cut-off defines older men with androgen deficiency who would safely benefit from treatment.

It is important to note that obesity[21] and both acute and chronic illness – which are increasingly prevalent with age – reduce serum testosterone in men.[22,23] Such conditions may cause symptoms similar to androgen deficiency.[24]

If a GP suspects that a symptom (or symptoms) in an older man might be due to androgen deficiency then appropriate laboratory assessment should be arranged. The Endocrine Society of Australia guidelines for diagnosing androgen deficiency in the ageing man, based on total testosterone values, include criteria for prescribing testosterone.[10] These criteria have been adopted by the PBS for the subsidy of testosterone therapy in this group of men (see the box on page 50).

Controversy remains over the role of testosterone replacement therapy in older men. Only a few randomised placebo-controlled trials of testosterone replacement in healthy ageing men have been published and the benefits of testosterone treatment are limited.[25,26] The most consistent effects to date have been improved bone mineral density, decrease in fat mass and increase in lean body mass.[27-29] Only limited benefits on selected aspects of mood and cognition have been demonstrated.[30,31] Although libido and sexual activity decline with age there is no real correlation with testosterone levels, and testosterone therapy is of limited benefit;[32] small falls in serum testosterone may be due to reduced sexual activity itself.[33] At present, the use of testosterone supplementation for ageing men who do not meet the established criteria cannot be advocated outside a clinical trial setting.

Further information for GPs and patients

Patient information about androgen deficiency (including diagnosis and treatment) is available free of charge from Andrology Australia in the form of a fact sheet and a more comprehensive guide. Summary guides on male reproductive health for GPs are also available. To order or download these resources, visit the Andrology Australia website (www.andrologyaustralia.org) or call 1300 303 878.

Conclusion

The presentation of androgen deficiency may be subtle and the diagnosis needs to be actively considered in the appropriate clinical context. Australian guidelines are available to assist in the diagnosis.[10] Proven androgen deficiency is associated with adverse health outcomes that are reversed by androgen replacement therapy. The diagnosis of androgen deficiency in older men may be difficult and treatment of symptomatic ageing men with borderline serum testosterone levels remains controversial, with the benefits and risks of testosterone therapy largely unknown. MT

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