



Androgen Deficiency

Diagnosis and management

Androgen deficiency (AD)

- Androgen deficiency is common, affecting 1 in 200 men under 60 years
- The clinical presentation may be subtle and its diagnosis overlooked unless actively considered

The GP's role

- GPs are typically the first point of contact for men with symptoms of AD
- The GP's role in the management of AD includes clinical assessment, laboratory investigations, treatment, referral and follow-up
- Note that in 2015 the PBS criteria for testosterone prescribing changed; the patient must be referred for a consultation with an endocrinologist, urologist or member of the Australasian Chapter of Sexual Health Medicine to be eligible for PBS-subsidised testosterone prescriptions

Androgen deficiency and the ageing male

- Ageing may be associated with a 1% decline per year in serum total testosterone starting in the late 30s
- However, men who remain in good health as they age may not experience a decline in testosterone
- The decline may be more marked in obese men
- Estimates suggest AD affects up to 1 in 10 men over 60 years
- Acute and chronic illnesses result in decreased serum testosterone and may present with AD-like symptoms
- The role of testosterone replacement therapy (TRT) in older men with modest declines in serum testosterone remains controversial
- The most consistent effects of TRT are on:
 - body composition and bone
 - selected aspects of mood and cognition
 - libido
- Most studies of men with age-related AD have not shown any significant improvement in erectile function (ED) with TRT
- The use of TRT for ageing men who do not meet the established criteria (PBS guide) is not recommended
- Older men treated outside of guidelines should be informed that long-term risks/benefits are not yet documented

Diagnosis

Medical history

- Undescended testes
 - Surgery of the testes
 - Pubertal development
 - Previous fertility
 - Genito-urinary infection
 - Co-existent medical illness*
 - Change in general well-being or sexual function**
 - Degree of virilisation
 - Prescription or recreational drug use
- * Pituitary disease, thalassaemia, haemochromatosis.

** AD is an uncommon cause of ED. However, all men presenting with ED should be assessed for AD

Examination and assessment of clinical features of AD

Pre-pubertal onset – Infancy

- Micropenis
- Small testes

Peri-pubertal onset – Adolescence

- Late/incomplete sexual and somatic maturation
- Small testes
- Failure of enlargement of penis and skin of scrotum becoming thickened/pigmented
- Failure of growth of the larynx
- Poor facial, body and pubic hair
- Gynecomastia
- Poor muscle development

Post-pubertal onset – Adult

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

Refer to Clinical Summary Guide 6: Testicular Cancer

Laboratory assessment of AD

- Normal range serum total testosterone 8-27 nmol/L (but may vary according to the assay used)
- Two morning fasting samples of serum total testosterone*, taken on different mornings

Guidelines for the diagnosis of AD (PBS criteria):

1. AD in a patient with an established pituitary or testicular disorder
2. For men aged 40+:
 - Testosterone < 6 nmol/L**
 - OR
 - Testosterone between 6 and 15 nmol/L and LH greater than 1.5 times the upper limit of the eugonadol reference range for young men**

* If a second total testosterone sample is indicated, a LH level should also be ordered.

** These criteria apply to men without underlying pituitary or testicular pathology, to be eligible for PBS subsidy.

Other investigations

- SHBG/calculated free testosterone (selected cases - obesity, liver disease)
- Semen analysis (if fertility is an issue)
- Karyotype (if suspicion of Klinefelter syndrome, 47,XXY)

Investigations if low total testosterone with normal or low LH/FSH:

- Serum prolactin (prolactinoma)
- Iron studies (haemochromatosis)
- MRI (various lesions)
- Olfactory testing (Kallmann's syndrome).

Causes of hypogonadism (AD)

Testicular (primary)

- Chromosomal: Klinefelter syndrome (most common cause)
- Undescended testes
- Surgery: bilateral orchidectomy
- Trauma
- Infection: mumps orchitis
- Radiotherapy/chemotherapy/drugs (spironolactone, ketoconazole)
- Systemic disease: haemochromatosis, thalassaemia, myotonic dystrophy

Hypothalamo-pituitary (secondary)

- Idiopathic hypogonadotrophic hypogonadism: Kallmann's syndrome
- Pituitary microadenoma (<1 cm) or macroadenoma (>1 cm) - functional or non-functional: in men typically macroprolactinoma
- Other causes of hypothalamic pituitary damage: surgery, radiotherapy, trauma, infiltrative disease such as haemochromatosis

Klinefelter syndrome

- Is the most common genetic male reproductive disorder (1 in 550 men)
- Is the most common cause of hypogonadism
- Reproductive features: small testes <4 mL, infertility, failure to progress through puberty, gynecomastia, eunuchoidal proportions, diminished or absent body hair, decreased skeletal muscle mass
- Other: learning difficulties & behavioural problems, particularly in adolescence

Refer to Clinical Summary Guide 10: Klinefelter Syndrome

Clinical notes and contraindications

- Absolute contraindications to TRT are known or suspected hormone-dependent malignancies (prostate or breast) or haematocrit >55%
- Relative contraindications include haematocrit >52%, untreated sleep apnoea, severe obstructive symptoms of BPH and advanced congestive heart failure
- Fertility: Exogenous testosterone results in suppression of spermatogenesis in eugonadal men. For men with secondary causes of AD, and in whom fertility is desired, gonadotropin therapy should be instituted
- Low-normal serum testosterone common in obesity or other illness may not reflect AD. Address underlying disorders first
- Withhold treatment until all investigations are complete
- Certain adverse effects must be prospectively sought, especially in older men, including polycythaemia and sleep apnoea, however the testosterone preparations discussed do not cause abnormal liver function

Management

Assessment of treatment indications

PBS-approved indications for the prescription of testosterone are:

- Micropenis, pubertal induction, or constitutional delay of growth or puberty, in males <18 years

- AD in males with established pituitary or testicular disorders
- AD (confirmed by at least 2 morning fasting samples, both < 6 nmol/L) in males aged 40+ who do not have established pituitary or testicular disorders other than ageing.

Testosterone replacement therapy (TRT)

Clinical note: Dosing ranges are provided below as dosage should be titrated according to clinical response and serum testosterone levels

T formulation	Usual (starting) dosage	Dosage range
Injections (IM)		
Sustanon®, Primoteston®	250 mg every 2 weeks	10 to 21-day intervals
Reandron®	1000 mg every 12 weeks following loading dose at 6 weeks (i.e. 0, 6, 18, 30 weeks)	Longer term: 8 to 16-week intervals
Transdermal patch		
Androderm®	2.5 mg and 5.0 mg preps: 5 mg applied nightly	2.5 to 5 mg daily
Transdermal gel		
Testogel®	1%: 50 mg in 5 g sachet or pump pack dispenser; applied daily	2.5 to 10 g gel (25 mg to 100 mg T) daily
Transdermal cream		
AndroForte®5	5% (50 mg/mL): 2 mL (100 mg) applied to the torso once daily	Review levels in 1 month, up to 4 mL daily
Oral undecanoate		
Andriol Testocaps®	40 mg capsule: 160 to 240 mg in 2 to 3 doses daily	80 to 240 mg daily

* Sustanon® is not available on the Australian Pharmaceutical Benefits Scheme (PBS)

Follow-up

Monitoring TRT is essential

- Testosterone levels: results should be interpreted in context of the treatment modality being used
- Prostate: PSA, as per standard guidelines
- Cardiovascular risk factors: blood pressure, diabetes, lipids, as per guidelines
- Osteopaenia/osteoporosis (fractures): bone density-DEXA
- Polycythaemia: haemoglobin and haematocrit, pre-treatment, at 3 and 6 months, and annually thereafter
- Sleep apnoea: clinical assessment for presence of sleep apnoea (polysomnography)

Specialist Referral

- It is a requirement for PBS-subsidised testosterone that the patient is referred for a specialist consultation (endocrinologist, urologist or member of the Australasian Chapter of Sexual Health Medicine) and the name of the specialist must be included in the authority application
- Refer to an endocrinologist to plan long-term management of AD
- Refer to a fertility specialist as needed
- Refer to a paediatric endocrinologist if >14.5 years old with delayed puberty