



# 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
<b>Injections (IM)</b>		
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
<b>Transdermal patch</b>		
Androderm®	2.5 mg and 5.0 mg preps: 5 mg applied nightly	2.5 to 5 mg daily
<b>Transdermal gel</b>		
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
<b>Transdermal cream</b>		
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
<b>Oral undecanoate</b>		
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