Androgen Deficiency

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The GP's role

GPs are generally the first point of contact for men with symptoms of androgen deficiency.

GPs are relied upon for clinical and laboratory examinations, appropriate referral, and ongoing patient management.

Patient referral to an endocrinologist, urologist or sexual health specialist is required for PBS-subsidised testosterone prescriptions.

Condition overview

Androgen deficiency is a syndrome caused by poor testicular function (hypogonadism), resulting from either primary (testicular) or secondary (hypothalamic-pituitary) disease, and is characterised by a low testosterone level accompanied by signs and symptoms[1, 2, 3].

It is estimated that approximately 5 in 1000 men have androgen deficiency warranting treatment with testosterone[4].

A low testosterone level alone does not constitute androgen deficiency[5], and neither does the normal age-related decline in testosterone (of approximately 1% annually[6]).

Androgen deficiency may have subtle effects on health and wellbeing, which can make diagnosis challenging.

Causes

Primary hypogonadism

- Chromosomal (e.g. Klinefelter syndrome (the most common cause of androgen deficiency)).
- Undescended testes.
- Trauma.
- Infection (e.g. mumps orchitis).
- Systemic disease (e.g. haemochromatosis, thalassaemia, myotonic dystrophy).
- Medical or surgical procedures (e.g. radiotherapy, chemotherapy, surgery (bilateral orchidectomy), medication (spironolactone, ketoconazole)).

See Clinical Summary Guide 10: Klinefelter Syndrome

Secondary hypogonadism

- Hypogonadotrophic hypogonadism (e.g. Kallmann's syndrome).
- Pituitary micro- or macro-adenoma: typically macroprolactinoma.
- Pituitary trauma or disease.
- Medical or surgical procedures (e.g. pituitary radiotherapy or surgery).

Diagnosis

Medical history

- Undescended testes.
- Testicular surgery.
- Pubertal development or virilisation.
- Fertility.
- Genitourinary infection.
- Coexistent illness (e.g. pituitary disease, thalassaemia, haemochromatosis).
- Sexual function (all men presenting with erectile dysfunction should be assessed for androgen deficiency, even though it is an uncommon cause).
- Drug use (medical or recreational).

Clinical examination and assessment

Prepubertal onset

- Micropenis.
- Small testes.

Peripubertal onset

- Delayed or incomplete sexual and somatic maturation.
- Small testes.
- Attenuated penile enlargement.
- Attenuated pigmentation of scrotum.
- Attenuated laryngeal development.
- Attenuated growth of facial, body and pubic hair.
- Poor muscle development.
- Gynecomastia.

Postpubertal onset

- Regression of virilisation.
- Small testes.
- Mood changes (low mood and/or irritability).
- Poor concentration.
- Lethargy.
- Hot flushes and sweats.
- Low libido.
- Reduced growth of facial or body hair.
- Low semen volume.
- Gynecomastia.
- Reduced muscle mass and strength.
- Increased fat mass.
- Bone fracture (resulting from low bone mineral density).

Laboratory examinations and assessment

Serum total testosterone* (morning, fasting):

- Young men: (21-35 years) 10.4-30.1 nmol/l[7]; (19-22 years) 7.4-28.0 nmol/l[8]
- Healthy older men (71-87 years), 6.6-26.7 nmol/l[9].

*Accurate serum testosterone measurements require mass spectrometry. Values from immunoassays are less reliable.

Serum FSH reference range

- Young adult: (21-35 years), 1.2-9.5 IU/ml[7]; (19-22 years), 1.3-12 IU/l[8].
- Older adult (74-84), mean 10.11, 95% confidence intervals 9.27-11.02 IU/l[10].

Serum LH reference ranges

- Young adult: (21-35 years), 1.5-8.1 IU/l[7]; (19-22 years), 5.1-18.7 IU/l[8].
- Older adult (74-78 years), median 4.1, interquartile range 3.0-6.1[11].
- Older adult (84-87 years), median 6.8, interquartile range 4.3-10.4[11].

At least two measurements of serum testosterone, LH and FSH (from samples collected on separate days) are required for diagnosis of androgen deficiency.

PBS criteria require androgen deficiency to be confirmed by serum testosterone below 6 nmol/l, or 6-15 nmol/l with LH 1.5 times higher than reference range (or above 14 IU/l).

Subsequent investigations for treatable causes of androgen deficiency:

- Serum prolactin (for prolactinoma and macroadenoma)
- Iron studies and full blood count (for haemochromotosis and thalasaemia)
- Anterior pituitary function (for hypopituitarism and/or hyperfunctioning adenoma)
- Karyotyping (for suspected Klinefelter syndrome)
- Y chromosome microdeletion analysis
- Magnetic Resonance Imaging (for various hypothalamic or pituitary lesions).

Management

Testosterone replacement therapy (TRT)

TRT is aimed at relief of symptoms and signs of androgen deficiency, using convenient and effective (intramuscular or transdermal) testosterone preparations[12].

Product name	Usual (starting) dose	Dose range
Injectable (IM)		
Combined testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, testosterone decanoate* Testosterone enantate*	250 mg fortnightly	250 mg at 10-21-day interval
Testosterone undecanoate	1000 mg twice at 6-week interval, followed by 12-weekly	1000 mg at 8-16-week interval
Transdermal patch		
Testosterone	5 mg nightly	2.5-5 mg nightly
Transdermal gel		
Testosterone	50 mg daily	25-100 mg daily
Transdermal cream		
Testosterone	100 mg daily applied to upper body 25 mg daily applied to scrotum	Up to 200 mg daily (to torso) Up to 50 mg daily (to scrotum)
Oral		
Testosterone undecanoate	80 mg 2-3 times daily	80-240 mg daily

*Not PBS-subsidised

Contraindications and clinical considerations for TRT

TRT should be withheld until all investigations are complete.

Absolute contraindications for TRT:

- Known or suspected cancer of the prostate or breast
- Haematocrit > 55%.

Relative contraindications for TRT:

- Haematocrit > 52%
- Untreated sleep apnoea
- Severe urinary obstructive symptoms of benign prostatic hyperplasia (international prostate symptom score > 19)
- Advanced congestive heart failure.

Exogenous testosterone suppresses spermatogenesis in eugonadal men. Men with secondary hypogonadism who wish to preserve fertility should be managed using gonadotrophin therapy.

Monitoring TRT

Alleviation of a patient's leading symptom is the best clinical measure of effective management.

Blood sampling for serum testosterone, LH and FSH measurement should be timed to allow estimation of steady-state testosterone levels, which is feasible by sampling during the trough (immediately before next dose) for men using injectable and transdermal preparations. Timing of sampling for accurate measurement in men taking oral testosterone is more difficult.

Random sampling of blood for measurement of serum testosterone, without consideration of dosage timing is effectively useless.

Persistently elevated LH levels during TRT may indicate inadequate dosing.

Periodic monitoring (1-2 year intervals) of bone mineral density may assist in monitoring TRT.

Haematology profile should be assessed 3 months after initiating TRT and annually thereafter.

Monitoring for prostate disease in men using TRT should occur as for eugonadal men of the same age.

Referral

PBS-subsidised prescription of TRT requires treatment by, or in consultation with, a specialist endocrinologist, urologist or registered member of the Australian Chapter of Sexual Health Medicine.

Long-term management of androgen deficiency is best planned in consultation with a specialist endocrinologist.

Refer to a fertility specialist as needed.

Refer males aged > 14.5 years with delayed puberty to a paediatric endocrinologist.

References

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