



# Testosterone deficiency in men

## *Diagnosis and management*

Carolyn A Allan,  
Robert I McLachlan



Carolyn A Allan, MBBS, FRACP, is Research Fellow, Prince Henry's Institute of Medical Research, and Department of Obstetrics and Gynaecology, Monash University, Victoria.



Robert I McLachlan, MBBS, FRACP, PhD, is Director of Clinical Research, Prince Henry's Institute of Medical Research, and Department of Obstetrics and Gynaecology, Monash University, Victoria.

**BACKGROUND** Testosterone deficiency (hypoandrogenism) is the commonest hormonal deficiency in men but its clinical presentation may be subtle and its diagnosis overlooked unless actively considered.

**OBJECTIVE** This article aims to provide an overview of the presentation of hypoandrogenism and the essential diagnostic role of the endocrine laboratory. We also seek to outline current treatment options and highlight the controversial area of age related hypoandrogenism with an emphasis on results from placebo controlled studies.

**DISCUSSION** The causes of hypogonadism in younger men are well documented but its presentation may be nonspecific and the diagnosis in older men may be difficult. It is likely that testosterone deficiency is widely under diagnosed. Endocrine testing provides essential supportive data for diagnosis and assists in monitoring treatment. The Endocrine Society of Australia has developed guidelines to assist practitioners in the diagnosis and management of hypoandrogenism in younger and older men. Testosterone replacement effectively restores sexual health and other androgen dependent actions on mood/cognition, muscle and bone. Testosterone treatment in symptomatic aging men with borderline hypoandrogenism is controversial and the benefits (and risks) of testosterone therapy remain uncertain.

Testosterone (androgen) deficiency (also termed hypoandrogenism) is the commonest hormonal disorder in males affecting approximately one in 200 men under the age of 60 years.<sup>1</sup> Yet it is under diagnosed as the symptoms and signs may be subtle or nonspecific. Consensus guidelines for the diagnosis and management of androgen deficiency, regardless of age, have been established by the Endocrine Society of Australia<sup>2</sup> and have been adopted by the Pharmaceutical Benefits Scheme for the subsidised prescribing of testosterone. The detection and treatment of hypoandrogenism in younger men should be an important goal for the general practitioner as treatment is highly effective in restoring normal sexual, bone and muscle health, potentially reducing cardiovascular disease risk, and improving overall quality of life.

### **Androgen physiology**

Testosterone is the predominant androgen in

males with 95% being secreted by testicular Leydig cells under the influence of luteinising hormone (LH) from the pituitary gland. Of the 6 mg of testosterone produced daily the majority is inactivated in the liver and excreted by the kidneys.<sup>3</sup> A small amount of testosterone is converted to bioactive metabolites: 4% to dihydrotestosterone via a 5 $\alpha$  reductase enzyme, and 0.2% to oestradiol via the enzyme aromatase.<sup>1</sup> Dihydrotestosterone is a more potent androgen with type 2 5 $\alpha$ -reductase being strongly expressed in the prostate.<sup>4</sup> There is a growing recognition of an important role of oestrogens in male bone health.<sup>5</sup>

### **Aetiology of androgen deficiency**

A list of the common causes of testosterone deficiency is given in Table 1. By far the commonest cause of primary hypogonadism is Klinefelter syndrome with a prevalence of 1/600 male births. The finding of small firm testes (<4 mL in volume in early adulthood) is highly suggestive and the diag-

nosis can be confirmed with karyotyping (47 XXY). Most subjects are diagnosed during puberty or in association with infertility, but a recent population based study suggests as many as 75% remain undiagnosed and untreated.<sup>7</sup>

All forms of primary testicular disease can be associated with impaired spermatogenesis; such that consideration of co-existing androgen deficiency is essential in the infertile man. Although hypoandrogenism requiring testosterone treatment is uncommon among men at the time they present with male infertility, such men require long term follow up as their testicular dysfunction may make them at greater risk of significant age related hypoandrogenism.

Secondary hypogonadism results from hypothalamo-pituitary disorders such pituitary tumours (especially prolactinoma) or iron overload disorders such as thalassaemia and haemochromatosis. In these settings, low gonadotrophin and testosterone levels may be accompanied by other anterior pituitary hormone deficiencies.

## Clinical assessment

The features of testosterone deficiency depend upon its time of onset and severity. One should specifically seek a history of:

- undescended testes
- pubertal development
- previous fertility
- genitourinary infection
- co-existent medical illness
- change in general well being and/or sexual function
- degree of virilisation, and
- the use of prescribed or recreational drugs.

## Examination findings

Prepubertal hypoandrogenism manifests as micropallus, small testes, delayed puberty, and, because of the failure of closure of the epiphyseal growth plates, excessive long bone growth leading to eunuchoid proportions (arm span exceeding height by 5 cm). In particular the clinical features of Klinefelter syndrome include a history of failure to progress through puberty, infertility, small firm testes, and decreased penis size, gynaecomastia, eunuchoid proportions, diminished or absent body hair (facial, axillary, pubic) and decreased skeletal muscle mass.

The postpubertal onset of testosterone defi-

**Table 1. Causes of hypogonadism**

### Testicular

Chromosomal: Klinefelter syndrome

Surgery: bilateral orchidectomy

Radiotherapy/chemotherapy/drugs (spironolactone, ketoconazole)

Infection: mumps orchitis

Maldescended testes

Trauma

### Systemic disease

Haemochromatosis, thalassaemia, myotonic dystrophy

### Hypothalamo-pituitary

Pituitary adenoma

Panhypopituitarism (postsurgery or radiotherapy)

Prolactinoma

Hypogonadotrophic hypogonadism (Kallmann syndrome)

ciency produces a number of typical features (Table 2) although the clinical scenario may vary dependent upon the rate and extent of the fall in testosterone levels. An important practical indicator is examination of the testes that should be part of any complete evaluation of male reproductive function. Low testicular volume is an important indicator of underlying pituitary or testicular pathology and a normal testis volume is a useful screening test to exclude overt hypoandrogenism.

## Endocrine laboratory assessment

Most circulating testosterone is bound to carrier proteins (44% tightly to sex hormone binding globulin [SHBG] and 54% loosely to albumin). As a result of this protein binding, evaluation of free testosterone levels (and thus the presumed biologically active fraction) has been proposed to correlate better with clinical features of hypoandrogenism.<sup>8</sup> However, the clinical value of free testosterone estimates is unclear, partly for methodological reasons (see below) and also because proof that it is diagnostically superior to total testosterone is lacking. At present the best available method for assessing androgenic status is a serum total testosterone. Measurements should be performed in the morning because of the circadian nature of testosterone production.<sup>9</sup> All abnormal values need to be confirmed with a

**Table 2. Clinical features of postpubertal onset of hypoandrogenism**

<b>General</b>
Lethargy, fatigue
Low mood, poor concentration, impaired short term memory
<b>Organ specific</b>
Bone: osteopaenia, osteoporosis
Muscle: loss of skeletal muscle especially pectoral girdle
Gynaecomastia
<b>Sexual/reproductive</b>
Decreased libido
Erectile dysfunction (uncommon)

**Table 3. Biochemical diagnosis of androgen deficiency in men over 40 years of age**

- Testosterone <8nM
- OR**
- Testosterone 8–15nM and LH >1.5 x upper limit of eugonadal reference range for young men

NB: Based on two separate morning blood samples. These criteria apply to men without underlying pituitary or testicular pathology

second test on a different day. Total testosterone values are an important part of the guidelines for the diagnosis of androgen deficiency in older men (Table 3).

In terms of free testosterone measures, its direct measurement by equilibrium dialysis or centrifugal ultrafiltration is considered to be the ‘gold standard’<sup>10</sup> but is impractical for routine use. Bioavailable testosterone (free plus albumin bound) is an alternative but is not widely available. Some laboratories purport to measure free testosterone using commercial kits, but these measurements are flawed, do not align with equilibrium dialysis values and should not be used.<sup>11</sup> The need for and utility of these measures is uncertain.

A calculated free testosterone can be generated based on the total levels of testosterone, SHBG and albumin.<sup>12</sup> To date, however, there are no published population based reference ranges. The Free Androgen Index (FAI) is a derived unitless calcu-

lation based on the formula of: FAI = (total testosterone/SHBG) x 100% and although validated for use in women, it is less reliable in men than the calculated free testosterone.<sup>13</sup>

Serum LH levels assist in the diagnosis of primary hypoandrogenism as they increase in response to declining negative testosterone feedback. A low serum LH in the presence of low testosterone raises the possibility of secondary hypogonadism and serum prolactin and other pituitary hormones may need to be measured. In addition to a testosterone and gonadotrophin profile (outlined below) other relevant investigations may include chromosome analysis, serum prolactin, iron studies, and pituitary imaging.<sup>2</sup>

**Androgen deficiency in aging men**

Aging is associated with a 1% per annum decline in serum testosterone<sup>14,15</sup> beginning in the late third decade. As SHBG levels fall with age, the decline in free testosterone is more marked, approximately 2–3% per year.<sup>14</sup> Using a total serum testosterone value of <8.7nM as diagnostic of hypoandrogenism, a prevalence of 8% has been reported.<sup>16</sup>

The prevalence of age associated hypoandrogenism is dependent upon the threshold testosterone value employed: this is generally set as the lower limit of the normal young male reference range. There remains uncertainty, however, as to whether this defines a level hypoandrogenism in older men that would safely benefit from treatment. Andrology Australia is currently working with the Royal College of Pathologists and Australasian Association of Clinical Biochemists to provide a pool of sera from healthy fertile young men for the establishment of a valid reference range.

It is important to note that both acute and chronic illness, increasingly prevalent as men age, result in decreased serum testosterone<sup>17,18</sup> and may present with symptoms similar to hypoandrogenism.<sup>19</sup> Obese men are more likely to have lower total testosterone levels<sup>20</sup> and given that 65% of the adult male Australian population is now overweight or obese<sup>21</sup> this may have important epidemiological implications for the prevalence of age related hypoandrogenism.

The clinician should consider whether individual or groups of symptoms (Table 2) might be due to hypoandrogenism and undertake appropriate laboratory assessment. The Endocrine Society

guidelines include criteria for prescribing of testosterone for age related hypoandrogenism (Table 3).<sup>2</sup> It should be noted that some older men will not have an appropriate LH response to a declining testosterone level due to age related changes in the hypothalamo-pituitary axis.

The role of testosterone replacement therapy in older men remains controversial. Only a small number of randomised, placebo controlled trials of androgen replacement in healthy aging men have been published and the benefits of treatment are limited.<sup>22,23</sup> The largest study to date showed an improvement in bone mineral density over placebo during a three year period only when the starting testosterone level was <10nM, a decrease in fat mass (-3 kg) and an increase in lean body mass (+2 kg).<sup>24,25</sup> There was no objective effect on physical strength. Only limited benefits on selected aspects of mood and cognition have been demonstrated<sup>26,27</sup> with no data regarding dementia. Although libido and sexual activity decline with age there is no real correlation with testosterone levels.<sup>28</sup> Small falls, however, may be due to reduced sexual activity itself.<sup>29</sup> Placebo controlled studies of men with low-normal baseline testosterone levels have not, to date, shown any clinically significant improvement in sexual function with testosterone therapy.<sup>25,30</sup> At present the use of testosterone supplementation for aging men who do not meet the established criteria cannot be advocated outside of a clinical trial setting.

## Testosterone formulations

Preparations currently available in Australia are listed in Table 4. Additional therapies available abroad and new preparations under development should offer greater choice and assist compliance in the future.

### Implants

Testosterone pellets (Organon) can be inserted subdermally in the abdomen (iliac fossa) or the buttock and can be performed in an office setting under local anaesthesia. The standard replacement dose is 600–800 mg implanted each 4–6 months.<sup>31</sup> The most common side effect is pellet extrusion (5–10%) with less common side effects being infection or bleeding.<sup>32</sup> Men should have demonstrated tolerance to exogenous testosterone before an implant procedure is performed. This is not usually suitable for treatment of older men where the

**Table 4. Testosterone preparations available on the PBS**

#### Implants

**Intramuscular:** testosterone enanthate, mixed esters

**Transdermal:** reservoir nonscrotal skin patch, cream\*

**Oral:** testosterone undecanoate

\* Only available in WA

intercurrent diagnosis of prostate cancer may require surgical removal of implants. Contraindications include bleeding disorders and proneness to keloid formation. Patient satisfaction among younger men is high with excellent continuation rates.<sup>32</sup>

### Intramuscular

A number of testosterone ester injectable preparations are available (Sustanon, Organon; Primoteston, Schering). Testosterone enanthate and testosterone cypionate have an optimal dosing schedule of 200–250 mg every 2–3 weeks although smaller doses (100 mg) may be appropriate initially particularly in the youngest or oldest men. They produce initial supraphysiological testosterone levels followed by a gradual decline. The dose and frequency of injections can be tailored for the patient to avoid nadir subtherapeutic levels. Intramuscular therapy is contraindicated in men with bleeding disorders, including those receiving anticoagulants.

### Transdermal

The development in recent years of vehicles delivering testosterone transdermally has had a significant impact upon prescribing practices for hypogonadal men. Nonscrotal reservoir patches<sup>33</sup> are available in Australia (2.5 and 5 mg Androderm, Mayne Pharma). Most men require a 5 mg patch that is applied nightly to the back, abdomen, upper arms or thighs and worn continuously for 24 hours. At least 10% of men discontinue treatment with the alcohol based reservoir patch because of skin irritation, while 50% of men report at least a transient mild irritation over a 12 month period;<sup>34</sup> these reactions may be ameliorated by co-treatment with corticosteroid (eg.



triamcinolone 0.05% cream under the reservoir). Testosterone gel, applied daily, is associated with much less skin irritation than the reservoir system<sup>35</sup> and in the USA now captures 50% of the market. In Western Australia, a cream preparation is available (Andromen, Lawley Pharmaceuticals) but it has not been approved by the Therapeutic Goods Administration for national sales.

### Oral

Testosterone undecanoate (Andriol, Organon) is the only oral form of natural testosterone available with absorption (via the lymphatic system) maximised by ingestion with food. The usual maintenance dose is 160–240 mg/day administered in 2–4 divided doses, although the starting dose may be as low as 40 mg twice per day. Due to an unpredictable absorption profile<sup>36</sup> serum testosterone levels cannot be used to monitor dosing, with dose adjustments being based on clinical response. Dosing frequency and gastrointestinal intolerance mean this is not usually first line therapy.<sup>2</sup>

### Monitoring of androgen replacement therapy

The benefits of treatment in testosterone deficient men are well established.<sup>37</sup> Normalisation of serum testosterone levels should be demonstrated. As hypogonadal men are protected from prostate disease, restoring testosterone levels to the normal range will return their risks to those of their eugonadal peers. Exclusion of significant prostate pathology is essential for those aged over 40 years at the commencement of therapy. Men receiving testosterone replacement therapy are subject to the same guidelines for screening for prostate cancer as their peers with normal testosterone levels. Monitoring of cardiovascular risk factors aligns with that of men of similar age in the general population.<sup>2</sup> Certain adverse effects must be prospectively sought including polycythemia and sleep apnoea, however, the testosterone preparations discussed above do not cause abnormal liver function. Older men treated outside of guidelines should be informed that the long term risk/benefit profile is not yet documented.

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### SUMMARY OF IMPORTANT POINTS

- The presentation of androgen deficiency may be subtle and needs to be actively considered in the appropriate clinical context.
- Androgen deficiency in younger men is associated with adverse health outcomes that are reversed by testosterone replacement therapy.
- The significance of borderline low testosterone levels in aging men is a controversial area and more information is needed about the risks and benefits of testosterone supplementation. Treatment cannot be recommended at this time.
- The Endocrine Society of Australia has published guidelines to assist in the diagnosis and management of testosterone deficiency.

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## CORRESPONDENCE

Associate Professor Rob McLachlan  
Andrology Australia  
C/o Monash Institute of Reproduction and Development  
Monash Medical Centre  
246 Clayton Road  
Clayton, Vic 3168  
Email: rob.mclachlan@med.monash.edu.au  
www.andrologyaustralia.org