Critical Commentary

Androgen Insufficiency in Ageing Men: how is it defined and should it be treated?

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Introduction

Does the andropause exist? Normal ageing in men is associated with physical, emotional and cognitive changes. Many of these symptoms are also seen in androgen deficiency. The rationale for the "andropause" concept is that the age-related decline in testosterone is responsible for these symptoms, and that testosterone therapy will arrest or reverse the ageing process. The clinical syndrome of androgen deficiency is poorly defined and there are few well designed studies of androgen treatment. The long term benefits and risks of testosterone, in particular for prostate or cardiovascular disease, are not established. Nevertheless, there is widespread public and medical enthusiasm for testosterone therapy and prescriptions have tripled in the past decade.[1] Professional bodies in Australia[2] and elsewhere[3] have guidelines for the diagnosis and treatment of androgen deficiency based on the limited information available. The continuing challenge for endocrinologists and clinical chemists is to evolve a rational, evidence-based approach to the definition and treatment of androgen deficiency.

The questions that need to be addressed are:

1. Is there a distinct clinical syndrome of androgen deficiency?
2. Are current testosterone assays adequate to help make the diagnosis of mild androgen deficiency?
3. What are the benefits and risks of testosterone treatment?

Definition of the Androgen Deficiency Syndrome

The true incidence and prevalence of androgen deficiency in middle-aged and elderly men is unknown. There is general agreement that testosterone treatment is appropriate in men with unambiguous testicular or pituitary disease, who have serum testosterone below the young adult reference limit. However, most men being assessed for possible androgen deficiency do not have clearly defined pathology. The symptoms of androgen deficiency are non-specific and overlap with normal ageing (Table 1). Furthermore, chronic illness, obesity and other external stressors may cause similar symptoms and further confound the issue.

Epidemiological cross-sectional and longitudinal studies show a gradual decline in total testosterone of 1 to 2 per cent per year from the fourth decade onwards. Free testosterone falls more rapidly, mostly accounted for by a simultaneous age-associated increase in sex hormone binding globulin. If androgen deficiency is defined only by serum total testosterone below the young adult reference limit, approximately 20% of men over 60 would be classified as androgen deficient.[3-5] If free or bioavailable testosterone is measured, this percentage increases further. Testosterone has significant biological variation, not taking into account assay performance. In a recent study where total testosterone was measured repeatedly over 8 weeks in men aged 69.3 ± 1.7 years, the variation was such that 8 of the 16 subjects would have been classified as eugonadal at some time points and hypogonadal at others.[6] This confirmed a previous study of 169 men aged 40 to 80, where the mean intraindividual CV of total testosterone was 16.9 ± 8.4% over 12 months: 9 men had intraindividual CV over 25%.[7]

As neither clinical symptoms nor serum testosterone are always reliable in isolation, consensus groups in the US and elsewhere have proposed using a combination of both parameters.[3,4] The first attempt to validate this approach was recently described in a prospective longitudinal cohort of men aged 40 to 70.[5] To be classified as having androgen deficiency, the subjects had to have three symptoms out of a possible eight, in combination with either total testosterone less than 6.94 nmol/L, or free testosterone below 0.3 nmol/L. The symptoms (see Table 1: marked with asterisk) were selected as significant parameters

Table 1. Effects of androgen deficiency identified by the Second Andropause Consensus meeting, compared to normal ageing (adapted from Araujo et al[5] and Liu et al[13])

Feature	Androgen deficiency	Ageing
Loss of libido*	+	+
Erectile dysfunction*	+	±
Depression*	+	
Lethargy*	+	
Inability to concentrate*	+	±
Sleep disturbance*	+	±
Irritability*	+	
Depressed mood*	+	
Loss of bone density	+	+
Loss of muscle strength	+	±
Regression of secondary sex characteristics	+	±
Decreased interest in activities	+	

*Symptoms assessed in a prospective longitudinal cohort by Araujo et al.[5]

identified by the Andropause Consensus meeting[3] for which the investigators had data. In this cohort, the prevalence of androgen deficiency doubled from 6% to 12.3% over the 8.8-year follow up period. However, there was no correlation between symptoms and testosterone at baseline. In addition, more than a third of men with total testosterone below 6.9 nmol/L had fewer than three symptoms. Although this might mean that men with gradual onset of androgen deficiency are unaware of any symptoms, or that some symptoms are more specific than others for androgen deficiency, this casts some doubt on the usefulness of the questionnaire.[4] Furthermore, there was no information on comorbidities such as obesity or chronic illness, which can lower testosterone levels and also cause similar non-specific symptoms. These limitations aside, this study was the first to apply a clinical diagnostic algorithm to a population followed over the long term. The goal now should be to find one that will be useful in the clinical setting.

Testosterone Assays

Pre-analytical Factors

A number of clinical and pre-analytical factors need to be considered in interpreting serum testosterone. Testosterone is reduced in several disorders including chronic renal, liver, cardiac or respiratory disease, inflammatory conditions, and severe acute illness.[3] Several drugs also lower serum testosterone. These include oestrogen and GNRH agonists or antagonists as well as opiates, thiazide diuretics, psychotropic agents and amiodarone.[3] More than 95% of circulating testosterone is bound to plasma protein: around 60-70% to sex hormone binding globulin (SHBG) with high affinity, and around 30-40% to albumin with low affinity. A number of medical conditions and drugs influence SHBG and hence total testosterone levels (Table 2). Testosterone is highest in the early morning and lowest during sleep. The nadir is from 15 to 50% lower than the peak.[8] For this reason blood should be drawn between 0800 and 1000.

Analytical Factors

The current Australian guidelines state that men over 40 years who do not have clearly defined testicular or pituitary disease may be diagnosed with androgen deficiency if they have total testosterone below 8 nmol/L, or total testosterone 8-15 nmol/L plus LH 1.5 times the upper reference limit, in two separate morning collections.[2] However, there was no specific recommendation as to the preferred method or platform that should be used or the performance of the assay, nor on how the reference interval should be determined. Recently an Australian reference panel was established from 150 young healthy men with normal physical examination and semen analysis.[9] A national study was performed to establish a uniform reference interval but this has not been universally adopted. In the prevalence study by Araujo et al.,[5] testosterone was measured in pooled serum from two morning samples drawn 30 minutes apart to minimize the effects of episodic testosterone secretion, but this approach is impractical in the routine clinical setting. Commercial assay platforms show a significant bias compared to reference methods, especially

Table 2. Factors influencing serum SHBG.

Increase	Decrease
↑ age	Obesity
↑ oestrogen	Androgen therapy
Hyperthyroidism	Hypothyroidism
Liver disease	Glucocorticoid therapy
Growth hormone insufficiency	Growth hormone excess

at the lower end of the reference interval which is critical in making the diagnosis of androgen deficiency.[4,10] The direction of bias varies: for example the DPC Immulite, Elecsys 2010, and Vitros ECi methods had a consistent negative bias and the Bayer Centaur had a positive bias compared to reference methods.[10,11] Some bias may be accounted for by matrix effect, as modern commercial chemiluminescence assays do not require a preliminary extraction step. Analytical issues are addressed in more detail in this issue of the Reviews.

Benefits and Risks of Testosterone Therapy

This topic was recently reviewed and recommendations made for monitoring testosterone therapy.[3,12,13] Potential benefits of testosterone therapy extrapolated from the response in young hypogonadal men include improvements in libido and erectile function, mood, energy levels, muscle mass and strength, and bone density. However, there is no evidence for a beneficial effect of testosterone on sexual function, mood or quality of life in men with testosterone in the lower reference interval.[3] On the contrary, in an Australian study of 1455 men with erectile dysfunction, only 5.7% of men had testosterone below the young reference limit and only men with total testosterone <7 nmol/L responded to therapy.[14]

Muscle mass increased consistently by 1-2 kg and fat mass decreased by 1.5-2.5 kg in the pooled results of nine randomised placebo-controlled trials of testosterone for at least three months in healthy men over 60 (n = 300 total), with a suggestion of a dose related effect.[13] The total number of men treated was small (n = 18), and only two showed a corresponding increase in physical strength. No study showed an improvement in overall physical function. Type II error is very probable, as a sample size of thousands would be required to determine a 3% increase in strength.[13] The clinical significance of this change in body composition has also not been defined. While reduced abdominal fat theoretically implies reduced insulin resistance, and consequently prevention of diabetes and associated conditions, this has not been substantiated by insulin clamp or other rigorous methods.[13]

Bone mineral density has been used as a surrogate marker for the effects of testosterone on fractures, because of small sample size. Bone density increased more in men on higher doses or with lower baseline serum testosterone. The effects of testosterone on bone are probably mediated though oestrogen, based on studies in young men treated with nonaromatizable androgens.[13]

The long-term risks of testosterone therapy are unknown. This is particularly important in the light of recent studies of oestrogen therapy in postmenopausal women; epidemiological evidence should not determine standard medical practice before benefit is confirmed in clinical trials. Prostate cancer and cardiovascular disease, the major safety concerns, increase with age even in untreated men.

Standard medical practice precludes testosterone treatment of men with prostate cancer or symptomatic benign prostate disease. The prevalence of prostate cancer was similar to the general population in a pooled analysis of trials lasting up to 36 months, but the long-term risk is unknown.[12]

Serum testosterone is inversely related to cardiovascular disease in epidemiological studies.[15] Surrogate endpoints such as lipids and inflammatory markers are improved or unchanged in testosterone treated men. These findings are reminiscent of the epidemiological evidence for cardiovascular benefit of oestrogen in women. There is no evidence for the effects of testosterone on cardiovascular disease using hard endpoints. Such a study would require thousands of subjects, and is unlikely to be approved before significant clinical benefits of testosterone can be demonstrated in smaller studies.

The other known adverse effects of testosterone include polycythaemia, which frequently necessitates dose reduction in clinical trials, and sleep apnoea. These effects are dose dependent (and more common with injectable than oral or transdermal testosterone) and again require monitoring.

Monitoring Testosterone Therapy

Testosterone is available in Australia as testosterone esters given 1 to 3 weekly by intramuscular injection; slow release pellets for subdermal insertion; transdermal patch for daily topical administration; and oral testosterone undecanoate which is usually taken several times daily. These formulations have different bioavailability and pharmacokinetic and side effect profiles (for example skin irritation with patches or gastrointestinal symptoms with the oral route). Although the usual recommendation is to aim for testosterone within the mid to high reference interval for healthy young men, this has not been validated. Most authors recommend monitoring for efficacy by clinical assessment and total testosterone after 1 to 2 months of therapy.[3,12] The optimum timing of the sample depends on the route of administration: for example 7 days after intramuscular injection or 3 to 10 hours after a patch.

Consensus groups recommended prostate specific antigen screening at baseline and monitoring at 3 and 6 months and then annually.[3,12] Prostate biopsy is recommended if PSA increases by 1.5 ug/L in 12 months. Baseline screening with PSA is controversial in itself, but population-based studies should be available in another five years.

Haematocrit should be monitored at the same time points as PSA with dose reduction if it rises above 52%.[3,12,13] 14 out of 46 men randomised to intramuscular testosterone needed a dose reduction from 200 mg to 160 mg.[16]

Summary

The concept that the age-related decline in testosterone levels is a medical condition which will respond to treatment has gained widespread acceptance with doctors and the public, in advance of the available evidence. The clinical assessment tools for diagnosing androgen deficiency have poor sensitivity and specificity. Furthermore, the commercially available testosterone assays are not sufficiently robust, particularly at the lower reference range, and in many cases a local reference range has not been determined in men known to have normal gonadal function. This is clearly an area where the clinical chemist can contribute.

The benefits and risks of prolonged exposure to testosterone in previously healthy older men are unknown. It is thus not recommended that men without clearly defined testicular or pituitary hypogonadism be treated with testosterone until this evidence is available.

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