

Singapore Urological Association **Andropause Guidelines**

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Late-Onset Hypogonadism in Males

Introduction

The global increase in mean life expectancy and the drastic reduction of fertility rates have resulted in a rapidly ageing world population. The UN projects that by 2025, 18.4% of the population in Singapore will be made up of those above 65 years of age¹. With the lengthening of life expectancy at birth, non-communicable disease, chronic illness and associated disability receive increasing importance. The mounting population of males over the age of 50 years requires that their special health needs be met. Among these needs, hormone replacement therapy for men rates high, as it has for postmenopausal women over the last 25 years.

Background

It is recognised that the endocrine changes associated with male ageing are not limited to sex hormones. Indeed, profound changes occur in other hormones such as growth hormone, dehydroepiandrosterone (DHEA), melatonin and, to a lesser extent, thyroxine. Furthermore, till now, it is not known for certain whether plasma levels of androgens reliably reflect a subject's androgenic status, particularly in old age. There could also be an impairment of the accumulation of androgens in target tissues or of the transcription of androgen action. The above issues remain to be investigated further. However, several authorities have developed a pragmatic approach, based on current evidence, to the issue of late-onset hypogonadism in males (LOH), also known as androgen decline in the ageing male (ADAM), partial androgen deficiency of the ageing male (PADAM), relative androgen deficiency, andropause or male climacteric.

Definition

Late-onset hypogonadism (LOH) is defined as a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. It may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems.

Diagnosis

The diagnosis is made when clinical manifestations of late-onset hypogonadism are supported by biochemical confirmation of androgen deficiency.

Clinical manifestations of LOH in males

1. Diminished sexual desire (libido) and erectile quality and frequency, particularly nocturnal erections
2. Changes in mood with concomitant decreases in intellectual activity, cognitive functions, spatial orientation ability, fatigue, depressed mood and irritability
3. Sleep disturbances
4. Decrease in lean body mass with associated diminution in muscle volume and strength
5. Decrease in body hair and skin alterations
6. Decreased bone mineral density resulting in osteopaenia, osteoporosis and increased risk of bone fractures
7. Increase in visceral fat

Not all of these manifestations need to be present for the diagnosis to be made. Furthermore, some manifestations may be more prominent than others for certain patients.

Biochemistry

Serum testosterone below or at the lower limit of accepted eugonadal reference range. Samples should be obtained between 7 and 11 am.

There are no specific lower limits of normal serum testosterone in older men. There is general agreement that total testosterone levels above 12 nmol/L (346 ng/dL) do not require substitution². Based on the data in younger men, there is a consensus that serum total testosterone levels below 8 nmol/L (231 ng/dL) require substitution². Since symptoms of testosterone deficiency become manifest between 8 and 12 nmol/L, trials of treatment can be considered in those in whom alternative causes of these symptoms have been excluded². (Grade C, level IV)

Total testosterone measurements need to be interpreted with caution. In the elderly and the obese, elevations of sex hormone binding globulin (SHBG) may mask true hypogonadism by reflecting normal total testosterone levels. Also, normal ranges of testosterone vary significantly from laboratory to laboratory. The results from each patient should be compared with the normal ranges established by each laboratory.

Free testosterone level measurements are hampered by the lack of accurate determinations by local laboratories as well as the absence of compatible

reference range in the local population. As such measurement of free testosterone levels in this group of men are not recommended at this point in time. (Grade C, level IV)

If testosterone levels are below or at the lower limit of accepted normal values, a second determination, together with assessment of serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) is recommended. Low testosterone values together with increased FSH and LH values suggest primary hypogonadism (testicular origin), whereas depressed FSH and LH values suggest secondary hypogonadism (hypothalamic-pituitary origin), and further endocrinological evaluation may be warranted.

In ageing men with the major complaint of erectile dysfunction, lipids, cardiovascular status and diabetes should be assessed.

Treatment

In ageing men, a clear indication based on the clinical picture together with biochemical evidence of low serum testosterone should exist prior to the initiation of testosterone substitution. In general, if the potential benefit exceeds the potential risk, then the patient may be started on replacement therapy.

Intervention studies of androgen supplementation in elderly males with subnormal testosterone levels have produced some positive benefits, albeit with inconsistent results. It has been shown to lead to a significant, albeit modest, increase in muscle mass with reduction in fat mass³⁻⁶. A few studies show an associated increase in muscle strength⁶. (Grade B, level IIa)

Androgen supplementation in elderly males with subnormal testosterone levels has been shown to increase bone mineral density of the lumbar spine, provided insufficient intake of calcium or vitamin D, if present, have been remedied⁷⁻⁸. (Grade B, level IIa)

Investigators have also reported that in elderly men, testosterone replacement leads to improved libido, mood, energy and sense of well-being^{3-4,9-11}. (Grade B, level IIb)

Goals of therapy

1. Restore sexual function, libido and sense of well-being.
2. Improve muscle strength and mental acuity.
3. Optimize bone density to prevent osteoporosis and minimize the risk of fractures

Testosterone replacement

The general principle in hormone replacement therapy is that the serum levels to be achieved over the 24 hours of the day must come close to normal reference values, and ideally follow the normal diurnal pattern. Thus an idea of adequate levels may be gained by determining testosterone levels before the administration of the next dose of androgen preparation.

Absolute contraindications for testosterone administration include suspected or having carcinoma of the prostate or breast.

Men with significant polycythaemia, untreated sleep apnoea, severe heart failure or significant bladder outlet obstruction should not be treated (see below under adverse effects).

Preparations

Preparations of natural testosterone should be used for substitution therapy. Due to the potential development of a contraindication during treatment (especially prostate carcinoma), short-acting preparations (oral, transdermal) are preferred over long-acting (intramuscular, subdermal) depot preparations in patients with LOH.

ITEM	Route	Dose	Remarks
Depo-testosterone (Testosterone cypionate) 200mg, 1000mg inj	I/M	50-400 mg every 2-4 weeks	
Testosterone implant 100mg, 200mg	S/C	100-600 mg every 4-5 mths	
Sustanon 250 inj (Testosterone propionate 30mg, T. phenylpropionate 60mg, T. isocaproate 60mg, T. decanoate 100mg)	I/M	1 mL (ampoule) every 3 weeks	
Andriol (Testosterone undecanoate 40 mg) cap	PO	60-80 mg bd for 2-3 weeks, then maintenance 20-60 mg bd	
Provironum (Mesterolone 25 mg) tab	PO	1 tab tds till improvement, then maintenance bd or om	
Nebido (Testosterone Undecanoate 1000mg) inj	I/M		Pending HSA approval
Androgel 25,50 mg Testosterone 1% gel	Topical	50-100 mg om	

Adverse effects

Liver

Alkylated androgen preparations such as 17 α -methyl testosterone may cause liver toxicity in the form of jaundice and altered liver function¹². As such, these should no longer be prescribed. (Grade B, Level III)

Lipid and cardiovascular safety

The complex relationships between androgens and cardiovascular risk factors have not been completely elucidated. Hence, caution is advised when supplementing androgens in men with significant risk factors for cardiovascular disease^{6,13}. (Grade B, Level III)

Haematology

Testosterone stimulates the bone marrow production of erythrocytes. Testosterone therapy in older men can result in a significant increase in red blood cell mass and haemoglobin^{6,14}. (Grade C, Level IV)

Dose adjustments or phlebotomies may be necessary if haematocrit rises to above 50%. Rarely, androgen replacement therapy (ART) has to be discontinued due to polycythaemia.

Prostate safety

No clear relationship has been established between testosterone replacement therapy, serum levels of sex hormones and prostate cancer^{6,15-16}. (Grade B, Level III)

However, there are anecdotal reports of prostate cancer linked to ART¹⁶. (Grade C, Level IV)

More long-term studies are needed to clarify this issue. Currently, the suspicion of prostate cancer is an absolute contraindication for androgen therapy.

Examination of the prostate should be done routinely and PSA levels should be determined annually. Suspicious digital rectal examination, rapidly increasing or high PSA levels warrant termination of ART and referral to the urologist, who may proceed with trans-rectal ultrasound guided biopsies¹⁷. (Grade C, Level IV)

Patients with bladder outlet obstruction represent relative contraindication to ART. Severe outlet obstruction may necessitate intervention by the urologist before ART is initiated¹⁷. (Grade C, Level IV)

Breast cancer and gynaecomastia

Testosterone may be aromatised to estradiol and lead to changes in sex hormone binding globulin levels. These may cause gynaecomastia. ART is also absolutely contraindicated in patients suspected of having carcinoma of the breast¹⁷. (Grade C, Level IV)

Mood and behaviour

ART normally results in improvements in mood and well-being. The development of negative behavioural patterns during treatment, which can occur rarely, necessitates dose adjustment or discontinuation of therapy¹⁸.

(Grade C, Level IV)

Sleep apnoea

Sleep apnoea may be a problem in some men. In patients with disordered sleep and day time fatigue, a sleep study should be done. ART should be withheld until the problem is adequately addressed¹⁹⁻²⁰. (Grade C, Level IV)

Monitoring

ART may be initiated for a variety of indications but treatment is normally for life, and hence lifelong monitoring is required. Monitoring should be tailored to the indications for the initiation of treatment, and to the individual needs of the patient. If the indication for ART is osteoporosis, then serial BMD determinations at 2-yearly intervals can be used to monitor response to therapy.

Besides monitoring therapeutic response, the physician also needs to look out for the potential adverse events as listed above.

During the first year of therapy, clinical response and the side effects should be monitored at 3 to 4 month intervals. For patients receiving parenteral injections, a serum testosterone level should be measured at the midpoint between injections to ensure that the value is near the middle of the normal range. This is not usually a problem with the transdermal or oral preparations.

The table below summarizes the blood investigations that are recommended while monitoring patients on ART.

Investigation	Start of ART	First year	Subsequent years
Fasting lipids	Yes	Yearly	Yearly
Hb and Hct	Yes	Quarterly	Yearly
Serum PSA	Yes	Quarterly	Yearly

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