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PATHCHAT

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Hypogonadism in the elderly male

Testosterone biochemistry

Testosterone is the principal male sex hormone, and is secreted primarily by the Leydig cells of the testicles in the presence of luteinizing hormone (LH). Small amounts are also secreted by the adrenal glands. Testosterone plays a key role in the development of male reproductive tissues (testis and prostate), as well as promoting secondary sexual characteristics (increased muscle and bone mass, and body hair growth). Testosterone is essential for health and wellbeing and is needed for the prevention of osteoporosis (via oestradiol).

The majority of circulating testosterone is bound to plasma proteins. Some 44 to 65% is tightly bound to sex hormone-binding globulin (SHBG), and 33 to 50% is bound to albumin with a much lower affinity.
Only 2% of circulating testosterone is unbound or free. The non-SHBG bound testosterone is thought to be bioavailable (for uptake into the tissues).

Testosterone is produced in a diurnal rhythm. Serum levels reach their peak in the early morning, followed by a progressive fall throughout the day, reaching their nadir during the first few hours of sleep. The peak and trough values can differ by more than 30%.

Ageing

Physiological changes associated with ageing include an increased fat mass, decreased immune function and bone mineral density, loss of muscle mass and strength, changes in mood (depression and anger) and a decrease in virility and sexual function[1]. These changes are similar to those in young men with hypogonadism, raising the possibility that a decrease in testosterone levels may be the cause.

The concentration of serum testosterone reaches its maximum around 25 to 30 years of age and starts a slow steady decline thereafter at a rate of about 1% per year. SHBG increases at the same time resulting in the free testosterone decreasing by 2 to 3% per year[2]. The age-related decline of testosterone shows high inter-individual variability, and the majority of men remain eugonadal even in advanced age[1]. LH levels also increase at a rate of 1% per year. This rise is less than would be expected from the decreasing testosterone alone, indicating that hypogonadism has both primary (testicular) and secondary components.

Late-onset hypogonadism (LOH)

LOH is defined as a 'clinical and biochemical syndrome associated with advancing age and characterised by symptoms and a deficiency in serum testosterone levels'[3]. The prevalence of biochemical hypogonadism is high in the elderly with 20% of men over 60, 30% over 70 and 50% over 80 years of age having low testosterone levels[4].

This does not imply clinical hypogonadism, as most men with low testosterone remain asymptomatic. There is little correlation between symptoms of hypogonadism and a low serum testosterone value. This is partly due to the non-specific nature of the symptoms ascribed to hypogonadism, as well as the accumulation of chronic conditions, which occurs in the elderly. Therefore, the diagnosis of LOH requires both symptoms and biochemical evidence of hypogonadism.

There are no clear and definite guidelines as to when a low testosterone level becomes 'pathological' or who would benefit from androgen replacement therapy (ART). Various societies have published their recommended cut-offs for considering ART. These values range from 7 nmol/l to 12 nmol/l[5].

Current guidelines

Guidelines on the diagnosis and management of androgen deficiency were published in 2010 by the Endocrine Society[6]. There is a scarcity of large-scale trials studying LOH and ART, hence most recommendations are based on weak evidence. A summary of the guidelines are given below:

- A diagnosis of LOH should only be made in men with consistent symptoms and signs of

androgen deficiency and unequivocally low serum testosterone levels. Symptoms of androgen deficiency are shown in Table 1.

- A morning total testosterone level should be the initial diagnostic test.
- The diagnosis should be confirmed by a repeat test.
- Free or bioavailable testosterone level, should be measured in men in whom total testosterone concentrations are near the lower limit of the normal range and in whom alterations of SHBG are suspected.
- Serum LH and FSH levels should be measured to distinguish between primary and secondary hypogonadism.
- Screening for LOH should not be performed in the general population.
- ART should be given to symptomatic men with LOH aimed at improving their sexual function, sense of wellbeing, and bone mineral density.
- Prostate risk should be assessed before starting ART. Patients with prostate or breast cancer should not be given ART.
- Patients should be evaluated three to six months after treatment initiation, then annually to assess whether symptoms have responded to treatment and whether the patient is suffering any adverse effects, and to check compliance.

Recommendations

Since standardised reference ranges for testosterone do not exist, and because of the large inter-assay variation in testosterone measurements, it is important to use local cut-off limits. A substantial portion of the men evaluated for LOH are obese or insulin resistant[7]. In these men, the SHBG level, and thus the total testosterone level, may be low, while the free testosterone level may be normal. To avoid over-diagnosis, we recommend using free testosterone as an initial test. Suggested cut-off levels are given in Table 2.

Goals of ART

The goals of ART are to safely restore testosterone to normal physiologic levels, while ameliorating symptoms associated with LOH and improving patient health and wellbeing. Trials of ART in older men have been suggestive of the possible benefit of testosterone therapy in a number of realms, but changes with therapy have been small and inconsistent.

The presence of sexual symptoms is one of the most common reasons for patients seeking treatment, but the data on the effect of ART on sexual function in men with LOH is limited. ART appears to moderately improve libido, nocturnal erections, erectile function and overall sexual satisfaction, but the beneficial effect is dependent on the degree of androgen deficiency.

ART has important effects on body composition, resulting in an increase in lean body mass, and a decrease in fat mass without a change in body weight. These changes do not reliably translate into improved muscle strength or functional improvements. Similarly, ART has been shown to have a modest beneficial effect on bone mineral density, yet evidence that this reduces the fracture rate is still lacking. ART may have some beneficial effects on obesity and insulin resistance, but data is limited.

Testosterone is still generally considered atherogenic because of its detrimental effect on the lipid profile, although studies on patients with coronary heart disease taking ART have shown no adverse effects.

Other potential adverse effects of ART are liver abnormalities, aggressive mood, erythrocytosis, and gynaecomastia. ART may theoretically increase the rate of prostate cancer, yet this has not been demonstrated in the limited clinical studies available. It is important to re-evaluate patients three to six months after starting ART, and then annually to assess whether symptoms respond to treatment, and to detect any adverse effects.

Conclusion

Although low levels of testosterone are frequently found in elderly men, LOH is a relatively infrequent condition. ART should be considered for men with a clear LOH diagnosis, but the beneficial effects of this treatment, as well as its potential risks are currently unknown.

Table 1: Symptoms and signs suggestive of androgen deficiency in men

More specific signs and symptoms	Less specific signs and symptoms
Sexual symptoms Reduced libido, erectile dysfunction, decreased spontaneous erection, reduced intensity of orgasm and genital sensation	Decreased energy or vitality, increased fatigue
Oligospermia or azoospermia	Depressed mood
Osteoporosis or low bone mineral density	Reduced muscle mass and strength
Hot flushes, sweats	Poor concentration and memory
Breast discomfort, gynaecomastia	Sleep disturbance, increased sleepiness
Loss of pubic and axillary hair, reduced shaving	Mild anaemia
	Increased body fat, body mass index
	Diminished physical or work performance

Table 2: Useful testosterone levels in diagnosing LOH

		Overt testosterone deficiency	Excludes hypogonadism
Roche platforms	Total testosterone	< 8 nmol/l	> 12 nmol/l
	Free testosterone	< 180 pmol/l	> 250 pmol/l
Beckman platforms	Total testosterone	< 6.1 nmol/l	> 10 nmol/l
	Free testosterone	< 170 pmol/l	> 210 pmol/l

For intermediate total testosterone levels, a free testosterone level below the 'hypogonadism exclusion cutoff' provides supportive evidence for treatment.

References

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