

Male andropause and ageing

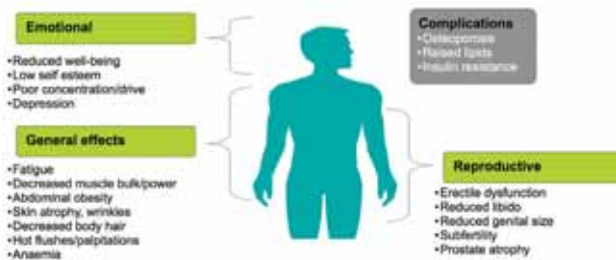
Looking and feeling healthy is paramount. We expect our quality of life to continue well into our latter years, with many of us looking forward to globe-trotting, learning new skills and enjoying a well-earned rest following years of hard work.

Testosterone deficiency in the ageing male has become a topic of great interest in recent years. Numerous longitudinal studies indicate that testosterone declines progressively with age. But does testosterone deficiency in the ageing male have a significant effect on quality of life? Is there any evidence that testosterone treatment is beneficial? Patients need to be well informed of the major health implications of their condition and weigh up the pros and cons of treatment.

It is well recognised that testosterone deficiency can affect multiple organ systems and have a significant negative impact on quality of life. Often referred to as the male andropause, the diagnosis of late onset hypogonadism (LOH) or testosterone deficiency syndrome (TDS) is based on clinical symptoms in association with confirmatory biochemical tests.

The recognition of LOH as a clinical entity has led to the development of international guidelines on the diagnosis, treat-

Clinical picture of the male andropause



ment and monitoring of LOH¹. Some population studies reveal prevalence rates as high as 38% of men over the age of 45 may be affected.

The testicular gland is responsible for testosterone production and comprises two main functional units. The seminiferous tubules, which are made up of germ cells, and Sertoli cells make up 90% of the testicular volume and supports spermatogenesis. Leydig cells, found between the seminiferous tubules, are responsible for testosterone hormone production.

Regulation of testosterone secretion is directly controlled by both the hypothalamus and pituitary glands. Gonadotrophin releasing hormone (GnRH) is secreted by the hypothalamus in a pulsatile fashion and results in the release of luteinising hormone (LH) and follicle stimulating hormone (FSH) by the pituitary: LH binds to Leydig cell receptors and stimulates the synthesis and secretion of testosterone hormone; whereas, both LH and FSH hormones are essential for sperm production and maturation.

The secretion of both GnRH and the pituitary hormones is tightly regulated by testicular function but in the ageing male there is a gradual decline in the pulsatile release of GnRH and subsequent decline in testosterone. About 60% of circulating testosterone in the blood is bound firmly to sex hormone bind-

ing globulin (SHBG), 38% is bound loosely to albumin and 2% is “free”. It is the loosely bound and free testosterone that is considered to be bioavailable.

With advancing age, SHBG rises and total testosterone steadily falls. However, bioavailable testosterone declines more rapidly, by 2–3% per year. Declining testosterone is significant because of its ubiquitous role: it helps regulate gonadal function and libido, affects mood and cognition, muscle mass, bone formation, liver function, red cell production (erythropoiesis) and immune function.

Erectile dysfunction and reduced libido are perhaps the most widely acknowledged symptoms of LOH. Testosterone plays a vital role in regulation of arterial blood flow and vasodilatation of the cavernosal smooth muscle through regulation of the nitric oxide cyclic-GMP pathways. Successful testosterone therapy can improve libido, erectile function, sexual activity, performance and desire. Numerous medical problems (diabetes mellitus, peripheral vascular disease, hyperprolactinaemia, bladder outlet obstruction, and certain drugs) may lead to erectile problems but hypogonadism accounts for up to 10–20% of cases.

In hypogonadal men, body composition is altered resulting in increased body fat, loss of lean muscle mass and muscle strength and increased waist-to-hip ratios. Testosterone administration has been shown to reverse this trend. Many of the features normally associated with the metabolic syndrome including obesity, hypertension, impaired glucose regulation, insulin resistance and abnormal lipid profile are present in hypogonadal men.

Results from a large longitudinal US study have demonstrated that low total testosterone is a significant marker for developing type 2 diabetes. Apart from restoring erectile dysfunction, testosterone therapy has been shown to reduce insulin resistance and improves glycaemic control in men with type 2 diabetes and hypogonadism.

There is compelling evidence that low testosterone is associated with an increased cardiovascular mortality. The EPIC study² clearly demonstrates that cardiovascular mortality is independently related to testosterone even after adjusting for age and common confounding risk factors.

Cardiovascular mortality

Similar results were observed in the Rancho Bernardo study³. This study comprised 794 men aged 50–91. Men whose total testosterone levels were lower than 8nmol/L were 40% more likely to die from all causes than those with higher levels, even after adjusting for common risk factors such as age, smoking, BMI and alcohol use.

Both low total and bioavailable testosterone levels predicted an increased risk of cardiovascular mortality. This study also re-

vealed lower total testosterone levels were associated with central obesity, insulin resistance, adverse lipid profile, blood pressure and new emerging risk factors such as adiponectin, leptin and C-reactive peptide.

There is a general perception that osteoporosis is almost exclusively a problem of older women but this remains untrue. The prevalence in men over 50 is approximately 4–6% and hypogonadism is a well-recognised risk factor for its development.

With at least 18 months of testosterone treatment, bone



mineral density (BMD) has been shown to increase in both the lumbar spine and hip but there remains no long-term study assessing the effect of testosterone treatment and reduction of hip and vertebral fractures.

Low testosterone is associated with reduced well-being and energy, increased lethargy and depressed mood. With successful treatment these symptoms can be reversed. There has also been recent interest in the role of testosterone therapy in patients with Alzheimer's disease as recent work has demonstrated improved mood and quality of life in men, although further more detailed research is required.

In patients with suspected LOH, a careful evaluation of the patient's symptoms followed by biochemical screening is required. An initial serum total testosterone level taken at approximately 9am should first be obtained. There is a general consensus that levels above 12nmol/L (350 ng/dl) are normal.

Patients with levels below 8nmol/L (230 ng/dl) should be considered for testosterone treatment. Levels between 8 to 12nmol/L are considered borderline. Under such circumstances, total testosterone should be retested with the addition of SHBG levels to help calculate the free testosterone level.

A level of less than 225pmol/L indicates a patient should be considered suitable for treatment. Measurement of LH and serum prolactin hormone should be included in the investigative work and proves invaluable to help differentiate between primary (testicular failure) and secondary (disorder of the hypothalamus/pituitary) hypogonadism and the requirement for further

investigations such as an MRI scan of the pituitary.

In LOH, there are concerns that testosterone therapy may lead to prostate cancer or benign prostatic hypertrophy (BPH) but there is no evidence of this. A pre-existing occult prostate tumour may, however, be unmasked by the introduction of testosterone treatment. For this reason, hypogonadal men over the age of 45 should be carefully evaluated and counselled about the potential benefits and risks before treatment is initiated and undergo surveillance of their prostate levels at regular intervals.

Testosterone therapy has been shown to increase prostate volume to a level equivalent to a man without hypogonadism. This, therefore, leads to a modest rise in PSA levels but does not directly lead to obstructive outflow problems. Nevertheless, the development of such symptoms should be monitored⁴.

The aim of testosterone treatment is to restore levels back into the normal physiological range, thereby alleviating features of testosterone deficiency and preventing long-term health risks associated with deficiency. Numerous preparations are available and include oral, buccal, subdermal, transdermal and intramuscular preparations. Most patients prefer topical gels, which are applied daily as this proves convenient with minimal side-effects. Testosterone levels reach physiological promptly and are maintained, provided patients adhere to daily applications. Alternatively, patients may choose an intramuscular injection administered at three monthly intervals. This proves to be a safe and effective mode of therapy, with physiological levels of testosterone being maintained with only four injections over the course of a year.

Before patients are considered for testosterone treatment, every patient should be thoroughly assessed and evaluated and informed of the benefits and risk of treatment. Baseline prostate specific antigen (PSA) levels and a digital rectal examination are recommended before treatment is initiated.

A full blood count and liver function tests are also valuable baseline tests. Patients started on testosterone should then be assessed at three months, 12 months and then at least annually to assess clinical response and side-effects and to monitor testosterone levels, haematocrit, liver function, lipids and PSA levels. Bone density scans are also advisable every two years.

Many features of ageing closely resemble those of testosterone deficiency and its prevalence is likely to increase, given the rising trends in the elderly population. Late-onset hypogonadism is clearly associated with numerous adverse features but early identification and successful treatment potentially can restore an individual's sexual function, quality of life and well-being.

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