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Late-Onset Hypogonadism (LOH): Incidence, Diagnosis, and Short-Term Effects

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Abstract

Late-onset hypogonadism (LOH) is a condition that affects an estimated 10% of men aged >50 years and up to 20% of men aged >60 years. Characterized by a measurable deficiency in serum testosterone levels, LOH is sometimes referred to as testosterone deficiency, or androgen deficiency in the ageing male (ADAM). There are a number of distinct physical, psychological, and sexual symptoms associated with LOH. The diagnosis of LOH is made on the basis of these presenting symptoms, accompanied by the biochemical establishment of low serum testosterone levels. Symptoms such as fatigue, sleep disturbance, short-term memory loss, changes in body composition, irritability, depression, a decrease in libido, and erectile dysfunction can compound to adversely affect patient quality of life and health status. This paper describes how to recognize and diagnose LOH and considers its short-term impact on patient health and well-being.

Keywords: Ageing male; Androgen deficiency in the ageing male; Late-onset hypogonadism; Testosterone deficiency

1. Introduction

Late-onset hypogonadism (LOH) in men is recognized as a growing clinical concern in an increasingly ageing population [1–4]. With advancing age, men experience a gradual reduction in circulating, biologically available testosterone [5]. A decline in serum testosterone levels is thought to progress at a rate of approximately 1% per year from as early as age 30 years, and a noticeable decline typically occurs after the age of 50 years, although the process is not constant and there can be great inter-patient variation [3,4].

As men age, there is a decline in the function of many endocrine systems, with reductions in the secretion rate not only of testosterone, but also of adrenal androgen precursors such as dehydroepiandrosterone (DHEA), thyroid hormones, growth hormone, insulin-like growth factor-I, renin, and angiotensin [6–8]. In contrast to the female menopause, which is typified by a dramatic and fairly abrupt reduction in ovarian function leading to distinct hormonal and reproductive changes, male age-related changes in testosterone – which have been described as the ''andropause'', the ''male climacteric'', the ''male menopause'', and testosterone deficiency – are in fact more subtle and gradual [1,3,5,6,9]. Because of the more insidious onset of declining testosterone levels in men compared with the menopause in women, a more appropriate term to describe the condition is late-onset hypogonadism – although androgen deficiency in the ageing male (ADAM) or PADAM (partial ADAM) are also used [1,3,4].

The decline in available testosterone reflects three separate phenomena of male ageing: a decline in testicular function, a decline in hypothalamic–pituitary function, and a rise in the levels of sex-hormone-binding globulin (SHBG). First, the decline in testicular function results from vascular supply to the testes diminishing with age, numbers of Leydig cells decreasing, and the testes becoming less responsive to luteinizing hormone (LH). Second, there is an age-related decline in hypothalamic–pituitary function, such that both the pulse frequency and the amplitude of secretion of gonadotrophins is reduced, resulting in a lower level of stimulation of the testes to produce testosterone. Testosterone

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levels vary diurnally but are generally within the range of 300–1000 ng/dL (10.4–34.7 nmol/L) in healthy men. Reductions in these peak and trough levels during ageing mean a general reduction in exposure to testosterone in all organ systems. Third, with ageing, there is a rise in the levels of SHBG, reducing the levels of free, unbound plasma testosterone available for action at target tissues [3,5,6].

2. Definition of LOH

The International Society for the Study of the Aging Male (ISSAM) has issued standards, guidelines, and recommendations for the investigation, treatment, and monitoring of LOH, and provides the following definition of the condition: "A biochemical syndrome associated with advancing age and characterized by a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgens ... It [LOH] may result in significant alterations in the quality of life and adversely affect the function of multiple organ systems" [3].

3. Incidence of LOH

The reported incidence of LOH varies, reflecting not only the change in incidence according to age of population studied, but also the uncertainty among the medical community as to the exact definition of LOH and a general under-appreciation of LOH as a clinical problem in ageing men [1]. As many as 20% of men aged >60 years are thought to have LOH; when the diagnosis of LOH is based on bioavailable testosterone, as many as 70% of men aged >60 years may be classifiable as hypogonadal [3]. Some of the best incidence data come from large-scale longitudinal studies conducted in ageing male cohorts. The Baltimore Longitudinal Study of Aging sampled blood on at least two occasions from a group of over 800 men aged 30–80 years and examined changes in total testosterone and in SHBG in order to estimate a free testosterone index [10]. Total testosterone decreased by around 3.17 ng/dL/year (0.11 nmol/L/year) and the free testosterone index fell even more steeply. This study found that 19%, 28%, and 49% of men aged >60 years, >70 years, and >80 years, respectively, had total testosterone levels below the norm seen in younger men, and the corresponding percentages of subjects with reduced free testosterone were 34%, 68%, and 91%, respectively [10]. These findings are supported by other large-scale studies, such as the Massachusetts Male Aging Study (MMAS) [11] and the Rancho Bernardo study [12], which indicate that biochemical hypogonadism is a very common occurrence in ageing men.

4. Diagnosing LOH

Many clinical cases of LOH are thought to go unrecognized, since the symptoms of testosterone deficiency can be insidious in onset, subtle in presentation, and are often viewed, by both patients and physicians, as an inevitable aspect of ageing [1].

Declining testosterone levels are associated with a host of symptoms and problems, such as gradual alterations in body composition, diminished energy and muscle strength, reduced sexual function, increased risk of osteoporosis and anaemia, and changes in mood and cognitive ability that may not be immediately attributable to LOH [1,3,4]. Appreciation of the impact of declining and low levels of free testosterone in LOH requires an understanding of the multiple physiological functions and action of testosterone in the normal young and healthy male (Table 1) [5].

Patients may present with single or multiple symptoms of LOH that require differential diagnosis and full assessment of clinical history, physical and mental condition, and clinical laboratory diagnosis of hypogonadism [2,3,5].

Symptoms that may lead a subject to seek medical advice include: reduced libido, erectile dysfunction or impotence, a noticeable decrease in muscle mass and strength or feeling of fatigue and lack of energy, a change in body composition characterized by an increase in visceral fat, increasing tendency to fractures suggestive of osteoporotic changes, and alterations in

Table 1
Biological actions of testosterone

- Stimulation of erythropoietin from kidneys to enhance haematopoiesis
- Retention of nitrogen to maintain normal muscle metabolism and mass
- Stimulation of bone mineralization by inhibiting osteoclastic activity while enhancing osteoblastic activity
- Inhibition of the inflammatory response in autoimmune rheumatic disease
- Stimulation of liver protein formation
- Mood stabilization, and amelioration of depression, irritability, and diminished self-esteem
- Enhancement of various parameters of cognition
- Enhancement of libido
- Maintenance of frequency of nocturnal erections and, to a lesser degree, volitional erections