Late-Life Onset Hypogonadism: A Review

Nazem Bassil, MD[a], John E. Morley, MB, BCh[b,c,*]

KEYWORDS

• Late-onset hypogonadism • Testosterone deficiency
• Diagnosis • Testosterone replacement therapy

Late-onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with advancing age, and it is characterized by a deficiency in serum testosterone levels.[1,2] The most easily recognized clinical signs of relative androgen deficiency in older men are a decrease in muscle mass and strength, a decrease in bone mass, osteoporosis, and an increase in central body fat. None of these symptoms are specific to the low-androgen state but they may suggest testosterone deficiency. In addition, symptoms such as a decrease in libido and sexual desire, forgetfulness, loss of memory, difficulty in concentrating, insomnia, and a decreased sense of well-being are more difficult to measure and differentiate from hormone-independent aging. This condition may result in significant detriment to quality of life and adversely affect the function of multiple organ systems.[3] LOH is important because it features many potentially serious consequences that can be readily avoided or treated, and the affected sector of the population is currently expanding. Prospective population-based studies reported in the past decade indicate that low testosterone levels are associated with an increase in the risk for developing type 2 diabetes mellitus and metabolic syndrome.[4] In men, endogenous testosterone concentrations are inversely related to mortality,[5] but this association could not be confirmed in the Massachusetts Male Aging Study (MMAS)[6] or the New Mexico Aging Study.[7]

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[a] Division of Geriatric Psychiatry, Department of Neurology and Psychiatry, Saint Louis University School of Medicine, St Louis, MO, USA
[b] Division of Geriatric Medicine, Saint Louis University School of Medicine, 1402 South Grand Boulevard, M238, St Louis, MO 63104, USA
[c] Geriatric Research Education and Clinical Center, Veterans Affairs Medical Center, St Louis, MO, USA
* Corresponding author. Division of Geriatric Medicine, Saint Louis University School of Medicine, 1402 South Grand Boulevard, M238, St Louis, MO 63104.
E-mail address: morley@slu.edu

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As the clinical symptoms of hormone deficiency in older men may be nonspecific, testosterone replacement therapy (TRT) is only warranted in the presence of clinical symptoms suggestive of hormone deficiency and decreased hormone levels.[8] Restoring serum testosterone levels to the normal range using TRT results in clinical benefits in some of these areas.

AGING AND HYPOGONADISM

The percentage of the population in the older age group is increasing. Testosterone deficiency is a common disorder in older men but it is underdiagnosed and often untreated. Clinicians tend to overlook it, and the complaints of androgen-deficient men are merely considered to be part of aging. Testosterone supplementation in the United States has increased substantially in the past several years.[9] However, it has been estimated that only 5% of affected men currently receive treatment.

The decline of serum testosterone levels seems to be a gradual, age-related process resulting in an approximate 1% annual decline after age 30 years. In men older than 65 or 70 years, the changes in total testosterone are overshadowed by a more significant decline in free testosterone levels.[10] This is a consequence of the age-associated increase of the levels of sex hormone-binding globulin (SHBG).[11] Although the decrease is gradual, by the eighth decade, according to the Baltimore Longitudinal Study, 30% of men had total testosterone values in the hypogonadal range, and 50% had low free testosterone values. The rate of age-related decline in serum testosterone levels varies in different individuals and is affected by chronic disease and medications.[12] There is evidence that many of these men are not symptomatic.[13] In addition, men with the prototypic symptom of hypogonadism (ie, low libido) often have normal testosterone and testosterone receptors.[14]

This decline of testosterone levels in aging men may result from reduced testicular responses to gonadotrophin stimuli with aging, coupled with incomplete hypothalamo-pituitary compensation for the decrease in total and free testosterone levels.[15,16]

DIAGNOSIS OF LOH

At present, the diagnosis of LOH requires the presence of symptoms and signs suggestive of testosterone deficiency.[1,17] The symptom most associated with hypogonadism is low libido.[18] Other manifestations of hypogonadism include erectile dysfunction (ED), decreased muscle mass and strength, increased body fat, decreased bone mineral density (BMD), osteoporosis, mild anemia, breast discomfort and gynecomastia, hot flushes, sleep disturbance, body hair and skin alterations, decreased vitality, and decreased intellectual capacity (poor concentration, depression, fatigue).[19] The problem is that many of the symptoms of late-life hypogonadism are similar in other conditions[20] or are physiologically associated with the aging process.[21–25] One or more of these symptoms must be corroborated with a low serum testosterone level.[25] Depression, hypothyroidism, and chronic alcoholism should be excluded, as should the use of medications such as corticosteroids, cimetidine, spironolactone, digoxin, opioid analgesics, antidepressants, and antifungal drugs. Diagnosis of LOH should never be undertaken during an acute illness that is likely to result in temporarily low testosterone levels (**Fig. 1**).

The Androgen Deficiency in Aging Males (ADAM)[26–28] and the Aging Male Symptoms Scale (AMS)[29] questionnaires (**Box 1**) may be sensitive markers of the low testosterone state (97% and 83%, respectively), but they are not tightly correlated with low testosterone (specificity 30% and 39%), particularly in the borderline low