Maturitas 84 (2016) 94–99

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

# EMAS position statement: Testosterone replacement therapy in the aging male

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ARTICLE INFO

*Article history:*

*Keywords:*
Late-onset hypogonadism
Testosterone replacement
Aging male

ABSTRACT

*Introduction:* Late-onset hypogonadism (LOH) represents a common clinical entity in aging males, characterized by the presence of symptoms (most usually of a sexual nature, such as decreased libido, decreased spontaneous erections and erectile dysfunction) and signs, in combination with low serum testosterone concentrations. Whether testosterone replacement therapy (TRT) should be offered to those individuals is still under extensive debate.
*Aims:* The aim of this position statement is to provide and critically appraise evidence on TRT in the aging male, focusing on pathophysiology and characteristics of LOH, indications for TRT, available therapeutic agents, monitoring and treatment-associated risks.
*Materials and methods:* Literature review and consensus of expert opinion.
*Results and conclusions:* Diagnosis and treatment of LOH is justified, if a combination of symptoms of testosterone deficiency and low testosterone is present. Patients receiving TRT could profit with regard to obesity, metabolic syndrome, type 2 diabetes mellitus, sexual function and osteoporosis and should undergo scheduled testing for adverse events regularly. Potential adverse effects of TRT on cardiovascular disease, prostate cancer and sleep apnea are as yet unclear and remain to be investigated in large-scale prospective studies. Management of aging men with LOH should include individual evaluation of co-morbidities and careful risk versus benefit assessment.


## 1. Introduction

Aging or the process of becoming older represents the accumulation of physical, psychological, and social changes in a human being over time, ultimately resulting in death. Late-onset hypogonadism (LOH) is characterized by decreasing circulating

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http://dx.doi.org/10.1016/j.maturitas.2015.11.003
0378-5122/

testosterone concentrations, in combination with a spectrum of clinical symptoms and signs, during normal aging [1].

Recently, new testosterone formulations, in combination with increased marketing efforts and wider recognition of LOH, have contributed to broad testosterone testing and supplementation, in many countries [2]. However, testosterone preparations seem to be increasingly prescribed and consumed even without documented testosterone deficiency, especially in the USA. Part of the currently discussed testosterone adverse effects might be attributed to this improper prescribing [3].

**Grading system**

EMAS clinical guides adopt the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, recommended by the Knowledge and Encounter Research (KER) Unit at the Mayo Clinic, to grade the level of evidence of each recommendation.

Strong recommendations use the number 1 and weak recommendations the number 2.

Cross-filled circles indicate the quality of the evidence:

| | |
|---|---|
| ⊕ | very low quality |
| ⊕⊕ | low quality |
| ⊕⊕⊕ | moderate quality |
| ⊕⊕⊕⊕ | high quality |

The aim of this position statement is to provide and critically appraise evidence on testosterone replacement therapy (TRT) in the aging male, focusing on pathophysiology and characteristics of LOH, indications for TRT, available therapeutic agents, monitoring and treatment-associated risks.

## 2. Pathophysiology and characteristics of LOH

A decline in testosterone concentrations starts at, approximately, 40 or even 30 years of age [4,5]. It has been estimated that 7% of 40–60-year-old men present with serum total testosterone concentrations of less than 12 nmol/l (3.5 ng/ml), increasing to 21% in 60–80-year-old and 35% of men aged 80 years or more [6]. Prospective data from the recent European Male Aging Study (EMAS), on 2599 men aged 40–79 years, have revealed a 2.1% prevalence of LOH, defined as three sexual symptoms, namely decreased libido, spontaneous erections and erectile dysfunction in the presence of low testosterone [7].

According to the most recent statement of the International Society for the Study of the Aging Male (ISSAM) [8], LOH, defined as a series of symptoms in older adults related to testosterone deficiency [9], combines features of both testicular (primary) and hypothalamic-pituitary (secondary) hypogonadism [10]. Recently, EMAS, by studying 3369 men between 40 and 79 years of age [11], defined LOH by the presence of at least three sexual symptoms, associated with total testosterone concentrations of less than 11 nmol/l (3.2 ng/ml) and free testosterone concentrations of less than 220 pmol/l (64 pg/ml). LOH might be attributed to a number of causes [e.g., decreased number of Leydig cells, reduced Leydig cell response to gonadotropins (LH, FSH), decreased testicular blood flow, hypothalamic-pituitary fatigue (changes in the pattern of LH release)], as well as external factors (e.g., systemic disorders, drugs, environmental, lifestyle) [10]. Clinical tools, such as the Saint Louis University Androgen Deficiency in the Aging Male (ADAM) and the Aging Male Symptom (AMS) rating have been developed for the screening of LOH, with a sensitivity of 96% and a specificity of 30%, respectively [12]. However, their use has not been established due to low specificity [13].

Signs and symptoms suggestive of androgen deficiency in older men can be more or less specific, comprising reduced libido and sexual activity, decreased spontaneous erections, gynecomastia, low trauma fracture and/or low bone mineral density, hot flushes/sweats, decreased energy and physical performance, dysthymia, poor concentration and memory, sleep disturbances, anemia, reduced muscle strength and increased body fat [14]. There is a rough correlation between LOH symptoms and testosterone concentrations [15,16]. Loss of libido represents the most specific symptom of male hypogonadism [11,17], mostly occurring below 15 or 12 nmol/l (4.3–3.5 ng/ml), while other symptoms (e.g., weakness and/or loss of muscle mass) are associated with much lower circulating total testosterone concentration (<5.2–6.9 nmol/l or <1.5–2.0 ng/ml) [18].

A number of recent studies suggest an association between low testosterone concentrations with poor sleep quality [19], insulin resistance, increased risk for diabetes mellitus, obesity, metabolic syndrome and an unfavorable cardiovascular risk profile in general [11,20–22]. Within the EMAS study population, both moderately [defined as total testosterone of 8 nmol/l (2.3 ng/ml) or greater and less than 11 nmol/l (3.2 ng/ml) and free testosterone less than 220 pmol/l (63 pg/ml)] and severely [defined as total testosterone less than 8 nmol/l (2.3 ng/ml) and free testosterone less than 220 pmol/l (63 ng/ml)] androgen deficient men showed lower hemoglobin, mid-upper arm circumference, estimated heel bone mineral density, physical function measured by SF-36 questionnaire, slower gait speed and poorer general health, while severe LOH was associated with larger waist circumference, insulin resistance and metabolic syndrome [7]. Regarding mortality, severe LOH has been related to an overall 5.5-fold higher risk of all-cause mortality [2-fold higher in those with testosterone ≤8 nmol/l (2.3 ng/ml), irrespective of symptoms, and 3-fold higher in those with three sexual symptoms, irrespective of testosterone concentrations] [23]. Additionally, several other epidemiologic studies and meta-analyses have demonstrated higher all-cause mortality and cardiovascular mortality in men with low testosterone concentrations [24,25].