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EMAS position statement: Testosterone replacement therapy in the aging male

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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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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].

3. Indications for TRT in LOH

Although the presence of LOH is well-established, there is ongoing debate and extensive discussion whether TRT should be given to these individuals or not [26]. High-quality data regarding benefit and risk of TRT in the aging male are rather limited so far.

Testosterone replacement therapy may be considered in men over 50 years of age, if they have i) clinical manifestations indicative of androgen deficiency ii) low serum, bioavailable or free testosterone levels and iii) no contra-indications to treatment [27]. Studies of the effects of TRT have generated intense debate. A randomized controlled trial of TRT given for 6 months to older men with low-normal testosterone found that it did not affect bone mineral density, cognitive function, functional mobility, well-being or muscle strength; on the other hand, it had beneficial effects on waist and insulin resistance, but harmful effects on lipids and metabolic syndrome [28]. Regarding the cardiovascular system, low testosterone has been associated with increased blood pressure, dyslipidemia, atherosclerosis, arrhythmia, thrombosis, endothelial dysfunction, as well as with impaired left ventricular function; however, TRT has not been proven so far to be beneficial with respect to cardiovascular disease; neither has it been definitely shown to have specific adverse cardiovascular effects [29]. Additional data from recent studies suggest a beneficial effect of TRT in special populations, such as men with testosterone deficiency and type 2 diabetes mellitus as far as survival [30], glycemic control, cholesterol concentrations, body composition, libido and sexual function [31], as well as patient-reported quality of life (QoL) [32] are concerned. According to the BLAST-study [33], achieving threshold serum concentrations seems to be of significant importance for the response to TRT.

Current guidelines agree that a combination of symptoms of testosterone deficiency and low testosterone concentrations are required for diagnosis and treatment of LOH [13,14,34]. Several recent epidemiological data from the USA [35], Australia [36] and Europe [37,38] have set 12 nmol/l (3.5 ng/ml) as the lowest value for testosterone serum levels in healthy men.

Measuring serum testosterone is justified only in aging men presenting with signs or symptoms suggestive of androgen deficiency [27]. According to the current clinical practice guidelines, a repeated measurement of serum testosterone concentrations should be performed in combination with sex hormone-binding globulin (SHBG) concentrations during the early morning hours [14,27], in order to assess free testosterone concentrations as well. Mass spectrometric methods (LC–MS/MS) represent the gold standard for measuring testosterone [39]. Medical conditions, such as moderate obesity, hypothyroidism, use of glucocorticoids, and diabetes mellitus are associated with decreased serum SHBG concentrations, while aging and hyperthyroidism induce increased serum SHBG concentrations [14]. Therefore, further weight reduction efforts alone may be appropriate in obese patients with free testosterone concentrations within the normal range.

Table 1
Currently available preparations for TRT in aging males with LOH.

Route of application	Dosing	Interval
Transdermal		
Gel	25–50 mg	daily
Patches	1.2–2.4 mg	daily
Topical solution	30–60 mg	daily
Buccal		
Testosterone tablets	30 mg	twice daily
Intramuscular		
Testosterone enanthate	250 mg	2–3 weeks
Testosterone undecanoate	1000 mg	12 weeks
Oral		
Testosterone undecanoate	3–4 × 40 mg	daily
Subcutaneous		
Testosterone pellets	4 × 200 mg	4–6 months

Modified according to Bhasin et al., Endocrine Society Clinical Practice Guideline [14].

4. How to treat—therapeutic agents

TRT is indicated in patients with symptoms of androgen deficiency and serum testosterone concentrations below the normal range [3].

Testosterone has already been in clinical use for almost eight decades [40]. Today, different preparations and modes of application, such as intramuscular, subdermal, transdermal, oral and buccal agents are available (Table 1) [3]. Natural testosterone preparations should be preferred, resulting in circulating serum testosterone concentrations as close to physiology as possible and avoiding supra-physiologically high or low testosterone concentrations [13,41].

Transdermal testosterone preparations can be used as a first choice, since their pharmacokinetics is closest to optimal androgen substitution and they mimic physiological diurnal variations. Additionally, short-acting transdermal preparations offer the advantage of rapid testosterone discontinuation upon removal should an adverse event (e.g., elevated hematocrit or prostate carcinoma) [42] occur. They should be, therefore, preferred over long-acting preparations, at least in the initial treatment of LOH [3,13].

In a recent study regarding comparative safety of different preparations, testosterone injections were associated with a greater risk of cardiovascular events (e.g., myocardial infarction, unstable angina and stroke, hospitalizations and death) compared with transdermal gels, whereas patches and gels showed comparable risk profiles [43]. This could be, in part, explained by varying pharmacokinetics, since injections cause spikes in testosterone concentrations, while transdermal patches and gels cause more subtle and sustained increases. TRT with intramuscular injections of testosterone esters (250 mg/2 weeks) can induce insulin resistance in healthy subjects [44].

Nonetheless, the selection of the optimal testosterone preparation should be a shared decision made by the patient and the treating physician [45].

5. Monitoring TRT in the aging male

Testosterone replacement therapy should be initiated with a target serum testosterone into a range that is mid-normal for healthy, young men (suggested target serum testosterone concentration in men receiving testosterone enanthate 350–750 ng/dl, 1 week after injection); a 6-month time interval may be necessary to show a reduction in symptoms [14,27]. No dose-effect correlation of TRT has been demonstrated so far; however, dose escalation in order to increase efficacy might increase adverse effects [46].

According to an Endocrine Society clinical practice guideline, men with LOH receiving TRT should have regularly scheduled testing for adverse events, optimally at 3, 6 and 12 months after initiation and, then, annually [14]. Parameters for surveillance include well-being, libido and sexual activity, measurement of serum testosterone concentrations, haemoglobin and haematocrit, prostate-specific antigen (PSA) and digital rectal examination, and, biannually, bone mineral density [3]. A decision on whether to continue treatment can be made at 6 months.

6. Treatment risks including contra-indications for TRT

Testosterone replacement therapy may cause a number of potential adverse events including erythrocytosis, acne and oily

skin, exacerbation of subclinical prostate cancer, growth of metastatic prostate cancer and reduced sperm production and fertility. Gynecomastia, male pattern balding, growth of breast cancer and/or induction or worsening of obstructive sleep apnea are less common and only weakly associated with TRT. Additionally, there are formulation-specific adverse effects [14].

TRT is associated with very high risk of certain serious adverse outcomes and therefore absolutely contra-indicated in men with metastatic prostate cancer or breast cancer. Medical conditions such as unevaluated prostate nodule or induration, PSA > 4 ng/ml, hematocrit > 50%, severe lower urinary tract symptoms associated with benign prostatic hypertrophy and/or uncontrolled or poorly controlled congestive heart failure are related to moderate to high risk of adverse outcomes with testosterone; hence, the Endocrine Society also refrains from using TRT in these individuals [14]. Age per se is not a contra-indication to TRT [13].

Recent studies have raised concern about the cardiovascular safety of TRT, especially in men with pre-existing heart disease and/or in men over the age of 65 [47–49]. This has lead the Food and Drug Administration (FDA—US) requiring that manufacturers of testosterone products add information to the labeling about this possible increase in cardiovascular risk [50]. However, this risk was not confirmed by other reports [31,51,52]. The European Medicines Agency, American Association of Clinical Endocrinologists and American College of Endocrinology have agreed that there is no consistent evidence that testosterone therapy either increases or decreases cardiovascular risk [53,54]. Thus, the Endocrine Society suggested that large-scale, controlled studies are needed to resolve this controversy [55], since even a small potential risk is unwarranted [44], when balanced against a small potential benefit.

There is also uncertainty about the potential effects of TRT on the risk of prostate cancer [13,56,57] and sleep apnea [44,58,59]. On the basis of limited data, TRT does not appear to increase the risk of prostate cancer [60]; however, it might increase serum PSA concentrations by 0.3 to 0.6 mg/dl [14]. The same meta-analysis, including 51 studies with a follow-up ranging from 3 months to 3 years, revealed that TRT was associated with a significant increase in hemoglobin and hematocrit and a decrease in high-density lipoprotein (HDL) cholesterol, while there was no significant effect on mortality or cardiovascular outcomes [60].

7. Conclusions

LOH represents a common clinical entity among aging males; TRT should be offered to these individuals, only if a combination of symptoms of testosterone deficiency and low testosterone is present. Patients receiving TRT could have positive effects on obesity, metabolic syndrome, type 2 diabetes mellitus, sexual function and osteoporosis, but should undergo scheduled regular testing for adverse events. Potential effects of TRT on cardiovascular disease, prostate cancer and sleep apnea are 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 estimation [5].

8. Recommendations

- Testing for testosterone deficiency should be only performed in men with symptoms of androgen deficiency; universal testosterone testing in aging males is not recommended (**1**|+◯◯◯).
- Symptoms compatible with androgen deficiency involve loss of libido, erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality and depressed mood (**1**|++◯◯).
- A general policy of offering TRT to all aging men with low testosterone concentrations is not recommended (**1**|+◯◯◯).
- Physicians should consider offering TRT, on an individual basis, to aging men with low testosterone concentrations on more than one occasion and clinically significant symptoms of androgen deficiency (**2**|+◯◯◯).
- Potential benefit of TRT should outweigh the cost, inconvenience and risks of therapy for aging males **(1|+◯◯◯)**.
- It is always advisable to encourage aging males with LOH to undertake lifestyle modifications, including reduced caloric intake, increased daily physical activity, smoking cessation, reduced alcohol consumption and adoption of a healthy diet, before considering initiation of TRT (**1**|+◯◯◯).
- Currently available percutaneous, transdermal, subcutaneous and buccal testosterone preparations are considered to be safe and effective (**2**|++◯◯).
- There is no consensus on the beneficial effects of TRT with regard to obesity, metabolic syndrome, type 2 diabetes mellitus, sexual function and osteoporosis (**2**|++◯◯).
- Specific populations, such as older men with low testosterone concentrations and type 2 diabetes mellitus might benefit from TRT (**1**|+++◯).
- TRT is absolutely contra-indicated in cases of metastatic prostate (**1**|++◯◯), or breast cancer (**1**|+◯◯◯), unevaluated prostate nodule or induration, PSA > 4 ng/ml (**1**|+++◯), hematocrit >50%, severe lower urinary tract symptoms and/or uncontrolled congestive heart failure (**1**|+++◯).
- If TRT is prescribed, serum testosterone concentrations should be therapeutically raised into a range that is mid-normal for healthy, young men (**2**|+◯◯◯).
- Patients receiving TRT should undergo regular testing for adverse events; a critical risk-versus-benefit estimation on whether to continue TRT should be made 6 months after treatment initiation**(1|++++)**.
- Risks and benefits of TRT should be very carefully weighed up in testosterone deficient aging men with or without pre-existing heart disease, until evidence from large randomized prospective trials regarding cardiovascular safety of TRT becomes available**(1|++◯◯)**.

Conflict of interest

None declared.

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