

Testosterone treatment in the aging male: myth or reality?

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Summary

The definition of late onset hypogonadism in the aging male is controversially debated, and according to the latest literature consists of at least three especially sexual symptoms such as loss of morning erection, low sexual desire and erectile dysfunction as well as a total testosterone <8–11 nmol/l. Testosterone replacement therapy in the aging male has been shown to have a beneficial effect on muscle and fat mass as well as on bone mineral density, with more conflicting effects observed on muscle strength, sexual function, mood and quality of life. The prescriptions for testosterone products for the aging male increased by over 170% in the previous five years. Furthermore, there is a lot of epidemiological data showing an inverse relationship between testosterone levels and obesity, insulin resistance, the metabolic syndrome and type 2 diabetes mellitus. However, only few small randomised placebo-controlled studies have investigated the effect of testosterone replacement therapy on insulin resistance and HbA1c levels, with controversial results. Importantly, so far the long-term safety and efficacy of testosterone replacement therapy has not been established. Although until now no clear evidence has been found that testosterone replacement therapy has a causative role in prostate cancer or indeed in changes of the biology of the prostate, in a recent meta-analysis a 4-fold increased risk of prostate-associated event rates in testosterone treated elderly men sounds a note of caution. Also the risk for cardiovascular events is still not clear and caution is warranted especially in elderly men with cardiovascular disease and limited mobility.

In summary, the actual available evidence of long-term risks and outcome of testosterone replacement therapy is still very limited and carefully designed placebo-controlled trials of testosterone administration to assess the risks and benefits of such a therapy are required. Until then, testosterone treatment in elderly men should be restricted to elderly men with clearly low testosterone levels in the presence of clinical symptoms, and the advantages and disadvantages need to be accurately weighted. A careful monitoring of potential side effects is necessary.

Key words: late onset hypogonadism; testosterone replacement therapy

Introduction

Testosterone is present in plasma as free (unbound) testosterone, albumin bound and sex hormone-binding globulin (SHBG)-bound testosterone. It is well established that testosterone levels in men decrease with age [1]. Specifically, in the aging man, there is on average a 1–2% decline of total testosterone levels per year with a more rapid decline in free testosterone levels because of a concomitant increase in SHBG with aging. Due to this slow decrease in testosterone levels the androgen deficiency of the elderly man is described as partial androgen deficiency of the aging male (PADAM) or late onset hypogonadism (LOH). This age-related decrease is primarily due to testicular dysfunction, however, an additional hypothalamic component is possible since it has been shown that elderly men with low testosterone levels have an increased luteinising hormone (LH) response to gonadotropin releasing hormone (GnRH) in the presence of normal basal LH levels [2].

At the same time, occurring in parallel to decreasing testosterone levels, clinical symptoms such as reduced libido and erectile dysfunction as well as mood symptoms and a decrease of quality of life are often observed in the aging male. However, these symptoms are unspecific and their association with decreased testosterone levels in older men is weak [3, 4]. Moreover, co-morbid conditions (e.g., diabetes mellitus, hypertension) and lifestyle influences (obesity, alcohol and tobacco use, psychological stress etc.) may be as strongly associated with declining testosterone levels as aging itself [5].

Therefore, there is considerable controversy regarding whether this age associated decrease in testosterone levels has clinical significance, and should be treated with testosterone supplementation.

Definition of LOH

The diagnosis of LOH should be made based on typical clinical symptoms in the presence of low testosterone levels. Clinical symptoms in men include sexual symptoms (such as decreased erectile function and decreased libido), decreased mood, decreased muscle and increased fat mass, and decreased bone density among others. Recently, Wu et al conducted a systematic investigation of a large random sample of aging men from the general population to pro-

duce criteria to diagnose LOH [3]. They found that many candidate symptoms, especially psychological symptoms, were not associated with decreased testosterone levels in aging men, however, they found a non-linear threshold relationship between sexual symptoms and testosterone levels. They concluded that LOH should be diagnosed in the presence of at least three sexual symptoms such as loss of morning erection, low of sexual desire and erectile dysfunction, and a total testosterone level of less than 8–11 nmol/l (2.30–3.19 ng/ml) and free testosterone levels of less than 222.2 pmol/l (<64 pg/ml). Using this definition, the prevalence of hypogonadism in this study was 2.1% and increased with age from 0.1% for men 40 to 49 years of age to 5.1% for those 70 to 79 years of age [3].

Potential benefits of testosterone replacement in elderly men

Effects of testosterone treatment on body composition, muscle strength and bone metabolism

It has been shown in several studies that increasing serum testosterone concentrations in elderly men increases lean mass especially of the trunk, and decreases fat mass particularly in the arms and legs [6–8]. However, despite this effect on body composition, data about the effect of testosterone replacement on muscle strength remain controversial. It has been shown that men with chronic obstructive pulmonary disease [9], those receiving glucocorticoids [10] and elderly men in rehabilitation [11] showed improvement in muscle strength or physical function after testosterone replacement therapy. Similarly, two recently published randomised, placebo-controlled trials showed a beneficial effect of testosterone treatment in intermediate frail or frail elderly men and in men with limited mobility on leg-press and chest-press strength, respectively [7, 8].

In contrast, testosterone replacement therapy in *otherwise healthy* elderly men showed no improvement in muscle strength in two randomised, placebo-controlled trials with a 36 month [6] and 6 month duration of testosterone or placebo treatment, respectively [12].

Testosterone is not only an important regulator of muscle and fat mass but also plays also an important role in the maintenance of bone density in men. Hypogonadism is a common cause of osteoporosis and rapid bone loss is

observed after castration or androgen deprivation therapy [13]. Furthermore, studies have shown that bone structural parameters (e.g., bone microarchitecture, cortical and trabecular bone mineral density) are impaired in men with hypogonadism [14]. A placebo-controlled study including 108 elderly men with mean testosterone levels of 12.8 nmol/l found no overall effect of a 3-year testosterone replacement therapy on bone density. However, a significant treatment effect with increased lumbar spine bone density was observed in elderly men with low pre-treatment testosterone levels (testosterone <10 nmol/l) [15]. In agreement with this study, a recent clinical trial showed that testosterone replacement therapy in men with testosterone levels in the low-normal range did not change bone density [12]. In two separate meta-analyses, there was a small benefit in lumbar spine bone mineral density in testosterone-treated elderly men without treatment-baseline testosterone level interaction [16, 17].

Effect of testosterone treatment on sexual function

Normal male sexual function depends on a complex interplay of psychological, neurological, vascular and endocrine factors [18, 19]. Several studies have shown that age, prostatic hyperplasia, body mass index, diabetes, chronic diseases such as heart diseases and hypertension, associated medications and indexes of anger and depression, influence and are independent factors for sexual dysfunction [18, 20]. Low testosterone levels in elderly men are associated with reduced libido [5, 21] but several studies have shown that there is no clear association between testosterone levels and erectile function [20–22]. A recent study showed that the probability of sexual symptoms in elderly men increases with decreased levels of testosterone and showed only good correlation when testosterone levels were clearly subnormal (total testosterone <8–11 nmol/l) [3].

Several studies have investigated the effect of androgen replacement therapy on sexual function in elderly men, with controversial findings. Some studies showed no beneficial effect [23, 24] whereas other studies showed an improved sexual function [25]. Two meta-analyses of randomised, placebo-controlled studies showed overall a small positive effect of testosterone replacement therapy in men with sexual dysfunction (erectile dysfunction, libido) and low testosterone levels [26, 27]. It is concluded that the effect

Table 1: Potential benefits and management of testosterone replacement therapy in elderly men [53, 54].

Potential benefits of testosterone replacement therapy	Management of testosterone replacement therapy
Body composition:	
<ul style="list-style-type: none"> Improvement of muscle mass Decrease of fat mass Improvement of muscle strength in intermediate frail or frail elderly men Possible small benefit in lumbar spine bone mineral density 	<ul style="list-style-type: none"> Bone mineral densitometry of the lumbar spine, femoral neck and hip after 1–2 years of testosterone replacement therapy in men with osteoporosis or low trauma fracture
Sexual function:	
<ul style="list-style-type: none"> Positive effect on sexual function in men with low pre-treatment testosterone levels 	<ul style="list-style-type: none"> Evaluate patients at baseline, at 3 to 6 months and then annually after beginning testosterone replacement therapy. Consideration of established therapy for erectile dysfunction.
Mood and quality of life:	
<ul style="list-style-type: none"> Beneficial effect in mood in patients with low pre-treatment testosterone levels No statistically significant improvement of quality of life 	<ul style="list-style-type: none"> Evaluate patients at baseline, at 3 to 6 months and then annually after beginning testosterone replacement therapy
Type 2 diabetes and components of the metabolic syndrome:	
<ul style="list-style-type: none"> Possible small positive effect on insulin resistance and HbA1c (few data with controversial findings!) 	<ul style="list-style-type: none"> No specific recommendations, if patient has a diagnosis of diabetes use guidelines of the ADA [55]

of testosterone replacement on libido and erectile dysfunction is clearly weaker in men with low-normal or normal testosterone levels compared to elderly men with hypogonadal testosterone levels.

Effects of testosterone treatment on mood and quality of life

Decreased testosterone levels are weakly associated with depressive symptoms and poor cognitive function and Alzheimer's disease [28, 29]. Experimental studies suggest that testosterone has neuroprotective effects. However, in intervention studies including elderly men, testosterone replacement only had a beneficial effect on mood in men with clearly subnormal testosterone levels [30] and it is important to keep in mind that sexual dysfunction can have a major impact on quality of life and psychosocial and emotional well-being [18, 31]. The results of placebo-controlled randomised trials on the effects of testosterone on quality of life and depressive mood have been inconsistent and often quality of life as assessed by different questionnaires did not improve significantly [7, 12].

Effects of testosterone treatment on type 2 diabetes and components of the metabolic syndrome

The metabolic syndrome is defined as glucose intolerance, central obesity, dyslipidaemia (including increased triglycerides, decreased high-density lipoprotein cholesterol concentration), hypertension, increased prothrombotic and antifibrinolytic factors, and risk for atherosclerotic diseases [32]. Low serum testosterone is common in men with type 2 diabetes and/or metabolic syndrome, and numerous studies have reported an inverse association between testosterone levels and obesity, insulin resistance and dyslipidemia. This can partly be explained by an increase of aromatase activity which is associated with a greater conversion of testosterone to estradiol (testosterone-estradiol shunt associated with increased subcutaneous fatty-tissue) [33]. Moreover, hypogonadal men seem to have an increased risk of developing type 2 diabetes mellitus and metabolic syndrome [34, 35]. However, so far, only very small placebo-controlled studies have investigated the effect of testosterone replacement on insulin resistance and HbA1c. Results are controversial with either no effect [36] or a small beneficial effect [37]. Another effect of testosterone replacement therapy is a decrease in total cholesterol, mainly because of a decrease in HDL cholesterol levels [12]. It is therefore too early to draw any conclusion about the effect of testosterone replacement on components of the metabolic syndrome and large randomised controlled studies are needed.

Potential risks of testosterone replacement in elderly men

Prostate hypertrophy and prostate cancer

The prostate is an androgen-dependent and an androgen-sensitive organ and testosterone is required to develop the gland and may have a causative role in prostate carcinogenesis [38]. The presence of androgen is required for the development of BHP and anti-androgen agents can decrease

prostate volume in patients with BHP [39]. Moreover, testosterone treatment can accelerate metastatic prostate cancer [40] and androgen withdrawal is the basis for the treatment of advanced prostate cancer. However, comparing circulating testosterone levels in men with and without prostate cancer have demonstrated widely varying results [41]. Importantly, serum testosterone levels do not reflect the hormone levels in prostate tissue, where testosterone is converted into Dihydrotestosterone which is the major intracellular androgenic metabolite. Therefore, all studies investigating an association of serum androgen levels and prostate cancer must be interpreted with caution. Nevertheless, taking this into consideration, several small placebo controlled trials with a maximum duration of 3 years so far showed no convincing evidence for a causative role of testosterone treatment in subsequent prostate cancer risk [42]. To determine the effect of testosterone replacement therapy on prostate tissue, Marks et al performed a randomised controlled trial and found no treatment related change in prostate histology, tissue biomarkers, gene expression or prostate cancer incidence or severity [43]. In addition, no disease progression was detected after testosterone replacement therapy in men who survived prostate cancer with hypogonadal symptoms [44]. Furthermore lower urinary tract symptoms in patients with benign prostate hypertrophy seem to improve with a testosterone replacement therapy [45]. However, as a note of caution, a meta-analysis of all randomised, placebo-controlled studies showed an alarming higher risk of detection of all prostate events (as defined as incidence of prostate cancer, increase in International Prostate Symptom Score (IPSS) or prostate-specific-antigen (PSA) and acute urinary retention) [46]. Considering these different results and especially results of this meta-analysis, caution seems to be warranted in these patients and the potential benefits of testosterone replacement therapy needs to be weighed against the still unclear risk of a progression of prostate-associated adverse events. Importantly, the longest randomised, controlled trial was conducted for 36 months, which is arguably too short to draw definitive conclusions about the risk of prostate cancer. Further long-term studies are required to answer this question. Until then, careful monitoring of the prostate is required in elderly men receiving testosterone replacement therapy.

Haematocrit

Haematocrit >50% is the most frequent testosterone-related adverse event in clinical trials. In a meta-analysis of 19 randomised controlled trials – including a total of 1084 subjects, 651 on testosterone, 433 on placebo – testosterone-treated men were nearly 4 times as likely as placebo-treated men to develop a haematocrit >50%. The clinical significance of this increase is still unclear, but carefully monitoring of this parameter should be performed regularly [46].

Cardiovascular diseases

A possible inverse association between testosterone levels and cardiovascular mortality remains controversial. In one study including 1686 men, sex steroids overall seemed to have a relatively weak negative association with all-cause and cause-specific mortality [47], and likewise an-

other study showed an inverse association with mortality, which was, however, only significant in elderly men with clearly low testosterone levels in the lowest percentile (<8.3 nmol/L) [48]. Low testosterone levels have been reported in type 2 diabetes, chronic obstructive pulmonary disease, alcoholic liver disease and chronic renal disease [49], and acute illness is known to reduce testosterone production. Therefore results from clinic-based studies may be biased by the strong possibility that low testosterone is simply an epiphenomenon of concurrent and possibly acute illness. This is also supported by a recent study, where Araujo et al conducted a meta-analysis of 12 studies and showed that low testosterone levels were associated with increased risk of all cause and cardiovascular disease death. However, considerable between-study heterogeneity suggests that these results were driven by some factors such as age, underlying health status and baseline total testosterone [50].

In a meta-analysis of 19 clinical trials the rate of cardiovascular events was not significantly different between groups receiving testosterone or not [46] suggesting a neutral effect of testosterone on the cardiovascular system [51]. However, a recent placebo-controlled randomised trial in elderly patients with limitations in mobility was terminated early because of higher rates of cardiovascular adverse events during testosterone replacement therapy [7]. This result is surprising since many studies with greater number of subjects showed no increased cardiovascular event rates. The reason for the increased cardiovascular event rates remains unclear and it is not excluded that the results are due to chance. However, these findings provide new caution about the administration of testosterone in elderly men with a history of cardiovascular disease and immobility [52]. Looking at these controversial data with regards to testosterone and cardiovascular events as well as cardiovascular and all-cause mortality, it is clear that we will need large, carefully designed trials of testosterone administration perhaps along the lines of the Women's Health Initiative [52].

Conclusion

Several benefits of testosterone replacement therapy in elderly men have been observed, especially an increase in muscle mass and bone density, and a decrease in fat mass, with more conflicting and controversial data on muscle strength, sexual function and mood. However, long-term risks, especially cardiovascular and prostate-associated risks, still remain unclear. Importantly, the long-term safety and efficacy of testosterone in the aging male has not been established and physicians should accurately weight the advantages and disadvantages of testosterone replacement therapy in the aging male. Furthermore, the diagnostic criteria as well as the aetiology responsible for the decrease in testosterone levels remain a matter of debate. So far, LOH should only be diagnosed in the presence of at least three (especially sexual) symptoms and a total testosterone level of less than 8–11 nmol/l. Treatment should be accompanied by an appropriate monitoring of the prostate, cardiovascular system and blood parameters conducted by a specialist.

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Table 2: Potential risks and management of testosterone replacement therapy in elderly men [53, 54].

Potential risks of testosterone replacement therapy	Management of risks testosterone replacement therapy
Prostate hypertrophy and prostate cancer:	
<ul style="list-style-type: none"> Possible higher risk of prostate events such as prostate cancer, increase in International Prostate Symptom Score (IPSS) or prostate-specific-antigen (PSA) and acute urinary retention 	<ul style="list-style-type: none"> Men >40 years and PSA levels greater than 0.6 ng/ml at baseline: PSA levels and digital examination at baseline, at 3 to 6 months and then in accordance with evidence-based guidelines for prostate cancer screening Urological consultation if <ul style="list-style-type: none"> increase of PSA levels >1.4 ng/ml per year detection of prostatic abnormalities on digital rectal examination
Haematocrit:	
<ul style="list-style-type: none"> Development of haematocrit >50%, unclear clinical consequences 	<ul style="list-style-type: none"> Determine Haematocrit at baseline, at 3 to 6 months and then annually If haematocrit is above 54% stop therapy and evaluate the patient for hypoxia and sleep apnea syndrome
Cardiovascular diseases:	
<ul style="list-style-type: none"> Increased cardiovascular event rates in elderly patients with limitations in mobility 	<ul style="list-style-type: none"> No specific recommendations. Evaluate patients at baseline, at 3 to 6 months and then annually after beginning testosterone replacement therapy. In case of cardiovascular event consider discontinuation of therapy and consult a cardiologist
Type 2 diabetes and components of the metabolic syndrome:	
<ul style="list-style-type: none"> Reduction of HDL cholesterol 	<ul style="list-style-type: none"> Evaluate patients at baseline, at 3 to 6 months and then annually after beginning testosterone replacement therapy

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