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Managing Hypogonadism in Older Men: Is Testosterone Therapy the Answer?

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Abstract

Introduction:

Age-related decline in testosterone production contributes to late-onset hypogonadism (LOH), characterized by reduced muscle mass, bone density, and sexual function. The increasing use of testosterone replacement therapy (TRT) in aging men has raised concerns about its efficacy

and safety. This review summarizes current evidence regarding the benefits and risks of TRT in older men.
Material and Methods:
A literature review was performed in PubMed, Scopus, Cochrane Library, and Web of Science, including studies from 2015–2025. Clinical trials, meta-analyses, and reviews on the effects of TRT on body composition, bone density, metabolic profile, sexual and cognitive function, cardiovascular health, and prostate safety were analyzed.
Results:
TRT improves lean body mass, reduces visceral fat, and enhances bone mineral density, especially in the lumbar spine. Moderate benefits are seen in sexual desire and erectile function, with no significant cognitive improvement. The most frequent adverse effect is erythrocytosis. Prostate safety appears acceptable when physiological testosterone levels are maintained.
Conclusion:
TRT can provide functional and metabolic benefits in older hypogonadal men but requires careful selection, individualized dosing, and regular monitoring due to potential hematologic and cardiovascular risks.

Keywords: Testosterone, Aging men, Hypogonadism, Testosterone replacement therapy, Bone density, Erythrocytosis

1. Introduction

Testosterone production in Leydig cells is regulated by the hypothalamic–pituitary–gonadal (HPG) axis through luteinizing hormone (LH). Disturbances within this axis may lead to various forms of hypogonadism. In the bloodstream, testosterone exists mainly in a protein-bound form: approximately 1–2% circulates as free testosterone, while 20–25% is loosely bound to albumin—together forming the bioavailable fraction. The remaining portion is tightly bound to sex hormone-binding globulin (SHBG) and is biologically inactive [2].

Aging in men is associated with a gradual decline in serum testosterone levels. In older men, testosterone deficiency is of mixed origin, combining features of both primary and secondary hypogonadism. This results from a reduction in the number and function of Leydig cells, decreased sensitivity of the HPG axis to feedback regulation, and a lower amplitude of LH pulses. With advancing age, the level of bioavailable testosterone decreases as SHBG production increases, thereby reducing the amount of active testosterone [1].

Normal ranges vary depending on assay and population, but typically fall between 300–1000 ng/dl. After the age of 30, testosterone levels decline by approximately 0.4–2% per year. By the seventh decade of life, 35% of men have lower testosterone levels than younger individuals, and 13% meet the diagnostic criteria for hypogonadism[2]. This phenomenon is referred to as late-onset hypogonadism (LOH). Hypogonadism is defined as a morning serum testosterone level below 280 ng/dl [4].

Reduced testosterone levels can also result from non-gonadal factors such as obesity, type 2 diabetes, metabolic syndrome, renal insufficiency, malignant tumors, hyperthyroidism, liver cirrhosis, and other chronic conditions. Therefore, first-line management should focus on treating underlying diseases. Certain medications, such as glucocorticoids and opioids, may also contribute to testosterone suppression [3,5,2].

In recent decades, there has been a marked increase in the prescription use of testosterone preparations. This trend is associated with population aging and greater health awareness. However, data suggest that the demand for testosterone therapy may exceed its actual clinical indications, raising questions about the appropriateness and safety of its widespread use [9].

The characterization of men with late-onset hypogonadism (LOH) is challenging, as symptoms of testosterone deficiency often overlap with natural aging. The benefits and risks of testosterone replacement therapy (TRT) in this group remain uncertain, leading to considerable controversy. Given the increased risk of adverse effects in older individuals, the decision to initiate TRT should be based on a careful, individualized assessment of potential benefits and risks [2]. The aim of this review is to discuss the benefits, risks, and controversies associated with TRT in older men.

Keywords: Testosterone, Aging men, Hypogonadism, Testosterone replacement therapy, Bone density, Erythrocytosis

2. Materials and Methods

A literature review was conducted to evaluate the effects of testosterone replacement therapy (TRT) in aging men, with particular emphasis on hypogonadism and its metabolic and physiological consequences. The search was performed in the PubMed, Scopus, Cochrane

Library and Web of Science databases. The following keywords were used: “testosterone”, “aging men”, “hypogonadism”, “testosterone replacement therapy”, “bone density”, and “erythrocytosis”.

Publications from the last ten years (2015–2025) were included, encompassing clinical studies, meta-analyses, and review articles addressing the effects of testosterone on the cardiovascular system, bone metabolism, erythropoiesis, prostate function, and metabolic syndrome. Preclinical animal studies and papers with incomplete methodology were excluded.

3. Research Results

3.1. Body Composition and Muscle Strength

Testosterone increases muscle and bone mass, elevates IGF-1 levels, reduces inflammatory markers (TNF, IL-6), and improves metabolism. Hormone therapy primarily leads to an increase in lean body mass, while physical exercise additionally enhances muscle strength and overall physical performance. Optimal effects on body composition and physical fitness are achieved through the combination of testosterone therapy (in men with confirmed deficiency) and regular physical training [7,8].

Studies indicate that the effectiveness of testosterone replacement therapy (TRT) in improving body composition varies depending on the route of administration. Oral preparations do not show a significant effect on muscle or fat mass compared to transdermal and parenteral forms, which may result from lower bioavailability or poorer patient adherence. Among the various forms of treatment, intramuscular administration has demonstrated the highest efficacy in increasing muscle mass and strength—particularly in the lower limbs—among middle-aged and older men [9].

Testosterone supplementation may positively influence body composition by increasing muscle mass and reducing fat, especially visceral fat; however, these effects require a longer treatment duration to become evident. Short-term therapy does not produce significant changes, and body

circumference measurements alone do not accurately reflect actual changes in the proportion of muscle to fat tissue [1].

Some studies have observed improvements in strength following TRT (e.g., in the six-minute walk test or limb exercises), but the results remain inconsistent. The benefits are more pronounced in older men with marked testosterone deficiency and frailty [8].

Individualized selection of the preparation and careful monitoring of treatment effects are essential to achieve optimal benefits while minimizing the risk of adverse effects.

3.2. Bone Density

Testosterone stimulates osteoblast proliferation and attenuates pro-apoptotic signaling through the regulation of protein kinase B activity, while concurrently inhibiting parathyroid hormone–induced osteoclast formation. With advancing age, the progressive decline in testosterone levels leads to a reduction in bone mineral density (BMD) and an increased risk of fractures [9].

In men over the age of 50, bone mass gradually decreases, with a more pronounced decline observed after the age of 70. Testosterone replacement therapy (TRT) appears to be most effective in individuals with markedly low baseline testosterone concentrations; however, it is currently not recommended as a primary treatment for osteoporosis. Regular, moderate physical activity may naturally elevate testosterone levels, enhance muscle and bone strength, and reduce the risk of falls in older men [6].

In the Bone Trial of the Testosterone Trials (TTrials), testosterone treatment was shown to significantly improve volumetric bone mineral density of the spine and femur, as well as increase areal bone mineral density and estimated bone strength compared with placebo. The greatest benefits were observed in trabecular bone density in the spine compared with cortical bone in the hip.[1].

In older men, it is important to consider not only testosterone levels but also dihydrotestosterone (DHT) and sex hormone–binding globulin (SHBG) concentrations, particularly in relation to hip fracture risk. Higher DHT levels have been associated with a lower risk of femoral fractures, whereas elevated SHBG concentrations were linked to an increased risk [10].

3.3. Sexual Function

Erectile dysfunction (ED) frequently coexists with metabolic disorders such as diabetes, hypertension, dyslipidemia, and obesity, as well as with aging and low testosterone levels. It may represent an early marker of endothelial dysfunction and serve as a predictor of late-onset hypogonadism (LOH). Testosterone replacement therapy (TRT) can improve sexual function in older men with androgen deficiency, particularly when low testosterone levels are accompanied by reduced libido or poor responsiveness to phosphodiesterase type 5 (PDE5) inhibitors. Although a full consensus on the role of androgens in libido regulation has not been established, low testosterone remains an important risk factor for ED [6].

In a study including 790 men aged ≥65 years with total testosterone levels below 275 ng/dl and symptoms of hypogonadism, participants were randomly assigned to receive either testosterone gel or placebo for one year. Treatment increased testosterone concentrations to levels typical of young men and significantly improved sexual activity, sexual desire, and erectile function ($P < 0.001$) [11].

Another study involving 1007 men with low testosterone levels evaluated the effects of intramuscular testosterone undecanoate (1000 mg every three months for two years) combined with a lifestyle modification program on sexual function, assessed using the International Index of Erectile Function (IIEF-15) questionnaire. Testosterone therapy improved scores across all five IIEF-15 domains, particularly sexual desire and orgasmic function, with the greatest effects observed in older men and those with depressive symptoms. This improvement was independent of baseline serum testosterone levels, and treatment did not significantly affect the severity of depressive symptoms. Regardless of treatment, reductions in waist circumference and depressive symptoms correlated with better sexual function, highlighting the importance of metabolic and psychological factors in sexual health. Clinically meaningful improvements in

sexual desire and erectile function were observed in approximately 10% and 3% of participants, respectively [16].

These findings suggest that testosterone therapy may moderately enhance sexual function—particularly sexual desire—while lifestyle and psychological factors play a substantial role in overall sexual health improvement.

3.4. Cognitive Function

Clinical studies investigating the effects of testosterone therapy on cognitive function in older men have yielded inconsistent results; however, the majority of evidence indicates no significant cognitive benefits.

In a study involving 493 men with age-associated memory impairment (AAMI), testosterone treatment compared with placebo did not result in improvements in any of the assessed cognitive parameters, including delayed and immediate paragraph recall, visual memory, spatial abilities, executive function, global cognition, or self-reported memory problems [12].

Similar findings were reported in an analysis of all 788 participants of the Testosterone Trials (TTrials). Although a slight improvement in executive function was observed, the effect was of limited clinical significance and did not extend to other cognitive domains [12].

In both men with AAMI and the overall TTrials cohort, testosterone therapy did not produce significant improvements in cognitive performance. These data suggest that testosterone administration in older men with low testosterone levels does not confer meaningful cognitive benefits.

Most observational studies also indicate that testosterone levels do not predict cognitive decline or the risk of developing Alzheimer’s disease. Likewise, randomized controlled trials have demonstrated that testosterone therapy does not significantly affect cognitive function in men with low or low-to-normal testosterone concentrations, regardless of pre-existing cognitive impairment [13].

3.5. Lipids and Cholesterol

There is a bidirectional relationship between testosterone levels and adipose tissue mass. On one hand, low testosterone concentrations promote the development of obesity; on the other, excessive adiposity leads to reduced serum testosterone levels, creating a metabolic vicious cycle. One of the key mechanisms underlying this process involves the activity of lipoprotein lipase (LPL), an enzyme located on the surface of adipocytes. LPL catalyzes the hydrolysis of circulating triglycerides, facilitating their uptake and storage within adipose cells. Physiologically, testosterone inhibits LPL activity in adipocytes, thereby limiting lipid accumulation and preventing adipocyte hypertrophy. In conditions of testosterone deficiency, this inhibitory effect is diminished, resulting in enhanced fatty acid uptake, adipocyte enlargement, and increased fat deposition [6].

Within the framework of the Testosterone Trials (TTrials), 788 men aged ≥65 years with low testosterone levels were studied across 12 clinical centers. A substantial proportion of participants were obese and had comorbid conditions, including diabetes and hypertension. The testosterone and placebo groups were well balanced in terms of clinical characteristics and concomitant medications. Lipid profile analysis showed that both groups experienced overall reductions in serum lipid concentrations over the 12-month observation period. After adjustment for baseline values, testosterone therapy was associated with a slightly greater decrease in total cholesterol (by 6.1 mg/dl compared with placebo; $P < 0.001$), as well as reductions in HDL cholesterol (difference –2.0 mg/dl; $P < 0.001$) and non-HDL cholesterol (difference –4.2 mg/dl; $P = 0.005$). The change in LDL cholesterol was borderline significant (difference 2.3 mg/dl; $P = 0.051$), while the effect of testosterone on triglyceride levels was not significant [14].

These findings suggest that the potential metabolic benefits of testosterone therapy in older men are limited and should be carefully considered within the broader context of each patient's overall cardiovascular risk profile.

3.6. Metabolic syndrome

The Three-City Study (3C) provided significant findings indicating that low testosterone levels are strongly associated with the presence of Metabolic Syndrome (MetS) and may play a key role in its pathogenesis. In men with MetS, lower concentrations of testosterone (both total and

bioavailable) were associated with a significantly higher risk of mortality, suggesting that hormonal disturbances may exacerbate the adverse metabolic consequences of the syndrome. Mediation analyses revealed that a substantial portion of the effect of low testosterone on mortality was mediated by the presence of MetS, indicating that testosterone may influence survival primarily through metabolic mechanisms. The authors emphasized that MetS may be an important factor modifying the relationship between testosterone and metabolic health, and its presence may help explain inconsistencies in previous findings regarding the impact of testosterone on cardiometabolic risk [22].

In their literature review, Hermoso et.al. (2020) analyzed the relationship between testosterone deficiency and metabolic syndrome in men, noting that lower androgen levels correlate with a higher prevalence of MetS and its components, such as abdominal obesity, insulin resistance, elevated triglycerides, and reduced HDL cholesterol. The authors pointed out that although numerous studies support the hormonal–metabolic association, it remains unclear whether low testosterone is a cause or merely a marker of metabolic deterioration. Therefore, further interventional studies are needed to determine whether correcting testosterone deficiency could have clinical relevance in the prevention or treatment of metabolic syndrome [23].

3.7. Erythrocytosis

Erythrocytosis, defined as an increase in hematocrit, represents one of the most common adverse effects of TRT in men with hypogonadism. This effect primarily results from testosterone-induced stimulation of erythropoiesis. Testosterone initially increases erythropoietin (EPO) secretion, leading to the establishment of a new equilibrium between EPO and hemoglobin levels. In addition, testosterone lowers hepcidin concentrations—a key regulatory protein in iron metabolism—and influences erythropoiesis through several indirect mechanisms. Evidence suggests that TRT-induced erythrocytosis may be associated with an increased risk of thromboembolic complications [18].

Therefore, in clinical practice, regular monitoring of hematological parameters (Hb, Hct) and identification of additional thrombophilic risk factors are essential in patients receiving testosterone therapy [19].

Baseline hemoglobin and hematocrit values should be assessed prior to initiating TRT and subsequently monitored at regular intervals—every 3–6 months, or according to the schedule of 3–4 months, 12 months, and annually thereafter. The occurrence of erythrocytosis (Hct >54%) warrants discontinuation of therapy or the performance of therapeutic phlebotomy; some clinicians recommend considering intervention already at Hct ≥50%. In the event of thromboembolic episodes, testosterone therapy should be immediately discontinued and appropriate anticoagulant treatment initiated. When evaluating patients for testosterone therapy, clinicians should also consider the presence of thrombophilic conditions (e.g., factor V Leiden mutation, antiphospholipid antibody syndrome, prothrombin gene mutations) as well as elevated levels of factor VIII or homocysteine [17].

3.8. Coronary Heart Disease

The TRAVERSE study focuses on a comprehensive assessment of testosterone therapy in men with hypogonadism, emphasizing not only the typical therapeutic effects but also potential cardiovascular and hematological risks. The authors highlight that in patients with testosterone deficiency and coexisting cardiovascular risk factors, close monitoring of parameters such as hemoglobin and hematocrit is essential due to the possible occurrence of erythrocytosis and related complications. This study represents an important step toward establishing a solid understanding of the long-term safety of testosterone therapy, underscoring the need to consider both its benefits and potential risks in therapeutic decision-making [20].

Previous studies on the effects of testosterone on the cardiovascular system have produced conflicting results. Some clinical trials suggested an increased number of adverse cardiovascular events in older men receiving testosterone, while others did not confirm such an effect, and some found no differences in the progression of atherosclerosis between the treatment and placebo groups. In the Cardiovascular Trial, a component of the TTrials program, it was demonstrated that one-year testosterone treatment in older men with hypogonadism was associated with a statistically significant increase in non-calcified coronary plaque volume compared with placebo. Although the clinical significance of this finding remains uncertain, the results suggest a potential adverse impact of testosterone on vascular wall structure. The authors emphasize that larger, long-term studies are needed to determine whether this observed effect translates into an increased risk of cardiovascular events [12].

3.9. Prostate Gland

In a randomized clinical trial published by Bhasin et al. (2023), the safety of the prostate was evaluated in men with hypogonadism receiving testosterone replacement therapy. The study included men aged 45–80 years with confirmed testosterone deficiency and at least one cardiovascular risk factor. Participants received either testosterone gel or placebo, maintaining testosterone levels within the physiological range (350–750 ng/dL). The results showed that testosterone treatment was not associated with an increased risk of prostate cancer, prostate enlargement, or worsening of lower urinary tract symptoms compared with placebo. The authors emphasized that testosterone therapy appears to be relatively safe for the prostate in men with low to moderate urological risk; however, further long-term follow-up studies are needed to fully assess the safety of this treatment, particularly in patients with an initially elevated risk of malignancy [21].

In their review, Barone et al. highlighted that in men with testosterone deficiency, therapy may be administered when clinically indicated, without evidence of a significant increase in the risk of prostate cancer or worsening of prostate disease following treatment—though they cautioned that long-term data remain limited. They also pointed out the need for individual assessment of prostate status before initiating testosterone therapy (TTh) and for ongoing monitoring thereafter. In light of these findings, testosterone appears to be relatively safe for the prostate when used in an appropriately selected clinical context, provided that caution is exercised and potential methodological limitations of available studies are taken into account [9].

4. Conclusion

An analysis of the available studies indicates that testosterone replacement therapy (TRT) in older men with confirmed hypogonadism may offer a range of physiological benefits. Increases in muscle mass, reductions in visceral fat, and improvements in lower limb strength [1,7,8,9] are particularly evident in patients with low baseline testosterone levels and when intramuscular formulations are used. TRT also exerts a beneficial effect on sexual desire [6,11,16] and provides moderate improvement in erectile function, especially in men who do not fully respond to PDE5 inhibitors.

With respect to the skeletal system, an increase in bone mineral density (BMD) [9,6,1,10] has been observed in the lumbar spine, along with prevention of bone mass loss in the femoral neck. At the same time, most studies have not demonstrated significant cognitive benefits of TRT [12,13], and the impact of therapy on lipid profile appears modest — showing a slight reduction in total cholesterol and HDL levels, with no significant changes in LDL or triglycerides [6,14].

The most common adverse effect reported was erythrocytosis [18,19,17], which requires regular blood count monitoring and individualized dose adjustment. Research findings have not shown an increased risk of prostate cancer or progression of benign prostatic hyperplasia when physiological testosterone levels are maintained [21,9].

Moreover, growing evidence suggests that low testosterone levels correlate with the presence of metabolic syndrome and may exacerbate its components; however, this relationship is complex and warrants further investigation [22,23].

Given the increased risk of complications associated with TRT in older individuals, treatment decisions should be based on a careful, individualized assessment of potential benefits, risks, and coexisting chronic conditions. A holistic approach to patient care is essential, taking into account the overall health status, comorbidities, and personal therapeutic goals.

DISCLOSURE

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