

Male Reproduction and Aging



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KEYWORDS

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

KEY POINTS

- Syndromic prevalence of late-onset hypogonadism is low.
- Testosterone can be considered a biomarker of health because comorbidities are associated with low testosterone concentrations.
- Efficacy of testosterone therapy in older men is modest.
- Testosterone therapy improves bone mass (but there are no fracture data); there is no conclusive evidence that it improves cognition.
- Long-term cardiovascular and prostate safety of testosterone therapy in older men remains unclear.

INTRODUCTION

Aging of humans is associated with functional alterations at all levels of the reproductive axis and affects both steroidogenic and spermatogenic compartments. Unlike female reproductive aging (menopause) or *organic* androgen deficiency in men (due to diseases of the hypothalamus, pituitary, or testes), male reproductive aging does not result in absolute cessation of testosterone production or spermatogenesis (**Table 1**). In fact, the decline in serum testosterone concentrations due to aging *per se* is mild, and in most men, testosterone concentrations are in the low-normal range. Nonetheless, in a minority of aging men, testosterone deficiency may occur, which is influenced by the presence of comorbidities. Recent data suggest that older men who remain fit and healthy generally continue to maintain normal serum testosterone levels.

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Table 1 Summary of differences in clinical features of reproductive aging in female menopause, organic male hypogonadism, and late-onset male hypogonadism			
	Female Menopause	Organic Male Hypogonadism	Late-Onset Hypogonadism
Rate of hormonal decline	Rapid	Generally rapid (may vary)	Gradual
Degree of hormone deficiency	Profound	Profound	Mild (most cases)
Nature of deficiency	Cessation of ovarian estrogen production	Cessation of testicular testosterone production	Androgen levels fluctuate (no absolute cessation)
Symptoms	Specific	Specific	Generally nonspecific

Age-related low testosterone in men has been referred to as andropause, viropause, partial androgen deficiency of the aging male, or late-onset hypogonadism (LOH); the latter term is used most often.¹ In this article, we review age-related changes in sex steroid levels and its consequences. We also discuss efficacy and safety of testosterone therapy.

Epidemiology of Late-Onset Hypogonadism

Although total testosterone levels are generally lower in some older men compared with their younger counterparts, unlike menopause, there is no clear age-based inflection point at which there is an abrupt decline in sex steroid production. Cross-sectional studies have suggested that testosterone levels peak in the second and the third decade of life and then decline gradually (at a rate of 1%–1.5% per year).² Aging is also associated with an increase in sex hormone-binding globulin (SHBG) level (1.0% per year), which results in an even steeper decline in free testosterone levels (2%–3% per year).^{3–5} Limited data show that metabolic clearance rate of testosterone also decreases with aging.⁶

Numeric Versus Syndromic Prevalence of Late-Onset Hypogonadism

Several cross-sectional studies have shown that after accounting for potential confounding factors (time of sampling, concomitant illness, medications, and hormone assays), serum total testosterone levels are lower in older men compared with those in young men.^{3,4,7} Two decades ago, data from the Baltimore Longitudinal Study on Aging showed that the *numerical prevalence* of low testosterone (total testosterone <325 ng/dL or free testosterone index <2.5th percentile) was as high as 68% in men in their 70s and 91% in men aged 80 years and older. However, this study did not assess the presence of specific signs and symptoms of androgen deficiency (syndromic androgen deficiency).⁷ Despite the marked increase in the number of testosterone prescriptions written for middle aged and older men, the syndromic prevalence of LOH remains low. Data from the European Male Aging Study (EMAS), in which the investigators carefully assessed symptoms associated with androgen deficiency in men aged 40 to 79 years, found that the *syndromic prevalence* of LOH was only 2.1%.⁸ Additional evidence regarding the low syndromic prevalence of LOH comes from the enrollment data of the Testosterone Trials (TTrials), a coordinated set of trials that assessed the efficacy of 1 year of testosterone therapy in men aged 65 years or older with age-related low testosterone and specific symptoms of androgen deficiency.⁹ Eligibility criteria included an average of 2 total testosterone

concentrations of less than 275 ng/dL and decreased vitality, sexual dysfunction, or physical dysfunction.¹⁰ Of the 51,085 men screened, only 931 men (1.8%) met eligibility criteria,¹⁰ suggesting that only a minority of older men meet subjective, objective, and biochemical criteria of androgen deficiency. Even though clinical practice guidelines recommend treatment of men with organic hypogonadism,¹¹ a large fraction of men are still prescribed testosterone for age-related low levels.

Comorbidities Influence Testosterone Levels

In addition to the effect of aging, comorbidities, including adiposity, also influence serum testosterone levels.¹² Additionally, use of certain medications (glucocorticoids and opioids) also suppresses gonadal axis. Among the comorbidities, obesity has a profound effect on serum androgen levels.² Data from EMAS show that obese men have lower serum testosterone concentrations than men with normal body mass index (BMI), irrespective of age (Fig. 1).⁸ Longitudinal data from the Massachusetts Male Aging Study show that the trajectory of age-related decline in serum testosterone is much steeper if a person becomes obese during the follow-up (Fig. 2).¹³ Mechanisms behind this obesity-related decrease remain unclear.

Pathophysiologic Basis of Age-Related Decline in Testosterone Levels

In this section, we will review alterations in the male gonadal axis as a consequence of aging. In healthy adult men, the rate of testosterone production ranges between 3 and 10 mg/d and serum concentrations range between 264 and 916 ng/dL.¹⁴ Testosterone is secreted in a circadian manner, with the highest levels seen in the morning.¹⁵

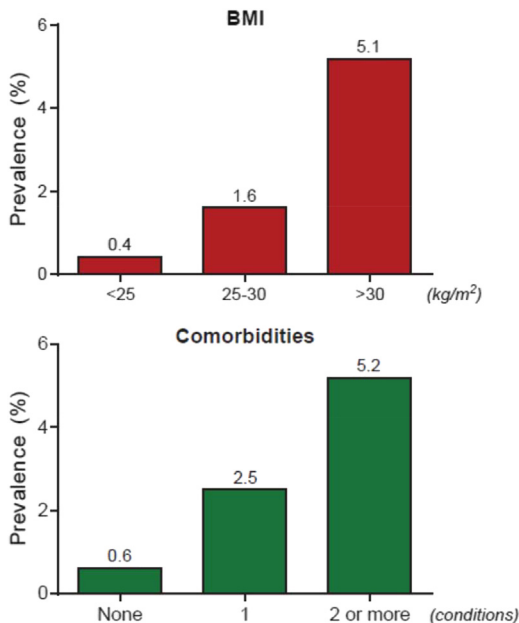


Fig. 1. Effect of adiposity and comorbidities on the prevalence of late-onset hypogonadism. (Data from Wu FC, Tajar A, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva F, Forti G, Giwercman A, Huhtaniemi IT, Kula K, Punab M, Boonen S, Vanderschueren D; European Male Aging Study Group. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *J Clin Endocrinol Metab.* 2008 Jul;93(7):2737-45.)

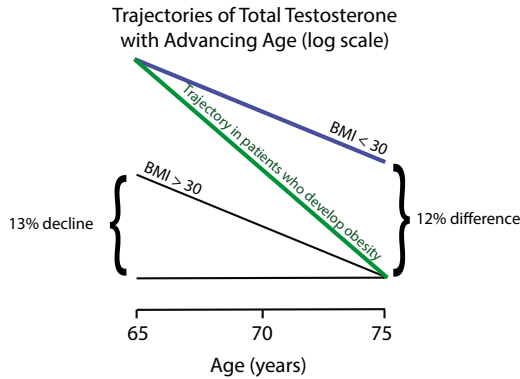


Fig. 2. Trajectory of decline in serum testosterone based on change in body weight. (Adapted from Travison TG, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. *J Clin Endocrinol Metab.* 2007 Feb;92(2):549-55.)

Testosterone is largely bound to plasma proteins with approximately 40% loosely bound to albumin and 58% tightly bound to SHBG; thus, approximately 2% of testosterone is unbound (free), the fraction considered to be biologically active.^{16,17} Dihydrotestosterone exerts its effects via binding to androgen receptor, whereas adrenal androgens androstenedione and dehydroepiandrosterone exert their effects through conversion to testosterone.

Men with organic hypogonadism due to hypothalamic, pituitary, or testicular disease have unequivocally low serum testosterone concentrations along with specific symptoms of androgen deficiency (see [Table 1](#)). To the contrary, men with LOH experience milder decline in serum testosterone levels; additionally, testosterone levels fluctuate in these men, often returning in the normal range during follow-up.¹⁸ The age-related decline in testosterone is multifactorial including reduced generation of gonadotropin-releasing hormone (GnRH) pulses, reduced testicular steroidogenesis, and alterations in the negative feedback system.¹⁹ Some men experience age-related attrition in the number of testicular Leydig cells that is manifested by diminished testosterone secretion (compared with young men) in response to stimulation by human chorionic gonadotropin or pulsatile GnRH.^{20,21} A modest increase in serum luteinizing hormone (LH) levels is also seen. Aging is also associated with atrophy of the seminiferous tubules, reflected by reduced testicular volume and increase in follicle-stimulating hormone (FSH) levels.^{22,23}

In most older men, LH levels are not elevated despite low testosterone levels,^{24,25} highlighting the inability of the hypothalamic-pituitary unit to maintain a robust LH drive to stimulate the testes. This reduction in LH drive is likely due to hypothalamic dysfunction because GnRH stimulation of the pituitary in older men generates a robust LH response that is comparable to that in young men, suggesting preserved function of the gonadotrophs.^{26,27} Indeed, older men display lower pulse amplitude and increased pulse frequency of LH secretion.^{28,29}

Clinical Evaluation of Late-Onset Hypogonadism

Population-level screening for LOH is not recommended because its cost-effectiveness and impact on public health remain unclear.¹¹ Before diagnosing a patient with LOH, organic (pathologic) causes of androgen deficiency, such as testicular injury, pituitary lesions, and infiltrative diseases, should be excluded because they can

occur in men of all ages. Diagnosis of LOH should be avoided during acute illness and use of opioids, glucocorticoids, and antiandrogens should be ascertained. Decreased vitality, depressed mood, impaired memory, and diminished exercise tolerance are nonspecific symptoms and commonly seen in normal aging. Similarly, sexual dysfunction, reduced muscle strength, and loss of bone mass are also seen with conventional aging.³⁰

Unlike men with organic hypogonadism in whom serum testosterone levels are unequivocally (and permanently) suppressed, testosterone levels in LOH are generally marginally low and often fluctuate around the lower limit of the normal range. In EMAS, ~3300 men (aged 40–79 years) were enrolled; they were asked about 32 candidate symptoms of testosterone deficiency and their total testosterone was measured using mass spectrometry (free testosterone level was calculated). Detailed analysis revealed that serum testosterone levels were associated with 3 sexual symptoms (*decreased sexual thoughts, weak morning erections, and erectile dysfunction*). The authors suggested that the diagnosis of LOH can be made in a man with these sexual symptoms and serum total testosterone level less than 230 ng/dL or serum total testosterone level of 230 to 317 ng/dL and free testosterone level less than 63 pg/mL. Using these criteria, LOH diagnosis was diagnosed in only 2.1% of the EMAS participants,⁸ much lower compared with previous estimates.^{3,31}

To make an accurate diagnosis of hypogonadism, the timing of the blood draw and the use of an accurate assay is important. Earlier studies had shown that the circadian rhythm of testosterone secretion is dampened in older men¹⁵; however, recent data suggest that circadian rhythm is maintained in healthy older men.³² Thus, *testosterone levels should be measured in the morning (irrespective of patient's age) using a reliable assay*. Additionally, patients should be asked to come after an *overnight fast* as testosterone levels have been shown to decrease postprandially.³³ The best screening test for the diagnosis of hypogonadism is serum total testosterone.¹¹ Levels less than 264 ng/dL should be confirmed by *repeat measurement* because testosterone levels are inherently variable and repeat levels may end up being normal.¹¹ Once the diagnosis of LOH is ascertained, gonadotropins should be measured. Data from EMAS show that most men will have inappropriately normal gonadotropins. We suggest measurement of serum prolactin, iron studies, and, if indicated, other pituitary hormones, to exclude organic pituitary dysfunction. Hyperprolactinemia, symptoms of mass effects (headaches, peripheral vision disturbances), and panhypopituitarism should be evaluated with sellar imaging. Men with class 3 obesity, in addition to having low total testosterone (due to low SHBG levels), may also have low free testosterone and low-normal gonadotropins, presumably due to hyperestrogenemia and/or hypothalamic inflammation.^{34,35}

Association Between Endogenous Testosterone and Health Outcomes

Epidemiologic studies have suggested associations of *endogenous* testosterone concentrations with several physiological processes. Low testosterone levels have been associated with sexual dysfunction, reduced lean mass, mobility limitation, increased risk of diabetes, depressed mood, unexplained anemia, and osteoporosis.³⁰ However, it is important to appreciate that epidemiologic studies do not establish causality. In this section, we review epidemiologic studies that evaluated association of *endogenous* testosterone levels with various health outcomes.

Sexual function

Sexual function in men is a complex process that includes both central (sexual desire and arousal) and peripheral (penile erection, orgasm, and ejaculation) process.³⁶

Testosterone replacement in young, androgen-deficient men improves sexual activity, libido, and spontaneous erections.^{37–39} Testosterone also contributes to optimal penile rigidity because it regulates nitric oxide synthase activity in the cavernous smooth muscle.⁴⁰ However, population studies show that erectile dysfunction and androgen deficiency are 2 common but independently distributed clinical disorders that often coexist in the same patient; approximately 8% to 10% of middle-aged men with erectile dysfunction also have low testosterone.⁴¹

Body composition and physical function

Sarcopenia is an inevitable consequence of aging; between the ages of 20 and 80 years, skeletal muscle mass declines by 35% to 40% in men, in part due to decreased muscle protein synthesis.⁴² Epidemiologic studies have shown an association of low testosterone levels with loss of muscle mass and mobility limitation.^{43,44} Low testosterone levels have also been associated with reduced muscle performance as well as self-reported physical function.^{45–48} Data from the Framingham Heart Study shows that low testosterone is an independent risk factor for incident mobility limitation.⁴³

Cognition and mood

Human aging is associated with a decline in cognitive function. Multiple domains of cognitive decline including verbal memory, visuospatial ability, and executive function have been associated with the age-related decline in testosterone.³⁰ The association between testosterone levels and depression in older men remains inconsistent.^{49–51}

Skeletal health

Testosterone deficiency is associated with low bone mass.⁵² Androgen deprivation therapy in men with prostate cancer results in bone loss and increased fracture risk.⁵³ Several epidemiologic studies of older men, including the Osteoporotic Fractures in Men Study (MrOS),⁵⁴ Rancho Bernardo Study,⁵⁵ Framingham Heart Study,⁵⁶ and the Olmsted County Study,⁵⁷ have found that testosterone levels are truly associated with bone density, geometry, and quality. In MrOS, the odds of having osteoporosis in men with total testosterone less than 200 ng/dL were 3.7-fold higher than those with normal testosterone levels; free testosterone was an independent predictor of osteoporotic fractures.⁵⁴

Cardiovascular health

Several studies have evaluated the association between testosterone levels and mortality. Some, but not all, studies have found higher all-cause and cardiovascular mortality in men with low *endogenous* testosterone levels compared with those with normal testosterone.⁵⁸ In a meta-analysis of epidemiologic studies of community-dwelling men, low testosterone levels were associated with an increased risk of all-cause and cardiovascular disease (CVD) deaths.⁵⁹ However, the strength of these inferences was limited by considerable heterogeneity in study populations, including differences in age distributions and health status of the study populations.

Metabolic health

Population studies have shown that higher *endogenous* serum testosterone concentrations are associated with a lower risk of metabolic syndrome and diabetes.^{60–62} Indeed, androgen deprivation therapy for prostate cancer is associated with increased risk of metabolic syndrome and diabetes.^{63–66} In a prospective cohort study, men with total testosterone concentration in the lower quartiles had an increased risk of incident diabetes.⁶⁷ Acute interruption of testosterone therapy in hypogonadal men worsens insulin sensitivity⁶⁸ while it improves with testosterone replacement.⁶⁹

Benefits of Testosterone Treatment

In men with *organic* hypogonadism, testosterone therapy is beneficial in maintaining secondary sexual characteristics and improvement in sexual function, energy, mood, and muscle mass. However, data from young men with organic hypogonadism cannot be extrapolated to older men with mild age-related decline in serum testosterone concentrations. The TTriaIs have provided valuable data on the efficacy of testosterone replacement in men with LOH.⁹ This section mainly reviews data from the TTriaIs.

Sexual function

Even though sexual symptoms are consistently associated with low *endogenous* testosterone levels in older men. Previous intervention trials of testosterone therapy have revealed inconsistent results. The TTriaIs investigated the effects of testosterone therapy in symptomatic older men with sexual dysfunction and unequivocally low testosterone levels.⁹ Men were randomized to transdermal testosterone gel or placebo gel treatment for 12 months.⁹ Treatment-induced increase in serum testosterone levels were associated with modest increases in sexual activity, sexual desire, and erectile function.

When men with LOH present with predominant complaints of erectile dysfunction, phosphodiesterase-5 (PDE-5) inhibitors might be the first line of therapy based on their superior efficacy. Previous small trials had shown benefit of adding testosterone therapy in men with erectile dysfunction who did not respond to monotherapy with PDE-5 inhibitors; however, this was not confirmed by a large randomized trial.⁷⁰

Physical function and mobility

In the Physical Function Trial of the TTriaIs, testosterone therapy did not increase the distance walked on the 6-minute walk test compared with placebo.⁹ However, when *all* TTrial participants were included in the analyses (including men who did not have mobility limitation), testosterone therapy resulted in a greater increase in distance walked compared with placebo.⁹ However, the meaningfulness of these findings in the larger cohort remains unclear. Other studies have shown that testosterone administration improves stair climbing power and self-reported physical function.⁷¹

Bone density and quality

The *Bone Trial* of the TTriaIs determined the effects of 1 year of testosterone replacement on volumetric bone mineral density and bone strength using quantitative computed tomography. Men randomized to testosterone, compared with placebo, experienced greater increases in volumetric bone mineral density and estimated bone strength.⁷² The treatment effects on volumetric bone density and bone strength observed in the TTriaIs compare favorably with those reported in trials of bisphosphonates; however, no trial of testosterone replacement has been large enough or long enough to assess fracture outcomes. Therefore, if a patient with LOH is at a high risk for fracture, it is prudent to commence treatment with a drug that has known antifracture efficacy (even if testosterone is started for hypogonadal symptoms).⁷³

Energy and mood

In the *Vitality Trial* of the TTriaIs, testosterone therapy for 12 months did not improve fatigue in older men who were carefully selected for low vitality.⁹ However, men receiving testosterone had small but statistically significant improvement in mood. Other randomized trials have confirmed these findings.^{74,75} However, in a randomized trial of adult hypogonadal men (mean age 55 years) with decreased energy or reduced sex drive, testosterone therapy for 9 months significantly improved energy as

assessed by a new questionnaire known as Hypogonadism Energy Diary.⁷⁶ The reasons for these conflicting findings remain unclear.

Cognition

Earlier trials evaluating the impact of testosterone therapy on cognitive function in either healthy^{77,78} or cognitively impaired older men^{79,80} were small and reported mixed findings. Recently, secondary analysis of the testosterone's effects on atherosclerosis progression in aging men (TEAAM) trial (testosterone therapy for 3 years in cognitively healthy older men) did *not* show improvement in cognitive function.⁸¹ Similar findings were reported by the *Cognitive Function Trial* of the TTrials.⁸² Thus, the current evidence suggests that testosterone therapy does not improve cognitive function and it is prudent not to initiate treatment in older men solely for the purpose of improving cognition.

Anemia

Testosterone stimulates erythropoiesis via multiple mechanisms: (1) increasing iron availability via suppression of hepcidin,^{83–85} (2) stimulation of erythroid progenitor cells, and (3) stimulation of erythropoietin secretion.⁸⁶ Indeed, anemia is a common consequence of androgen deprivation therapy in prostate cancer,⁸⁷ whereas erythrocytosis is a common adverse event associated with testosterone therapy. Population studies also show that lower *endogenous* testosterone levels are associated with an increased risk of anemia.^{88,89}

In the TTrials, testosterone therapy significantly increased hematocrit in anemic men,⁹⁰ and these improvements were associated with changes in walking speed.⁹¹ In the TEAAM trial, testosterone-induced attenuation of the age-related decline in aerobic capacity (VO₂peak) was also associated with increase in hemoglobin levels.⁹² These observations suggest that testosterone-induced increments in hemoglobin contribute, at least partly, to improvements in physical function. However, it should be noted that anemia *alone* is *not* an indication for testosterone therapy.

Glycemic control

Despite the beneficial association of *endogenous* testosterone levels with male metabolic health reported in population studies, randomized trials of testosterone therapy have been conflicting. In the TTrials, testosterone therapy only resulted in modest improvements in fasting insulin and homeostasis model assessment of insulin resistance compared with placebo.⁹³ To the contrary, a 3-year intervention trial of testosterone therapy in older nondiabetic men with low-to-low-normal serum testosterone levels did not improve insulin sensitivity compared with placebo.⁹⁴

In a study of diabetic men, aged 35 to 70 years, testosterone treatment for 40 weeks did not improve insulin sensitivity or HbA1c compared with placebo.⁹⁵ Conversely, in a small trial of diabetic men with hypogonadotropic hypogonadism, testosterone therapy for 24 weeks improved insulin sensitivity.⁶⁹ A recent large randomized trial showed an improvement in metabolic outcomes and a reduced risk of developing incident diabetes after 2 years of testosterone treatment compared with placebo, when combined with lifestyle intervention.⁹⁶ Although these data are encouraging, physical activity, metformin, and GLP-1 agonists might be preferable to testosterone therapy in such patients, especially considering their cardiovascular benefits. Importantly, metabolic dysfunction *alone* is *not* an indication to initiate testosterone therapy.

Risks of Testosterone Therapy

Well-known adverse effects of testosterone therapy include acne, oiliness of the skin, lower extremity edema, gynecomastia, and reversible suppression of spermatogenesis. Elevation in liver enzymes, hepatic neoplasms, and peliosis hepatis, reported with oral 17- α alkylated androgens, are not observed with physiologic testosterone replacement with transdermal or injectable formulations.⁹⁷ Erythrocytosis is the most common adverse effect seen in clinical trials of testosterone replacement, mainly in older men (who have reduced metabolic clearance rate of testosterone) and men on high doses of injectable formulations.¹¹ Erythrocytosis can be avoided by using physiologic doses.

Long-term safety data on the effects of testosterone therapy on the risk of prostate cancer and major adverse cardiovascular events are lacking. In this section, we summarize the current knowledge regarding these 2 concerns.

Cardiovascular safety

Although benefits of testosterone therapy in *select* older men are modest, its potential impact on cardiovascular safety continues to invoke interest.^{58,98–100} Some observational studies^{101–103} and randomized trials have shown higher cardiovascular events in men receiving testosterone.¹⁰⁴ In 2013, the FDA issued an updated testosterone labeling that included warning of *possible increased risk* of stroke and myocardial infarction, and to *limit* the use of testosterone in men with “age-related hypogonadism.”¹⁰⁵ Cardiovascular safety of testosterone therapy garnered more attention with the publication of the Cardiovascular Trial of the TTrials that showed a greater increase in the volume of noncalcified plaque in men treated with testosterone compared with placebo¹⁰⁶ (Fig. 3).

To the contrary, other observational studies have not reported increased cardiovascular risk with testosterone therapy.^{107–109} The TEAAM Trial showed that testosterone therapy for 3 years was not associated with either progression of carotid intima—

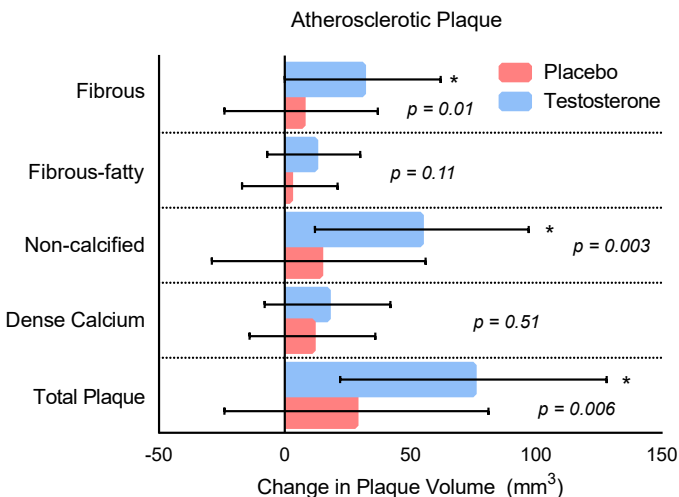


Fig. 3. Changes in coronary plaque volume seen in the Cardiovascular Trial of the TTrials. * indicates $P < 0.05$ for comparison between testosterone and placebo groups. (Adapted from Gagliano-Jucá T, Basaria S. Testosterone replacement therapy and cardiovascular risk. *Nat Rev Cardiol.* 2019 Sep;16(9):555-574.)

media thickness or coronary calcium scores.⁷⁵ In fact, some studies have even suggested that testosterone treatment is associated with reduced cardiovascular risk.^{110–112}

The reason behind these conflicting data is likely the fact that no published randomized trial was adequately powered to assess cardiovascular event rate. The ongoing Testosterone Replacement therapy for Assessment of long-term Vascular Events and efficacy Response in hypogonadal men (TRAVERSE) trial was designed to assess the effects of testosterone treatment on the incidence of major adverse CV events in middle-aged and older men with low testosterone. This trial is nearing completion¹¹³ and has randomized ~5,400 men (aged 45–80 years) with serum total testosterone level less than 300 ng/dL (10.4 nmol/L) who are at high risk of cardiovascular disease (*primary prevention*) or with known history of cardiovascular disease (*secondary prevention*), to receive testosterone gel or placebo gel for ~5 years. Until the results of the TRAVERSE trial become available, risks of cardiovascular disease with testosterone therapy remain unclear, and require an open discussion with patients before testosterone therapy is started.

Prostate safety

Prostate cancer, the most common solid cancer in men, is an androgen-responsive disease,¹¹⁴ and men with advanced disease are treated with androgen deprivation therapy. Histological foci of occult prostate cancer are commonly seen in autopsies with the detection rate increasing with age.¹¹⁵ Thus, there remains a (theoretical) concern that testosterone therapy may exacerbate preexisting occult prostate cancer. This issue is complicated by the fact that no trial of sufficient duration and size has been conducted to determine the risk of prostate cancer with *long-term* testosterone therapy.

Meta-analyses and registry studies have not shown an increased risk of prostate cancer or prostate-related events with testosterone therapy.^{98,116,117} Thus, there seems to be a consensus among experts that *short-term* testosterone treatment in hypogonadal men without preexisting prostate disease does not increase the risk of incident prostate cancer. However, concerns remain regarding stimulation of preexisting occult prostate cancer.

Considering the looming uncertainty regarding the safety of testosterone therapy on the prostate, older men who are candidates for testosterone therapy may consider the evaluation for prostate cancer risk before starting treatment. However, it should be noted that prostate cancer screening and monitoring may increase the risks of unnecessary prostate biopsy (as testosterone therapy increases prostate-specific antigen (PSA) levels in androgen-deficient men) which might result in overdiagnosis of clinically insignificant organ-confined disease. Thus, at this time, risks of prostate disease with testosterone therapy remain unclear and require an open discussion with patients before starting testosterone therapy.

SUMMARY

Despite the increase in prescription rates of testosterone in middle-aged and older men, the syndromic prevalence of LOH is low. Adiposity and other comorbidities play an important role in influencing the trajectory of decline in testosterone levels. Thus, testosterone is likely a *biomarker of health*. Trials of testosterone therapy in older men have shown modest benefits, whereas long-term prostate and cardiovascular safety remains unclear.

Considering the existing evidence, the expert panel of the Endocrine Society recommended against routine testosterone therapy for all men aged 65 years or older with

low testosterone. Instead, the panel suggested that testosterone therapy be offered to *select* older men with unequivocally low morning testosterone and specific symptoms of androgen deficiency on an individualized basis, only after discussion of potential risks and benefits.¹¹ The TRAVERSE trial will likely provide insights regarding long-term risks of testosterone therapy.

CLINICS CARE POINTS

- Syndromic prevalence of LOH is low (~2%).
- Adiposity and comorbidities influence the trajectory of decline in testosterone levels.
- Efficacy of testosterone therapy in older men is modest with improvements in sexual function, anemia (not a primary indication for therapy) and bone mass (no fracture data available).
- Long-term risks of testosterone therapy on the prostate and cardiovascular system remain unknown.

CONFLICT OF INTEREST

The authors report no conflict of interest. This work was supported in part by the Mid-Career Mentoring Award K24AG070078 to Dr SB.

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