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Is Testosterone Replacement Therapy in Older Men Effective and Safe?

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Abstract

The number of older adults over 65 years of age is expected to increase to almost 100 million in the US by 2050, more than double the current figure of 46 million. Advanced age is associated with increased frailty among older Americans and often leads to increased disability, hospitalization, institutionalization, and, eventually, mortality. In search of means to improve age-related risks for adverse health outcomes, the question of restoring diminishing sex hormones has gathered much interest and has led to the practice of sex hormone replacement therapies in older men. Recent data suggest that androgen prescription rates in the US for men older than 60 years of age quadrupled from the years 2001 to 2011. While prescription sales of testosterone have increased from $150 million in 2000 to $1.8 billion in 2011, a significant portion of men prescribed testosterone replacement therapy did not meet the laboratory criteria for hypogonadism. While some clinical trials reported an association between testosterone insufficiency in older men and increased risk of death, the exact effects and consequences of testosterone replacement therapy, specifically in older men, remain unclear. This review is aimed at discussing the possible benefits and complications of testosterone replacement therapy in older men over 60 years of age.

1 Introduction

Recent advancements in medicine and technology have allowed for an impressive lifespan extension in industrialized nations [1-3]. In the US alone, the number of older adults over 65 years of age is expected to double from 46 million to nearly 100 million by 2050. In fact, by 2030, older adults are projected to outnumber children for the first time in the US history [4].

The fact that libido and sexual performance may decline with advancing age is widely accepted, and has been so at least since the Golden Age of Athens, about 25 centuries ago; Aristophanes' comedies include several pertinent remarks [5]. In addition, the Bible also contains multiple reports of patriarchs fathering children in very old age.

Sexual functioning has been associated with the gonads since antiquity. In *Historia Animalium,* Aristotle observed, "If castration occurred in roosters after their growth was

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completed … the comb would turn yellow, they would cease to crow and no longer desire sexual intercourse".

For centuries, people believed that gonadal failure was responsible for many of the symptoms of old age. In 1889, renowned French physiologist Brown-Sequard prepared a dog testicle extract and injected it into himself. He reported that these injections improved his vigor and capacity for work. However, it is now clear that these aqueous extracts contained minimal amounts of testosterone, a steroid that is not soluble in water. Today, although it is clear that the aging process cannot be attributed to a simple lack of sex steroids, the general public perceives impotence and/or reduced libido in men as a definite sign of aging, regardless of whether the problem is due to hormonal changes.

Furthermore, advanced age is associated with increased frailty among older Americans and often leads to increased disability, hospitalization, institutionalization, and, eventually, mortality [6]. In search of means to improve age-related risks for adverse health outcomes, the question of restoring diminishing sex hormones has garnered much interest and has led to the practice of sex hormone replacement therapies in older adults. In previous years, the prevalence in women older than 65 years of age lead to a significant body of research being conducted, with large-scale studies reporting the benefits and health risk factors related to estrogen replacement therapy. According to the latest data from the US Census Bureau, the ratio of men to women over 65 years of age has changed dramatically over the past 2 decades, from 67 older men per 100 older women in 1990, to current rates of 79 older men per 100 older women, and projected to be 82 older men per 100 older women by 2030 [4]. As early epidemiological studies suggested that declining function in older men is related to levels of bioavailable testosterone [7, 8], an intervention to improve the health span of older men was proposed in the form of testosterone replacement therapy.

Testosterone is a vital sex hormone, circulating levels of which are regulated by the hypothalamic-pituitary-gonadal axis. Every 90 min, the hypothalamic pulse generator secretes gonadotropin-releasing hormone into the hypothalamic-pituitary system, with subsequent release of luteinizing hormone into systemic circulation. Finally, luteinizing hormone reaches the testes and stimulates the production of testosterone from Leydig cells [9]. Physiologically, only approximately 2% of total testosterone circulates in the free form, while the remaining 98% is tightly bound to sex hormone binding globulin or albumin [10]; however, albumin binding is not very strong and most of that fraction of testosterone is eventually bioavailable, which can then be measured and reported as the bioavailable testosterone fraction.

Serum testosterone levels display both circadian and ultradian rhythms. While circadian rhythm of serum testosterone peaks during the early morning hours, the actual serum levels fluctuate approximately every 90 min, representing a burst-like secretory pattern [9]. In young, healthy men (20–30 years of age), the normal levels of serum testosterone (400–700 ng/dL) are controlled by the feedforward and feedback components of the hypothalamic-pituitary-gonadal axis, and are maintained within the normal range of 300–800 ng/dL. Serum testosterone levels decline gradually with age at an approximate rate of 1% per year after the third decade of life. Since the biological effects of testosterone are mainly related

to free or weakly bound testosterone, the decline of bioavailable testosterone with age is even more drastic since aging is associated with an increase in sex hormone binding globulin [11]. In some older men, serum concentrations of testosterone decline to such an extent as to be classified as hypogonadal. The mechanisms responsible for an age-dependent decrease in serum testosterone levels include age-related increased sensitivity of the hypothalamic-pituitary system to the negative feedback mechanism of testosterone [12]. The age-related decrease in serum testosterone levels also correlates with the decline in Leydig cell numbers in testes [13] and decreased Leydig cell secretion of testosterone in response to stimulation with human chorionic gonadotropin [14].

In the US, the trend for androgen prescribing in men over 60 years of age has dramatically increased, from 1.32% of men receiving testosterone in 2001 to 3.75% of men in 2011 [15]. A recent market analysis reports that prescription sales of testosterone have increased from US$150 million in 2000 to US$1.8 billion in 2011 worldwide, with US and Canada driving the growth in sales numbers [16]. Interestingly, a significant portion of men prescribed testosterone replacement therapy did not meet laboratory criteria for hypogonadism, according to a market analysis [16]. Meanwhile, the prevalence of hypogonadism, defined by early morning serum testosterone levels below 280 ng/dL, in older men over 65 years of age is approximately 16–18% [17, 18].

The increase in interest towards testosterone replacement therapy has further stimulated pharmaceutical industry for the development of a variety of testosterone formulations; therefore, it is expected that testosterone sales will continue to grow in the nearest future. In addition, recent results from a population-based study of 794 men aged 50–91 years reported that testosterone insufficiency in older men is associated with an increased risk of death over the following 20 years, independent of multiple risk factors and several pre-existing health conditions [19]. However, the effect and consequences of long-term testosterone replacement therapy, specifically in older men, remain significantly understudied.

In this review, we aimed to discuss the possible benefits and complications of testosterone replacement therapy in healthy, older men over 60 years of age without chronic diseases. Clinical trials discussed in this review were selected based on a duration of testosterone replacement therapy of no less than 6 months, with several follow-up time points, and which reported statistically significant increases in testosterone levels upon the initiation of treatment and throughout the timeframe of the clinical trial.

2 Testosterone Effects on Lean Muscle Mass

Testosterone has been reported to produce a substantial anabolic effect in young and middle-aged men with hypogonadism [20]. However, very limited data are available on the effects of prolonged testosterone replacement therapy on lean body mass in healthy older adults.

In the study by Srinivas-Shankar et al., 138 older community-dwelling intermediate-frail and frail men over 65 years of age received testosterone treatment in the form of a transdermal patch at a dose of 50 mg/day for 6 months [21]. Although the study screened subjects and excluded those with major cardiovascular and other risk factors, the health of the recruited

subjects was not described. The authors reported a significant increase in lean body mass in the treated group and suggested that testosterone therapy may prevent loss of muscle strength [21]. These findings were in line with an earlier 3-year study by Snyder and colleagues that demonstrated a significant increase in lean mass and a decrease in fat mass in 54 men with baseline levels of serum testosterone below 350 ng/dL treated with 144 mg/day testosterone delivered in the form of a scrotal patch [22]. Subjects included in this study were screened for medications that affected bone and prostate cancer, but not cardiovascular risks, however the general health of study participants was not reported [22]. Later, another 3-year study in healthy older men with total testosterone levels below 350 ng/dL and no cardiovascular risk factors also showed that 46 subjects treated with injectable testosterone enathane at a dose of 200 mg every 2 weeks presented a significant increase in lean body mass and decrease in fat mass [23]. Finally, the latest 3-year clinical trial by Storer and colleagues also confirmed the effects of testosterone replacement therapy, using 7.5 g of 1% testosterone gel, on lean body mass in 135 community-dwelling older men over 60 years of age with baseline total testosterone levels of 100–400 ng/dL and free testosterone of <50 pg/mL [24]. In this study, subjects with moderate to severe cardiovascular disease (history of heart failure and myocardial infarction) were excluded, however subjects with several cardiovascular risk factors were enrolled, including those with arterial hypertension to 160 mmHg systolic blood pressure (42% of subjects), diabetes (15% of subjects), and mild to moderate cardiovascular disease (15% of the studied population).

3 Testosterone Effects on Muscle Strength and Function

Following very limited data on the effects of testosterone replacement therapy in older adults, substantial discrepancy in the effects of testosterone on physical function and muscle strength has also been observed.

For example. in the same study by Srinivas-Shankar et al., where muscle mass was increased by testosterone treatment, the authors failed to demonstrate an improvement in muscle strength and physical function measured using the 6-min walking test, Tinetti Balance and Tinetti Gait Tests, and others [21]. Another study that used a similar 6-month testosterone replacement therapy protocol in 165 subjects over 65 years of age with serum testosterone levels 100–350 ng/dL (free testosterone below 50 pg/mL) showed that testosterone therapy significantly improved leg and chest muscle strength and stair-climbing power. However, walking speed, a key determinant of mobility, did not change significantly between the groups [25]. In addition, although subjects with cardiovascular risks such as unstable angina and uncontrolled hypertension, as well as diseases such as heart failure or myocardial infarction, were excluded, the study did not provide information on the health of the enrolled subjects. The latest 3-year Testosterone’s Effects on Atherosclerosis Progression in Aging (TEAAM) clinical trial has reported that testosterone replacement therapy in the form of 1% testosterone gel in older men over 65 years of age with low to low-normal 100–350 ng/dL serum levels of total testosterone significantly improved both loaded and unloaded stair-climbing performance. Interestingly, gait speed remained unchanged in these older adults (*publication pending*).

The beneficial effects of testosterone therapy have also been found in longer-duration studies with 12-month replacement therapy. Results from testosterone trials (TTrials) that included 193 and 197 older men with serum testosterone levels below 275 ng/dL who received testosterone treatment in the form of 1% testosterone gel daily or placebo, respectively, for a duration of 12 months reported modest improvement in the 6-min walking test. Although subjects reported a consistent improvement in walking ability, it is important to emphasize that results were based on self-reported data and therefore require additional testing [26]. In addition, although subjects with severe cardiovascular disease such as heart failure and myocardial infarction were excluded, no data on the health of the enrolled subjects were provided.

Finally, while earlier 3-year studies on the effects of testosterone in older men with low to low-normal levels of testosterone failed to show an increase in muscle strength measured by the strength of knee extension and flexion [22], more recent 3-year trials reported a significant increase in muscle performance. In particular, Storer et al. showed that 135 subjects with low to low-normal testosterone levels significantly outperformed those in the placebo-treated group in unloaded and loaded stair-climbing power tests, as well as in muscle strength measured during chest-press and leg power tests [24]. Page and colleagues also reported that testosterone treatment in 46 older men significantly improved performance in the timed functional test, and increased hand-grip strength [23].

4 Testosterone Effects on Bone

The effects of testosterone replacement therapy on bone mineral density have also been controversial. For example, the earlier study by Snyder et al. evaluated the effect of testosterone treatment, in the form of a patch, in 54 older men with total serum testosterone levels below 350 ng/dL over a period of 3 years. Although the authors did not see the effect of mineral bone density measured in the lumbar spine in the treated group, they have reported that the effect of treatment was dependent on the baseline serum levels of testosterone, with the greatest effect observed in those subjects with low baseline serum testosterone levels [22].

On the contrary, the later 3-year study by Amory et al. in older men over 65 years of age with total testosterone levels below 350 ng/dL showed that 50 men treated with testosterone had significantly increased bone mineral density at the lumbar spine [27]. In this study, subjects with medications affecting bone, as well as those with severe illness, were excluded, and no information on the health status of the enrolled population was provided. Furthermore, the latest study by Snyder et al., reported that 12-months' treatment with 5 g/day of 1% testosterone gel in 110 men over 65 years of age and serum testosterone levels below 275 ng/dL resulted in a significant increase in volumetric bone mineral density, measured using dual energy X-Ray absorptiometry at baseline and 12 months [28]. In that study, subjects with medications known to affect bone, except for calcium and over-the-counter vitamin D, were excluded. The health report of study participants included only a diagnosis of diabetes (approximately 40% in the treatment group) and prior habits of smoking and alcohol consumption. No other information on the health of the study participants was provided.

5 Testosterone Effects on Sexual Function and Mood

Testosterone as a sex hormone plays an important role in sexual function, and 1-year replacement therapy in hypogonadal young men with a mean age of 55 years has been shown to significantly improve sex drive and energy [29]. While Brock et al. did not exclude any subjects with cardiovascular pathology, no data on the health of subjects were provided [29]. Similarly, 1-year replacement therapy with 5 g/day of 1% testosterone gel in 234 older men with low libido and average serum testosterone levels below 275 ng/dL has also significantly improved 10 of 12 measures of sexual activity assessed using the Psychosexual Daily Questionnaire [30, 31]. The population selection in this trial was solely based on a reported low libido and a score of <20 on the Derogatis Interview for Sexual Function–Sexual Desire Domain. Furthermore, the exclusion criteria consisted of high cardiovascular risks, such as recent myocardial infarction, stroke, unstable angina, and heart failure. Interestingly, subjects with arterial hypertension to 160 mmHg systolic blood pressure were included in this study. Additionally, the 3-year study that enrolled 156 subjects, with serum testosterone levels of 100–400 ng/dL, for replacement therapy failed to confirm the beneficial effect of testosterone on overall sexual function or health-related quality of life [32]. In that study, over 45% of participants had hypertension, 14% had diabetes, 40% were obese, 80% suffered from hyperlipidemia, and 24% of subjects had prior coronary artery disease.

6 Testosterone Effects on Mood and Cognitive Function

While there is a limited body of knowledge on the effects of testosterone on mood in human subjects, several limited studies have suggested that low levels of testosterone in young men may be associated with depressive disorders. Considering that the prevalence of major depressive disorders increases with age, many practitioners assumed the connection between low testosterone and depressive syndromes; however, multiple cross-sectional and longitudinal clinical studies failed to prove the existence of such a connection [33]. In line with other studies, the 1-year treatment of older men with low testosterone levels has also failed to demonstrate a definitive effect of testosterone on mood and showed only modest benefit with respect to mood and depressive symptoms [31].

Similarly, a connection between age-related cognitive decline and testosterone levels has also been proposed. Epidemiological studies, including the Baltimore Longitudinal Study on Aging, demonstrated that higher free testosterone levels are associated with better performance in some, but not all, cognitive domains [34]. Furthermore, studies of chemical castration in men with prostate cancer have also suggested that low serum testosterone may be associated with cognitive decline [35]. In addition, low levels of testosterone have been associated with mild cognitive impairment and Alzheimer’s disease in older adults [36].

Earlier limited clinical trials with testosterone treatment in older men yielded controversial results, with one trial reporting that biweekly injections of testosterone for 12 months in 17 men over 50 years of age had no effect on memory across several domains of cognition [37], while another study reported an improvement in two of five cognitive tests in 24 men treated for 12 months [38]. Neither study reported the health status of subjects, except for

exclusion criteria that consisted of heart failure and low performance on cognitive tests such as the Mini-Mental State Examination. However, a recent 3-year clinical trial in older men over 60 years of age with low to normal-low testosterone levels reported no improvement in 155 subjects who were prescribed replacement therapy [39]. In this study, subjects with normal cognitive performance, as well as those without heart failure, history of myocardial infarction, and untreated arterial hypertension, were enrolled.

7 Testosterone Effects on the Cardiovascular System

Earlier studies have suggested a potential beneficial effect of testosterone replacement therapy in older men, on the cardiovascular system. Specifically, Page et al. showed that 3-year testosterone therapy in 46 older men was accompanied with a significant decrease in total cholesterol, low-density lipoprotein, without affecting high-density lipoprotein [23]. Furthermore, several clinical trials and meta-analyses have not demonstrated any significant adverse cardiovascular outcomes in older men treated with testosterone [40-42]. However, most of the studies were small, included patients of different ages, and were of different treatment duration. Among other potentially beneficial effects of testosterone replacement therapy on cardiac function, the findings from two randomized clinical trials reported that testosterone replacement attenuated the age-related increase in QTc interval during electrocardiography [43]. The study included a number of subjects with hypertension, diabetes, obesity, hyperlipidemia, and a history of coronary artery disease. Therefore, the clinical implications of these findings require further investigation.

When evaluating the effects of testosterone on the progression of atherosclerosis, a 3-year clinical trial in older men with serum testosterone levels at recruitment of 100–400 ng/dL showed that testosterone treatment had no effect on the rates of change in common carotid artery intima-media thickness, or coronary calcium [32]. Although this study has not demonstrated any adverse cardiovascular events, it was not sufficiently powered to evaluate the cardiovascular safety of testosterone use in older men.

In contrast, a clinical trial that included older men over 65 years of age with serum testosterone levels below 350 ng/dL and mobility limitations was stopped early due to the increased incidence of cardiovascular events in the treated group. Of 106 subjects who were enrolled into the testosterone arm of the study, 23 treated subjects reported cardiovascular-related adverse events [44]. In that study, both control and treatment groups had a high prevalence of hypertension, obesity, diabetes, hyperlipidemia, and pre-existing cardiovascular disease. A greater proportion of men in the testosterone group than in the placebo group reported that they had received a diagnosis of hyperlipidemia or were taking a statin. Furthermore, Finkle et al. reported an increased risk of non-fatal myocardial infarction in older men during the first 90 days following the initial prescription of testosterone, with a subsequent decline in baseline risk in the 91–180 days after treatment, using a large healthcare database [45]. In this cohort study, only subjects with a history of myocardial infarction were excluded and no data on the health status of subjects evaluated were provided. In another retrospective national cohort study, testosterone replacement also increased the risk of death, myocardial infarction, and stroke in older men with a pre-existing cardiac condition and those who underwent cardiac angiography [46]. In that

study, no health information of study participants was presented, except for those who were excluded from analysis due to a prior myocardial infarction event or cancer.

Overall, due to a current lack of long-term safety studies on testosterone therapy, testosterone replacement therapy in older men should be used with caution.

8 Testosterone Effects on Prostate Tissue

Current knowledge dictates that the presence of testosterone is crucial for the development of prostatic hyperplasia, and chemical or surgical castration has been reported to result in reduced prostate volume [47]. Multiple earlier clinical studies failed to show complications associated with benign prostatic hyperplasia during testosterone supplementation in older men with low to normal-low baseline testosterone levels [37, 38, 48, 49]. However, a recent large clinical trial was still not powered enough to determine whether testosterone replacement therapy may impose a risk of developing prostate cancer in older men. Testosterone treatment over a 3-year period significantly increased the serum levels of prostate-specific antigen in older men with low to normal-low pretreatment levels of serum testosterone [32], but no excess cases of prostate cancer were detected. Inconsistency in the clinical trial literature, which is limited by a small number of publications and a sample size not powered enough to evaluate the risks of prostate cancer in older men with testosterone replacement therapy, indicate only very large clinical trials involving several thousand patient-years of treatment can provide an answer.

9 Testosterone Effects on Polycythemia

Testosterone is known to induce erythropoiesis. It is reported that during puberty, hemoglobin levels increase by approximately 20%, in parallel with changes in testosterone levels, and hemoglobin levels in adult men are higher than in women. In older men, testosterone levels are also associated with mild anemia [50]. Recent clinical trials report that testosterone replacement therapy in older men with low to normal-low baseline testosterone levels result in increased hemoglobin and hematocrit levels [32]

Although an increase in hematocrit and hemoglobin levels is generally considered beneficial in patients with anemia, elevation above normal levels may result in undesired consequences, such as increased blood viscosity, which, in the elderly, may impose significant risks for the development of coronary and cerebrovascular events. Therefore, hematocrit and hemoglobin levels should be closely monitored in older men receiving testosterone replacement therapy.

10 Conclusions

Increasing rates of testosterone prescriptions in men over the past decade have warranted evaluation of the multi-organ effects of testosterone replacement therapy. While the effects of testosterone in younger men have been well-described, the effects of testosterone replacement therapy in older men over 60 years of age remain significantly understudied. Current knowledge obtained from recent clinical trials in older men over the age of 60 years, and with a duration of therapy no shorter than 6 months, is reported in Table 1.

To date, clinical trials reported some benefits of testosterone replacement therapy in older men, including improved bone density and bone strength, improved body composition, such as an increase in lean body mass and a decrease in fat mass, as well as a modest but significant improvement in physical function. Testosterone treatment has also been reported to improve hemoglobin concentrations, which also seemed to improve the anemia irrespective of etiology. Testosterone treatment has also improved sexual function and mood in older men. In contrast to some benefits in mood, testosterone treatment had little to no effects on cognition in older men without age-associated cognitive impairment.

It is important to mention that the majority of clinical trials of testosterone replacement therapy in older men that reported beneficial effects did not provide data on cardiovascular risk factors such as blood pressure, coagulation factors, and inflammatory markers. Therefore, the effect of testosterone treatment in these trials cannot be clearly described. Meanwhile, comorbidities such as obesity and diabetes mellitus were relatively high in testosterone clinical trials. Considering that previous studies suggested an association between metabolic syndrome and testosterone levels, obesity and diabetes may contribute to the androgen deficiency-like symptoms and reduced testosterone concentrations in older men, and therefore should be carefully considered as a target prior to administration of testosterone [51-53].

One of the TTrials performed in frail older men, as well as those with limited mobility and pre-existing cardiovascular disease, have been reported to significantly increase the risks for the development of cardiovascular events that led to premature termination of the clinical trial [44]. Therefore, it appears that testosterone effects in older men may be heavily dependent on pre-existing comorbidities and risk factors.

Overall, it appears that testosterone treatment has a variety of effects, with modest improvements in a relatively healthy population with low levels of serum testosterone, and with some potentially adverse effects in the population of older men with pre-existing cardiovascular diseases. Almost all large trials involved only 1 year or less of actual replacement; the larger, longer trials also raise the possibility of gradually declining compliance and/or effectiveness of treatment. The need for a large-scale clinical trial is further underscored by the results from another large-scale clinical trial on the effects of hormone replacement therapy in women that has revealed the misleading results from other earlier conducted epidemiological studies [54]. The study suggested that hormone replacement therapy was associated with increased morbidity and a greater likelihood of cardiovascular events, but not increased mortality, in opposition to what was suggested with earlier smaller clinical trials.

We believe that, at the present time, the decision to treat or not should be highly individualized and the patient should have a good understanding of the potential benefits and risks as best as can be assessed in their particular case. In general, it is good practice, at the present time, to avoid treating patients with significant cardiovascular and cerebrovascular disease history, hypercoagulable states, prostate cancer, and overtly symptomatic benign prostatic hypertrophy.

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References

1. Bergman H, et al. Understanding and meeting the needs of the older population: a global challenge. Can Geriatr J. 2013;16(2):61–5. [PubMed: 23737931]
2. Sierra F, Kohanski R. Geroscience and the trans-NIH Geroscience Interest Group, GSIG. Geroscience. 2017;39(1):1–5. [PubMed: 28299635]
3. Yabluchanskiy A, et al. Advances and challenges in geroscience research: an update. Physiol Int. 2018;105(4):298–308. [PubMed: 30587027]
4. Colby SL, Ortman JM. Projections of the Size and Composition of the US Population: 2014 to 2060. US Department of Commerce, Economics and Statistics Administration, US Census Bureau; 2015. pp. 1–13.
5. Aristophanes L 1994: Dover edition. Dover ed. New York: Dover; 1994.
6. Clegg A, et al. Frailty in elderly people. Lancet. 2013;381(9868):752–62. [PubMed: 23395245]
7. Perry HM 3rd, et al. Testosterone and leptin in older African-American men: relationship to age, strength, function, and season. Metabolism. 2000;49(8):1085–91. [PubMed: 10954031]
8. Morley JE, Perry HM 3rd. Androgen deficiency in aging men: role of testosterone replacement therapy. J Lab Clin Med. 2000;135(5):370–8. [PubMed: 10811051]
9. Borst SE, Mulligan T. Testosterone replacement therapy for older men. Clin Interv Aging. 2007;2(4):561–6. [PubMed: 18225456]
10. Pardridge WM, Landaw EM. Testosterone transport in brain: primary role of plasma protein-bound hormone. Am J Physiol. 1985;249(5 Pt 1):E534–42. [PubMed: 4061642]
11. Harman SM, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001;86(2):724–31. [PubMed: 11158037]
12. Winters SJ, Sherins RJ, Troen P. The gonadotropin-suppressive activity of androgen is increased in elderly men. Metabolism. 1984;33(11):1052–9. [PubMed: 6436639]
13. Neaves WB, et al. Leydig cell numbers, daily sperm production, and serum gonadotropin levels in aging men. J Clin Endocrinol Metab. 1984;59(4):756–63. [PubMed: 6434579]
14. Harman SM, Tsitouras PD. Reproductive hormones in aging men. I. Measurement of sex steroids, basal luteinizing hormone, and Leydig cell response to human chorionic gonadotropin. J Clin Endocrinol Metab. 1980;51(1):35–40. [PubMed: 7189758]
15. Baillargeon J, et al. Trends in androgen prescribing in the United States, 2001 to 2011. JAMA Intern Med. 2013;173(15):1465–6. [PubMed: 23939517]
16. Bandari J, et al. Marketing and Testosterone Treatment in the USA: a systematic review. Eur Urol Focus. 2017;3(4–5):395–402. [PubMed: 29174614]
17. Surampudi PN, Wang C, Swerdloff R. Hypogonadism in the aging male diagnosis, potential benefits, and risks of testosterone replacement therapy. Int J Endocrinol. 2012;2012:625434. [PubMed: 22505891]
18. Wu FC, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123–35. [PubMed: 20554979]
19. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab. 2008;93(1):68–75. [PubMed: 17911176]

20. Bhasin S, Woodhouse L, Storer TW. Proof of the effect of testosterone on skeletal muscle. J Endocrinol. 2001;170(1):27–38. [PubMed: 11431134]
21. Srinivas-Shankar U, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2010;95(2):639–50. [PubMed: 20061435]
22. Snyder PJ, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab. 1999;84(6):1966–72. [PubMed: 10372695]
23. Page ST, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab. 2005;90(3):1502–10. [PubMed: 15572415]
24. Storer TW, et al. Effects of testosterone supplementation for 3 years on muscle performance and physical function in older men. J Clin Endocrinol Metab. 2017;102(2):583–93. [PubMed: 27754805]
25. Travison TG, et al. Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation. J Gerontol A Biol Sci Med Sci. 2011;66(10):1090–9. [PubMed: 21697501]
26. Bhasin S, et al. Effect of testosterone replacement on measures of mobility in older men with mobility limitation and low testosterone concentrations: secondary analyses of the Testosterone Trials. Lancet Diabetes Endocrinol. 2018;6(11):879–90. [PubMed: 30366567]
27. Amory JK, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab. 2004;89(2):503–10. [PubMed: 14764753]
28. Snyder PJ, et al. Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. JAMA Intern Med. 2017;177(4):471–9. [PubMed: 28241231]
29. Brock G, et al. Effect of testosterone solution 2% on testosterone concentration, sex drive and energy in hypogonadal men: results of a placebo controlled study. J Urol. 2016;195(3):699–705. [PubMed: 26498057]
30. Cunningham GR, et al. Testosterone treatment and sexual function in older men with low testosterone levels. J Clin Endocrinol Metab. 2016;101(8):3096–104. [PubMed: 27355400]
31. Snyder PJ, et al. Effects of testosterone treatment in older men. N Engl J Med. 2016;374(7):611–24. [PubMed: 26886521]
32. Basaria S, et al. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: a randomized clinical trial. JAMA. 2015;314(6):570–81. [PubMed: 26262795]
33. Johnson JM, Nachtigall LB, Stern TA. The effect of testosterone levels on mood in men: a review. Psychosomatics. 2013;54(6):509–14. [PubMed: 24016385]
34. Moffat SD, et al. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab. 2002;87(11):5001–7. [PubMed: 12414864]
35. Almeida OP, et al. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. Psychoneuroendocrinology. 2004;29(8):1071–81. [PubMed: 15219659]
36. Almeida OP, Flicker L. Testosterone and dementia: too much ado about too little data. J Br Menopause Soc. 2003;9(3):107–10. [PubMed: 14670195]
37. Sih R, et al. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab. 1997;82(6):1661–7. [PubMed: 9177359]
38. Kenny AM, et al. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci. 2002;57(5):M321–5. [PubMed: 11983727]
39. Huang G, et al. Effects of long-term testosterone administration on cognition in older men with low or low-to-normal testosterone concentrations: a prespecified secondary analysis of data

from the randomised, double-blind, placebo-controlled TEAAM trial. Lancet Diabetes Endocrinol. 2016;4(8):657–65. [PubMed: 27377542]

40. Haddad RM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc. 2007;82(1):29–39. [PubMed: 17285783]
41. Fernandez-Balsells MM, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2010;95(6):2560–75. [PubMed: 20525906]
42. Calof OM, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci. 2005;60(11):1451–7. [PubMed: 16339333]
43. Gagliano-Juca T, et al. Effects of testosterone replacement on electrocardiographic parameters in men: findings from two randomized trials. J Clin Endocrinol Metab. 2017;102(5):1478–85. [PubMed: 27992261]
44. Basaria S, et al. Adverse events associated with testosterone administration. N Engl J Med. 2010;363(2):109–22. [PubMed: 20592293]
45. Finkle WD, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One. 2014;9(1):e85805. [PubMed: 24489673]
46. Vigen R, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013;310(17):1829–36. [PubMed: 24193080]
47. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972;22(4):232–40. [PubMed: 4625049]
48. Pechersky AV, et al. Androgen administration in middle-aged and ageing men: effects of oral testosterone undecanoate on dihydrotestosterone, oestradiol and prostate volume. Int J Androl. 2002;25(2):119–25. [PubMed: 11903662]
49. Dobs AS, et al. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. J Clin Endocrinol Metab. 1999;84(10):3469–78. [PubMed: 10522982]
50. Basaria S, Dobs AS. Risks versus benefits of testosterone therapy in elderly men. Drugs Aging. 1999;15(2):131–42. [PubMed: 10495072]
51. Salam R, Kshetrimayum AS, Keisam R. Testosterone and metabolic syndrome: the link. Indian J Endocrinol Metab. 2012;16(Suppl 1):S12–9. [PubMed: 22701831]
52. Yao QM, et al. Testosterone level and risk of type 2 diabetes in men: a systematic review and meta-analysis. Endocr Connect. 2018;7(1):220–31. [PubMed: 29233816]
53. Kelly DM, Jones TH. Testosterone and obesity. Obes Rev. 2015;16(7):581–606. [PubMed: 25982085]
54. Rossouw JE, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results. From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321–33. [PubMed: 12117397]

Key Points

Testosterone replacement is likely beneficial in healthy older subjects with significant hypogonadism.

Testosterone replacement in individuals with borderline low or low-normal testosterone levels is yet to be proven effective and may not outweigh the risks.

Testosterone should NOT be used in individuals with significant cardiovascular diseases and prostate cancer. Extreme caution may be needed in cases of benign prostatic hyperplasia.

The long-term effectiveness of testosterone treatment (beyond 2 years) is questionable based on the few controlled long-term treatment studies.

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Table 1

Summary of the effect of testosterone replacement therapy in older men

	Sample size	Baseline total testosterone levels (ng/dL)	Replacement therapy duration (months)	Formulation and dose	Effect reported
Lean muscle mass	138	≤350	6 [21]	Transdermal patch 50 mg/day	↑ Lean muscle mass
	54	≤444	36 [22]	60 cm^2 scrotal patch daily	↑ Lean muscle mass ↓ Fat mass
	46	≤350	36 [23]	Injectable testosterone enathane, 200 mg every 2 weeks	↑ Lean muscle mass ↓ Fat mass
	135	100–400	36 [24]	7.5 g of 1% testosterone gel	↑ Lean muscle mass
Muscle strength and function	138	≤350	6 [21]	Transdermal patch 50 mg/day	No improvement in 6-min walking test, Tinetti balance, Tinetti Gait Test
	165	100–350	6 [25]	10 g testosterone gel daily	Improvement in leg and chest muscle strength and stair-climbing power No change in walking speed
	197	≤275	12 [26]	1% testosterone gel daily	Modest improvement in 6-min walking test, consistent improvement in walking ability
	54	≤444	36 [22]	60 cm^2 scrotal patch daily	↑ In muscle strength measured by knee extension and flexion
	135	100–400	36 [24]	7.5 g of 1% testosterone gel	↑ Performance in stair-climbing power tests, chest press and leg power tests
	46	≤350	36 [23]	Injectable testosterone enathane, 200 mg every 2 weeks	↑ Performance in timed functional test and increased hand-grip strength
Bone	54	≤444	36 [22]	60 cm^2 scrotal patch daily	Biggest effect was observed in the group with the lowest baseline testosterone levels
	50	≤350	36 [27]	Injectable testosterone enathane, 200 mg every 2 weeks	↑ Bone mineral density at the lumbar spine
	110	≤275	12 [28]	1% testosterone gel, 5 g/day	↑ In volumetric bone mineral density
Sexual function and mood	234	≤275	12 [30, 31]	1% testosterone gel, 5 g/day	Improvement in 10 of 12 measures of sexual activity measured using the Psychosexual Daily Questionnaire
	156	100–400	36 [32]	7.5 g of 1% testosterone	No effect on overall sexual function
Cognitive function	17	Total testosterone not measured. Subjects with free testosterone < 60 ng/dL were included	12 [37]	Injectable testosterone cypionate 200 mg/every 14–17 days	No effect on memory function
	67	Total testosterone not measured. Subjects with free testosterone < 128 ng/dL were included	12 [38]	Transdermal testosterone 2–2.5 mg patches/day	Two of five cognitive tests showed improvement in 24 treated men

	Sample size	Baseline total testosterone levels (ng/dL)	Replacement therapy duration (months)	Formulation and dose	Effect reported
Cardiovascular system	46	≤350	36 [23]	Injectable testosterone enathane, 200 mg every 2 weeks	↓ Total cholesterol, low-density lipoprotein No effect on high-density lipoprotein
	308	100–400	36 [32, 43]	1% transdermal gel 7.5 g/day	↓ Age-related increase in ECG QTcF duration No effect on the rates of change in common carotid artery intima-media thickness or coronary calcium
	106	≤350	6 [44]	10 g 1% transdermal gel	Stopped early due to increased incidence of cardiovascular events in the treated group
Polycythemia	156	100–100	36 [32]	7.5 g of 1% testosterone	↑ Hemoglobin and hematocrit

ECG electrocardiogram, *QTcF* Fridericia's corrected QT interval, ↑ indicates increased, ↓ indicates decreased