# Revisiting the Role of Testosterone: Are We Missing Something?

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Testosterone is a pleiotropic hormone that plays an important role in the human body. Classically, testosterone was thought to be predominantly involved in androgenesis and physiology in boys and men. Through its conversion to estrogen, testosterone affects bone health, including bone density. Recently, there has been a renewed interest in the systemic role of testosterone in pain, well-being, and cardiovascular function in women and men alike. In this review, we discuss the historic significance of testosterone, its traditionally known physiology, and its molecular and cellular effects. We also discuss evidence for testosterone's lesser known effects, including its role in women's health. We suggest a need to revisit the clinical role of testosterone given its potential for applications to treat mood, cognitive health, and other illnesses, and its anabolic role in bone and muscle; we also suggest consideration of the current debate on risks of its use.

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**KEY WORDS**

Testosterone • Testosterone replacement therapy • Coronary heart disease

In a radical self-experiment, Charles Édouard Brown-Séquard injected himself with a mixture containing liquid extracted from the testicles of dogs or guinea pigs in 1889. The filtered liquid was injected 10 times over 3 weeks, during which the 72-year-old neurologist noted marked physical changes: an increase in his forearm flexor strength, a more forceful urinary stream, the ability to defecate more easily, and a subjective improvement in his cognitive abilities.[1] At the time, Brown-Séquard's claims seemed stunning and implausible, given the lack of a formal study, yet his findings are regarded to have spurned further interest into the chemical substances produced by the testes.[2] Once an unknown component of the so-called "Elixir of Life," testosterone has many well-studied anabolic, metabolic, and developmental properties that affect target organs in men and women. The potential uses of this compound prompted several teams of biochemists to race for isolation of the testicular hormone in the early 20th century.[3] With these advances came a surge of androgen research, along with some of the first papers describing what was then referred to as the "male climacteric" of symptoms, including sleeplessness, nervousness, depression, decreased libido, and impotence. Since then, a great deal of attention has been given to the physiologic effects of decreasing serum testosterone that occurs in aging men.[4-6] More recently, experts have debated the use of testosterone therapy in men who might benefit from replacement of declining hormone levels. The controversy surrounding this issue stems mostly from the dearth of long-term randomized studies that answer the question of whether or not testosterone therapy in normal, healthy, aging men is safe and improves quality of life. Several medical societies have provided their recommendations, but often with conflicting ideas with regard to replacement. With the recent prolongation of life expectancy, especially in men, the question concerning testosterone replacement in older men has become more important.[7-9]

There are greater uncertainties regarding testosterone therapy in women. A clinical practice guideline published by the Endocrine Society in 2006 recommended against the generalized use of testosterone in women, due to the lack of clear indications of use and inadequate long-term safety data. It is more difficult to make broad recommendations regarding testosterone therapy in women because there is no well-defined clinical syndrome caused by androgen deficiency.[10] Also, many of the serum testosterone assays are not particularly sensitive due to lower overall concentrations found in women.[11]

The effects of declining testosterone in the elderly have been an important scientific discussion since the discovery of the hormone. However, its role as a treatment in both men and women remains without a unified, recommended stance.[12] This review discusses the role of testosterone in men and women, highlights the risks and benefits of using testosterone supplements, notes the complexities of measuring testosterone levels, and draws attention to how these challenges may hinder clinicians' ability to safely use testosterone supplementation to improve quality of life in many adults.

## Testosterone Production in Men

To understand why measuring testosterone levels is challenging, it is essential to appreciate androgen production and regulation. Fetal Leydig cells within the developing testis cords secrete the androgens necessary to develop the male reproductive tract. These specialized cells have origins in the mesonephros, and their precursor cells supply both the testes and the adrenal cortex during early embryogenesis.[13] Evidence from genetic studies of fetal testicular tissue has shown that adrenocorticotropic hormone can stimulate fetal Leydig cells to produce steroids, reinforcing the link between adrenal and testicular tissue.[14] Androgens help preserve male reproductive organs through adulthood; prepubertal castration causes regression of the function of these tissues and affects the development of secondary sexual characteristics.[15]

Most testosterone, the major circulating male androgen, is produced in the testes from the substrates cholesterol and acetate. The zona reticularis of the adrenal cortices contributes minimally to the testosterone precursor pool by secreting dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S), the androgenic steroids produced in greatest abundance in humans. DHEA and DHEA-S serve largely as prohormone substrates for the formation of more potent androgens such as testosterone and dihydrotestosterone (DHT) by peripheral conversion, although Brooks[16] demonstrated that they directly affect transcriptional activity through binding androgen receptors. A portion of the total testosterone pool is converted intracellularly via 5α-reductase into DHT, a more potent form of the hormone, within androgen-sensitive tissues such as the prostate, hair follicles, epididymis, and testes. Free testosterone and/or DHT then bind the intracellular androgen receptor, enabling the complex to bind DNA regions and exert androgenic effects.[17] Testosterone can also be

converted to estrogen via aromatase, a member of the cytochrome P450 enzyme family, in target areas including neural tissue, adipose, liver, and bone. In men, estrogen from this reaction is important for maturation of sperm and libido maintenance.[15,18] In women, testosterone and its precursor, androstenedione, are synthesized within the zona fasciculata of the adrenal cortex and ovarian stromal and thecal cells; both organ sites account for 50% of total secretion. The remainder of testosterone production occurs in peripheral tissues such as bone, breast, muscle, and fat.[19]

Androgen synthesis in the gonads of men and women is regulated by secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulating the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. LH stimulates synthesis of testosterone in testicular and ovarian tissue. There is feedback inhibition of GnRH and LH release from the hypothalamus and pituitary, respectively, by testosterone.[20]

It had been known for some time that elderly men have declines in serum testosterone levels, but researchers disputed whether this process naturally occurred or if it was secondary to concurrent comorbidities and related factors.[21] Large-scale prospective trials, such as the Massachusetts Male Aging Study,[22] clearly demonstrated declines in testosterone with increasing age. These findings were validated with several longitudinal studies that showed relatively constant declines in serum testosterone independent of common disease states and risk factors that could confound accurate levels in the blood.[23] More specifically, increasing age was found to bring about gradual decreases in free and total testosterone, with increases in gonadotropins, LH, and FSH. Reductions in free testosterone levels were greater than total testosterone, thereby reducing the greatest biologically active pool.[23]

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In the plasma of healthy men, the testosterone distribution pool is comprised of roughly 2% free testosterone, 38% albumin-bound testosterone, and 60% sex hormone-binding globulin (SHBG)-bound testosterone; the latter two are typically unable to enter the intracellular environment and exert their biochemical effects.[16] For many years, scientists found evidence that non–protein-bound steroid hormones such as cortisol were the only biologically active fraction in human plasma.[24] This concept extended to testosterone as well. In women, high total testosterone states such as hyperthyroidism and pregnancy, associated with higher SHBG levels, did not cause changes in the metabolic clearance rate or blood production rate of testosterone.[25] More recent evidence, however, demonstrated that albumin-bound testosterone is also biologically active given the low affinity of testosterone for the protein.[26] Additionally, it was found that steroid-bound SHBG can generate secondary messengers within target cells by binding to high-affinity membrane receptors. This interaction allowed particular steroids to exert their effects without entering cells.[27] Although the latter notion adds to our understanding of how hormones affect target cells at the molecular level, Vermeulen and colleagues[28] maintain that free testosterone and albumin-bound testosterone continue to be a relatively accurate measure of a patient's clinical and hormonal composition, more so than total hormone levels. Another rationale for the use of total testosterone and free testosterone is that, with current laboratory methods, it is impossible to determine the amount of testosterone generated at the intracellular level via conversion of prohormones and it is impossible to know how steroid-bound SHBG affects transcriptional activity.[28]

Numerous small, cross-sectional and longitudinal studies chronicling the changes in androgen and SHBG levels throughout the pre-, peri-, and postmenopausal transitions show conflicting results.[29] A prospective longitudinal study of 172 Australian women during a 7-year follow-up period fails to demonstrate a significant decrease in total testosterone levels and DHEA-S after menopause, with a mean SHBG level decrease of 43%, only partially explained by lower estrogen concentrations. These decreased binding globulin levels correspond to an increase in free androgens.[30] This evidence suggests that there are other unknown factors at play with regard to sexual functioning and symptoms after onset of menopause. An important question, therefore, arises. How do we accurately and reliably measure the quantities of free and nonspecifically bound fractions of testosterone?

## Measuring Testosterone in Humans

Measuring serum testosterone levels has been an ongoing challenge for years. Testosterone assays play a vital role in workup and diagnosis of many endocrine disorders.

Assays in men are used to diagnose clinical hypogonadism in patients with prostate cancer treated with GnRH analogs,[31] and in children to monitor signs and symptoms of advanced and delayed puberty.[32] Assays in women are used to help diagnose those with hyperandrogenic states, including hirsutism and androgen-secreting ovarian and adrenal tumors, and in infant girls with congenital adrenal hyperplasia due to 21-hydroxylase deficiency.[33]

Testosterone secretion follows a circadian rhythm in young and aging men, with the highest levels generally occurring in the early morning hours[34]; therefore, blood samples for testosterone should ideally be drawn in the morning in order to properly assess patients' androgen status.[35] Another critical point of concern is the considerable variability among laboratories regarding normal values for total and free testosterone in men. This poses a major obstacle for more consistent diagnoses of androgen insufficiency in men and women. Given that women have far lower total and free serum testosterone levels compared with men, difficulties in the sensitivity and accuracy of laboratory assays remain problematic for reliably measuring hormone levels in women.[36]

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Physicians should also be cognizant that varying measurements between laboratories may be consequences of the method used, rather than a reflection of actual changes in testosterone levels.[37] Morales and colleagues[38] discuss the alternatives to serum testosterone measurements and the necessary considerations when interpreting levels. One proposed solution is to measure free rather than serum testosterone, which can be measured by equilibrium dialysis. In this method, free testosterone passes through a membrane into a dialysate solution but protein-bound testosterone does not. Free testosterone measurements avoid the intraindividual variances in bioavailable testosterone and provide better evaluation of hypogonadism. Other studies of testosterone measurement advocated that individual laboratories should have their own reference intervals.

## Effects on Musculoskeletal System

Sex hormones play a crucial role in the maintenance and growth of bone in both men and women. Androgen receptors are expressed in chondrocytes in growth plates, osteoblasts, and osteocytes.[39] Androgens can also cause osteoclastic apoptosis, ultimately decreasing bone resorption.[40] The most important effects of testosterone on bone are through its aromatization to estradiol, which activates bone α and β estrogen receptors, decreasing bone resorption and increasing bone mineral density.[41] Studies have shown that the bone mineral density of vertebral bone in men with idiopathic osteoporosis can be increased with testosterone replacement therapy (TRT).[42] Testosterone has also been shown to have associations with vitamin D, which plays an important role in calcium homeostasis. Nimptsch and associates[43] found a statistically significant correlation between vitamin D and free testosterone levels after adjustment for potential confounders, including age and body mass index. Though causality could not be derived from the study, the initial data warrant further investigation of the relationship between these two bone density modulators.

*Testosterone also has beneficial effects on lean muscle mass and body fat.*

Testosterone also has beneficial effects on lean muscle mass and body fat. Finkelstein and associates[44] analyzed two cohorts to see the effects of testosterone and estradiol on body composition. The first cohort was given goserelin acetate to suppress endogenous androgen production and randomly assigned to receive testosterone gel or placebo for 16 weeks. The second cohort was given an aromatase inhibitor to prevent conversion of testosterone to estradiol, in addition to goserelin acetate and testosterone or placebo gel. The study found that lower levels of androgens contributed to decreases in lean muscle mass, strength, and size in the first group. Decreases in estrogen seen in the second cohort also caused increases in body fat. This study highlights that both testosterone and estradiol levels interact to increase muscle mass and decrease body fat. These data also suggest that aromatizable androgens may provide an advantage over nonaromatizable forms in replacement therapy regimens. Although the study did have limitations in terms of patient profiles and duration, it did provide valuable information on the complex effects of testosterone.[45]

The benefits of increased testosterone levels have been corroborated in other studies. A randomized, double-blind trial by Kvorning and coworkers[46] assigned men aged 60 to 78 years to strength training, testosterone therapy, or placebo for 24 weeks. Testosterone therapy or placebo was added at 12 weeks in the strength-training group. They found that strength training in older men with low-normal testosterone levels improved muscle function but not lean body mass. Combined with TRT, strength training led to increased muscle function and mass. Testosterone therapy alone did not improve function or mass over the study period. This analysis underlines that testosterone is not the sole determinant of muscle function and mass, but that it interacts with factors such as strength training.

It is also important to note that the musculoskeletal benefits do not persist after cessation of TRT. Forbes and coworkers[47] demonstrated that lean body mass decreases within 6 months after discontinuing TRT, although it remains above baseline.

## Potential Alternative Uses

The surge of athletes hoping to benefit from the anabolic effects of testosterone began in the first half of the 20th century. It was not until researchers controlled for exercise routines and protein intake that testosterone was shown to accelerate increases in strength, fat-free mass, and overall muscle mass in exercising men. Young, hypogonadal men and healthy, older men showed modest benefit in fat-free mass and muscle strength. These studies also underscored the possibility of using testosterone in patients with chronic diseases such as human immunodeficiency virus and AIDS wasting syndrome, and cachexia from cancer.[48]

Several studies have explored the use of TRT in new applications. Testosterone supplementation in hormone-deficient men with benign prostatic hypertrophy has also been shown to modulate urinary tract symptoms. Ko and colleagues[49] provided 246 subjects with intramuscular TRT for 1 year. These subjects were found to have unchanged prostate-specific antigen levels after TRT completion, as well as improved storage and voiding symptoms. In addition, several case studies found that TRT is safe following radical prostatectomy for prostate cancer. The rationale for this finding is based on a proposed saturation model, which suggests that prostate cancer growth is highly sensitive to testosterone when serum levels are low. When levels are high in TRT, androgen receptor-binding sites are saturated and the potential growth of prostate cancer is no longer sensitive to testosterone levels. Recommendations also included waiting at least 6 months after successful prostate cancer treatment to initiate TRT.[50]

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Studies analyzing the beneficial effects of supraphysiologic testosterone levels have provided inconsistent results. In subjects undergoing open prostatectomy, preoperative nandrolone administration produced a significant reduction in 24-hour postoperative symptoms but not at 48 hours.[51] A pilot trial of 25 men undergoing knee replacement found that preoperative administration of testosterone provided no benefits in terms of hospital stay length. The treatment group did show statistically significant improvements in the ability to stand, walk, and stair climb 3 days postoperatively.[52] It is important to note that these studies were completed with small sample sizes. Follow-up studies are necessary to adequately evaluate TRT in these circumstances. Other applications of TRT may be in geriatric patients who require rehabilitation. In a study of 65- to 90-year-old men who were admitted to a rehabilitation unit at a Veterans Affairs hospital, functional improvements were seen in patients given 100 mg of weekly intramuscular testosterone compared with placebo.[53] These benefits did not extend to muscle strength during periods of prolonged bed rest. Although testosterone administration (200 mg weekly) has been shown to help maintain protein balance in men during 28-day bed rest, in the absence of daily ambulatory activity there were no positive effects on muscle strength when compared with placebo.[54] From these studies, it appears that many of the advantages of testosterone administration are apparent only in conjunction with physical activity. This information may be used to guide rehabilitation efforts in patients in whom testosterone supplementation is considered.

## Mental and Cognitive Health

Testosterone is also thought to play a role in modulation of both cognitive abilities and mental health. Studies have provided conflicting results in terms of the cognitive benefits of testosterone supplementation in older men. A study

of 237 older men with low-normal testosterone levels randomized to receive either twice daily capsular testosterone or placebo found that the men receiving treatment had increases in lean body mass, decreases in fat, and improved insulin sensitivity. These men did not show significant improvements in cognitive abilities.[55] In a randomized double-blind trial, healthy older men were given 100 mg of weekly testosterone intramuscularly or placebo for 6 weeks. The study found that the treatment group demonstrated significant short-term improvements in spatial and verbal memory.[56] However, this study did not have long-term follow-up, nor did it analyze whether the effects were due to increased testosterone, increased estradiol, or both.

Testosterone has also been shown to play a role in mood and mental health. In a 2-month study of 51 hypogonadal men, subjects were withdrawn from their previous TRT for at least 6 weeks before enrollment and subsequently restarted after enrollment. Every 20 days, the subjects rated mood parameters using the Likert scale, including anger, irritability, nervousness, and energy. The study found that TRT improved positive mood parameters (energy, well-being) and decreased negative mood parameters (anger, irritability). The study also found that the largest increases in mood occurred when subjects were in the low-normal serum testosterone range.[57]

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## Risks and Side Effects

Epidemiologic data from the Framingham Heart Study showed that menopausal and postmenopausal women are at a greater risk of coronary heart disease (CHD) and mortality from CHD compared with premenopausal women and men, thought to be largely due to differences in hormonal status. Decreasing levels of estrogen in the postmenopausal period and/or an overall greater serum concentration of testosterone led to more thrombotic events.[58] Matsuda and associates[59] demonstrated that testosterone augments platelet responsiveness by increasing the density of receptors for the platelet metabolite thromboxane A2. These factors were implicated in thrombotic coronary events. Moreover, there were many reported cases of myocardial infarction and heart disease in men who supplemented with testosterone for hypogonadism or abused high-dose anabolic steroids for personal gain.[60] These experiences and knowledge of the pathophysiology of CHD should make clinicians wary of using TRT. Nevertheless, it is important to keep in mind that testosterone used at physiologically appropriate levels may not be as risky and may benefit patients with cardiovascular disease.

Several studies challenged the preconceived notion that higher concentrations of testosterone may explain more deaths from heart disease in men versus women by showing that men with less testosterone were discovered to have more coronary artery and aortic disease.[61] Remarkably, a randomized, double-blinded study from the United Kingdom found that low-dose transdermal testosterone significantly improved the electrocardiographic signs and pain perception in patients with chronic stable angina, particularly in men with lower concentration of baseline testosterone. The authors noted that estrogen levels in the men treated in the study did not change, thereby disproving the notion that aromatization of testosterone to estrogen explained the phenomenon. In addition, when men with coronary disease were given diethylstilbestrol, they had increased cardiac mortality.[62] Further studies have validated findings regarding anginal pain and have shown that low testosterone levels are associated with increased incidence of metabolic syndrome, insulin resistance, peripheral artery disease, and cerebrovascular disease, even after controlling for other risk factors.[63] One study using data from the Massachusetts Male Aging Study found that higher free testosterone levels were associated with ischemic heart disease mortality, whereas total testosterone and SHBG levels were not associated with mortality.[64] Although our understanding of the effects of testosterone on cardiovascular health continues to evolve, a meta-analysis of studies that reviewed these types of effects cautions that large, randomized trials of men with and without existing cardiovascular disease treated with testosterone need to be performed before clinicians can be more comfortable prescribing it.[65] A retrospective cohort study compared the cardiovascular safety of various forms of TRT administration in men. The study found that injections were associated with an increased risk of cardiovascular events (myocardial infarctions or unstable angina) when compared with gels. Injections were also associated with a higher rate of hospitalizations and death.[66] This study did not prove causality, and highlighted the need for

proper dosing of TRT for adequate symptomatic relief while mitigating adverse event risks.[67] A recent randomized controlled trial found that older men with low or low-normal serum testosterone levels did not report increased quality of life when supplemented with testosterone gel for 3 years when compared with placebo. The same study also concluded that there was no difference in atherosclerosis between the groups, but noted that no conclusions regarding overall cardiovascular safety could be drawn.[68]

The literature on this topic has almost exclusively been focused on men; however, the need for trials in women who generally have naturally low levels of testosterone may provide greater insight into relationship between testosterone and cardiovascular health. Further, it may open the door for treatment of another patient population. Most recently, both the US Food and Drug Administration (FDA) and the European Medicines Agency advocated for restrictions on testosterone therapy usage. The FDA report states that the benefits of testosterone therapy in older patients with idiopathic hypogonadism are equivocal and need further investigation. This recommendation was primarily based on two studies, the first of which was an observational study of older men in the US Veterans Affairs system with low serum testosterone levels. The study found a 30% increased risk of stroke, myocardial infarction, and death in the patients who received testosterone replacement.[69] Another observational study of men taking testosterone therapy found that men both over and under 65 with pre-existing cardiovascular disease had an increased risk of heart attack while on TRT. Men under 65 without history of cardiovascular disease, however, did not have an increased risk of heart attacks on TRT.[70] These results may parallel studies with estrogen replacement in women. According to the Women's Health Initiative study,[71] women starting estrogen replacement therapy in their early 50s have a different predictive cardiac mortality rate than those starting supplements at age 63. The FDA plans to continue to evaluate the risk of stroke, heart attack, or death in these patients and encourages physicians to seriously weigh the risks and benefits of TRT prior to prescription. The Endocrine Society Clinical Guideline Practice recommends that men should be diagnosed with androgen deficiency if they present with consistent symptoms and low serum testosterone levels. Other recommendations included initiation of TRT for symptomatic relief, followed by close monitoring with a standardized plan.[72]

It is important to note that TRT should be administered with caution due to potential side effects outside the cardiovascular system. Studies have shown that oral forms of testosterone may be associated with hepatic tumors and hepatotoxicity.[73] Other effects include gynecomastia, which is caused by conversion of testosterone to estradiol in adipose tissue.[74] Patients may experience infertility from the decreased production of gonadotropins secondary to increased testosterone levels, causing decreased spermatogenesis.[75] Patients with azoospermia usually have a recovery of sperm count and fertility within 18 months of TRT cessation.[76] Another major concern of patients eligible for TRT is the potential aggression associated with testosterone administration, especially with spikes in testosterone from monthly intramuscular injections. Though TRT may help augment mood, as previously discussed, results about changes in anger are inconsistent. A double-blind study of testosterone in eugonadal men found no changes in anger levels with testosterone when compared with placebo.[77] A placebo-controlled study looking at the effects of intramuscular testosterone on aggression in both eugonadal and hypogonadal men found no increases in aggression in the eugonadal group. Increases in hostility and verbal aggression were statistically significant in the hypogonadal group.[78] These potential adverse effects should be considered and disclosed to the patient prior to initiation of TRT, and knowledge of these complications can help physicians titrate doses accordingly.

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## Conclusions

Though testosterone has been traditionally thought to have effects predominantly in men, several studies have documented that its effects are varied and somewhat unpredictable. The benefits of testosterone with regard to mental health, mood, cognition, bone density, and pain control should not be overlooked. It is important to remain cognizant of the risks, primarily cardiovascular, associated with elevated testosterone levels. Based on the current review, we conclude that the clinical role of testosterone should be reassessed, and that physicians should be aware of its potential but uncommon uses. ■

## References


1. Brown-Séquard CE. Note on the effects produced on man by subctaneous injections of a liquid obtained from the testicles of animals. *Lancet*. 1889;134:105-107.
2. Benedum J. The early history of endocrine cell transplantation. *J Mol Med (Berl)*. 1999;77:30-35.
3. Hoberman JM, Yesalis CE. The history of synthetic testosterone. *Sci Am*. 1995;272:76-81.
4. Gray A, Berlin JA, McKinlay JB, Longcope C. An examination of research design effects on the association of testosterone and male aging: results of a meta-analysis. *J Clin Epidemiol*. 1991;44:671-684.
5. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab*. 2008;93:68-75.
6. Harman SM, Metter EJ, Tobin JD, et al; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab*. 2001;86:724-731.
7. Bain J, Brock G, Kuzmarov I; International Consulting Group. Canadian Society for the Study of the Aging Male: response to Health Canada's position paper on testosterone treatment. *J Sex Med*. 2007;4:558-566.
8. Liverman CT, Blazer DG, eds. *Testosterone and Aging: Clinical Research Directions*. Washington, DC.: The National Academies Press; 2004.
9. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2006;91:1995-2010.
10. Wierman ME, Basson R, Davis SR, et al. Androgen therapy in women: an Endocrine Society Clinical Practice guideline. *J Clin Endocrinol Metab*. 2006;91:3697-3710.
11. Matsumoto AM, Bremner WJ. Serum testosterone assays—accuracy matters. *J Clin Endocrinol Metab*. 2004;89:520-524.
12. Swerdloff R, Anawalt BD. Clinical decisions. Testosterone-replacement therapy. *N Engl J Med*. 2014;371:2032-2034.
13. Svechnikov K, Landreh L, Weisser J, et al. Origin, development and regulation of human Leydig cells. *Horm Res Paediatr*. 2010;73:93-101.
14. O'Shaughnessy PJ, Fleming LM, Jackson G, et al. Adrenocorticotropic hormone directly stimulates testosterone production by the fetal and neonatal mouse testis. *Endocrinology*. 2003;144:3279-3284.
15. Mooradian AD, Morley JE, Korenman SG. Biological actions of androgens. *Endocr Rev*. 1987;8:1-28.
16. Brooks RV. Androgens. *Clin Endocrinol Metab*. 1975;4:503-520.
17. Liao S, Fang S. Receptor-proteims for androgens and the mode of action of androgens on gene transcription in ventral prostate. *Vitam Horm*. 1969;27:17-90.
18. Simpson ER, Mahendroo MS, Means GD. Aromatase cytochrome P450, the enzyme responsible for estrogen biosynthesis. *Endocr Rev*. 1994;15:342-355.
19. Burger HG. Androgen production in women. *Fertil Steril*. 2002;77(suppl 4):S3-S5.
20. Schally AV, Arimura A, Kastin AJ, et al. Gonadotropin-releasing hormone: one polypeptide regulates secretion of luteinizing and follicle-stimulating hormones. *Science*. 1971;173:1036-1038.
21. Vermeulen A. Androgen replacement therapy in the aging male—a critical evaluation. *J Clin Endocrinol Metab*. 2001;86:2380-2390.
22. Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. *J Clin Endocrinol Metab*. 1991;73:1016-1025.
23. Morley JE, Kaiser FE, Perry HM 3rd, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism*. 1997;46:410-413.
24. Westphal U, Firschein HE, Pearce EM. Binding of hydrocortisone-4-C14 and progesterone-4-C14 to serum albumin, demonstrated by paper electrophoresis. *Science*. 1955;121:601-602.
25. Saez JM, Forest MG, Morera AM, Bertrand J. Metabolic clearance rate and blood production rate of testosterone and dihydrotestosterone in normal subjects, during pregnancy, and in hyperthyroidism. *J Clin Invest*. 1972;51:1226-1234.
26. Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. *J Clin Endocrinol Metab*. 1981;53:58-68.
27. Rosner W, Hryb DJ, Khan MS, et al. Sex hormone-binding globulin mediates steroid hormone signal transduction at the plasma membrane. *J Steroid Biochem Mol Biol*. 1999;69:481-485.
28. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab*. 1999;84:3666-3672.
29. Rozenberg S, Bosson D, Peretz A, et al. Serum levels of gonadotrophins and steroid hormones in the post-menopause and later life. *Maturitas*. 1988;10:215-224.
30. Burger HG, Dudley EC, Cui J, et al. A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. *J Clin Endocrinol Metab*. 2000;85:2832-2838.
31. Kuhn JM, Billebaud T, Navratil H, et al. Prevention of the transient adverse effects of a gonadotropin-releasing hormone analogue (buserelin) in metastatic prostatic carcinoma by administration of an antiandrogen (nilutamide). *N Engl J Med*. 1989;321:413-418.
32. Müller J, Juul A, Andersson AM, et al. Hormonal changes during GnRH analogue therapy in children with central precocious puberty. *J Pediatr Endocrinol Metab*. 2000;13(suppl 1):739-746.
33. Pavičić Baldani D, Škrgatić L, Bukvić Mokos Z, Trgovčić I. Hyperandrogenemia association with acne and hirsutism severity in Croatian women with polycystic ovary syndrome. *Acta Dermatovenerol Croat*. 2013;21:105-112.
34. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab*. 1983;56:1278-1281.
35. Wheeler MJ, Barnes SC. Measurement of testosterone in the diagnosis of hypogonadism in the ageing male. *Clin Endocrinol (Oxf)*. 2008;69:515-525.
36. Miller KK, Rosner W, Lee H, et al. Measurement of free testosterone in normal women and women with androgen deficiency: comparison of methods. *J Clin Endocrinol Metab*. 2004;89:525-533.
37. Collier CP, Morales A, Clark A, et al. The significance of biological variation in the diagnosis of testosterone deficiency, and consideration of the relevance of total, free and bioavailable testosterone determinations. *J Urol*. 2010;183:2294-2299.
38. Morales A, Collier CP, Clark AF. A critical appraisal of accuracy and cost of laboratory methodologies for the diagnosis of hypogonadism: the role of free testosterone assays. *Can J Urol*. 2012;19:6314-6318.
39. Clarke BL, Khosla S. Androgens and bone. *Steroids*. 2009;74:296-305.
40. Roux S, Orcel P. Bone loss: Factors that regulate osteoclast differentiation - an update. *Arthritis Res*. 2000;2:451-456.
41. Kalb S, Mahan MA, Elhadi AM, et al. Pharmacophysiology of bone and spinal fusion. *Spine J*. 2013;13:1359-1369.


## MAIN POINTS

- Testosterone is a pleiotropic hormone that plays an important role in the human body. Through its conversion to estrogen, testosterone affects bone health, including bone density. Recently, there has been a renewed interest in the systemic role of testosterone in pain, well-being, and cardiovascular function in both women and men.
- Experts have debated the use of testosterone therapy in men who might benefit from replacement of declining hormone levels. The controversy surrounding this issue stems mostly from the dearth of long-term randomized studies that answer the question of whether or not testosterone therapy in normal, healthy, aging men is safe and improves quality of life. With the recent prolongation of life expectancy, especially in men, the question concerning testosterone replacement in older men has become more important.
- There are greater uncertainties regarding testosterone therapy in women. It is more difficult to make broad recommendations regarding testosterone therapy in women because there is no well-defined clinical syndrome caused by androgen deficiency.
- The benefits of testosterone with regard to mental health, mood, cognition, bone density, and pain control should not be overlooked; however, it is important to remain cognizant of the risks, primarily cardiovascular, associated with elevated testosterone levels.

42. Francis RM. The effects of testosterone on osteoporosis in men. *Clin Endocrinol (Oxf)*. 1999;50:411-414.
43. Nimptsch K, Platz EA, Willett WC, Giovannucci E. Association between plasma 25-OH vitamin D and testosterone levels in men. *Clin Endocrinol (Oxf)*. 2012;77:106-112.
44. Finkelstein JS, Lee H, Burnett-Bowie SA, et al. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med*. 2013;369:1011-1022.
45. Handelsman DJ. Mechanisms of action of testosterone—unraveling a Gordian knot. *N Engl J Med*. 2013;369:1058-1059.
46. Kvorning T, Christensen LL, Madsen K, et al. Mechanical muscle function and lean body mass during supervised strength training and testosterone therapy in aging men with low-normal testosterone levels. *J Am Geriatr Soc*. 2013;61:957-962.
47. Forbes GB, Porta CR, Herr BE, Griggs RC. Sequence of changes in body composition induced by testosterone and reversal of changes after drug is stopped. *JAMA*. 1992;267:397-399.
48. Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med*. 1996;335:1-7.
49. Ko YH, Moon du G, Moon KH. Testosterone replacement alone for testosterone deficiency syndrome improves moderate lower urinary tract symptoms: one year follow-up. *World J Mens Health*. 2013;31:47-52.
50. Coward RM, Carson CC III. Testosterone replacement therapy after prostate cancer. *Trends in Urology & Men's Health*. 2011;2:22-26.
51. Pourmand G, Salem S, Karami A, et al. Anabolic-androgenic steroid effects on early morbid symptoms after open prostatectomy: a pilot study. *Aging Male*. 2008;11:123-127.
52. Amory JK, Chansky HA, Chansky KL, et al. Preoperative supraphysiological testosterone in older men undergoing knee replacement surgery. *J Am Geriatr Soc*. 2002;50:1698-1701.
53. Bakhshi V, Elliott M, Gentili A, et al. Testosterone improves rehabilitation outcomes in ill older men. *J Am Geriatr Soc*. 2000;48:550-553.
54. Zachwieja JJ, Smith SR, Lovejoy JC, et al. Testosterone administration preserves protein balance but not muscle strength during 28 days of bed rest. *J Clin Endocrinol Metab*. 1999;84:207-212.
55. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. *JAMA*. 2008;299:39-52.
56. Cherrier MM, Asthana S, Plymate S, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology*. 2001;57:80-88.
57. Wang C, Alexander G, Berman N, et al. Testosterone replacement therapy improves mood in hypogonadal men—a clinical research center study. *J Clin Endocrinol Metab*. 1996;81:3578-3583.
58. Gordon T, Kannel WB, Hjortland MC, McNamara PM. Menopause and coronary heart disease. The Framingham Study. *Ann Intern Med*. 1978;89:157-161.
59. Matsuda K, Ruff A, Morinelli TA, et al. Testosterone increases thromboxane A2 receptor density and responsiveness in rat aortas and platelets. *Am J Physiol*. 1994;267(3 Pt 2):H887-H893.
60. Fineschi V, Baroldi G, Monciotti F, et al. Anabolic steroid abuse and cardiac sudden death: a pathologic study. *Arch Pathol Lab Med*. 2001;125:253-255.
61. Mäkinen J, Järvisalo MJ, Pöllänen P, et al. Increased carotid atherosclerosis in andropausal middle-aged men. *J Am Coll Cardiol*. 2005;45:1603-1608.
62. English KM, Steeds RP, Jones TH, et al. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. *Circulation*. 2000;102:1906-1911.
63. Malkin CJ, Pugh PJ, Morris PD, et al. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. *Heart*. 2004;90:871-876.
64. Araujo AB, Kupelian V, Page ST, et al. Sex steroids and all-cause and cause-specific mortality in men. *Arch Intern Med*. 2007;167:1252-1260.
65. Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc*. 2007;82:29-39.
66. Layton JB, Stürmer T, Brookhart MA. Comparative safety of testosterone dosage forms. *JAMA Intern Med*. 2015;175:1875-1876.
67. Wierman ME. Risks of different testosterone preparations: too much, too little, just right. *JAMA Intern Med*. 2015;175:1197-1198.
68. Basaria S, Harman SM, Travison TG, 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;314:570-581.
69. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013;310:1829-1836.
70. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*. 2014;9:e85805.
71. Yang XP, Reckelhoff JF. Estrogen, hormonal replacement therapy and cardiovascular disease. *Curr Opin Nephrol Hypertens*. 2011;20:133-138.
72. Bhasin S, Cunningham GR, Hayes FJ, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95:2536-2559.
73. Westaby D, Ogle SJ, Paradinas FJ, et al. Liver damage from long-term methyltestosterone. *Lancet*. 1977;2:262-263.
74. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. *Ther Clin Risk Manag*. 2009;5:427-448.
75. Bagatell CJ, Bremner WJ, Androgens in men—uses and abuses. *N Engl J Med*. 1996;334:707-714.
76. World Health Organization Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. *Fertil Steril*. 1996;65:821-829.
77. Tricker R, Casaburi R, Storer TW, et al. The effects of supraphysiological doses of testosterone on angry behavior in healthy eugonadal men—a clinical research center study. *J Clin Endocrinol Metab*. 1996;81:3754-3758.
78. O'Connor DB, Archer J, Hair WM, Wu FC. Exogenous testosterone, aggression, and mood in eugonadal and hypogonadal men. *Physiol Behav*. 2002;75:557-566.