Annual Review of Medicine

Benefits and Risks of Testosterone Treatment in Men with Age-Related Decline in Testosterone

Marcelo Rodrigues dos Santos[1,2] and Shalender Bhasin[1]

[1]Research Program in Men's Health: Aging and Metabolism, Boston Claude D. Pepper Older Americans Independence Center, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA; email: sbhasin@bwh.harvard.edu

[2]Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paulo 05508-220, Brazil; email: marcelo.rs@usp.br

Annu. Rev. Med. 2021. 72:16.1–16.17

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-050219-034711

Keywords

Late-onset hypogonadism, testosterone replacement, monitoring of testosterone treatment, adverse effects of testosterone treatment, aging men, reproductive aging of men

Abstract

The substantial increase in life expectancy of men has focused growing attention on quality-of-life issues associated with reproductive aging. Serum total and free testosterone levels in men, after reaching a peak in the second and third decade of life, decline gradually with advancing age. The trajectory of age-related decline is affected by comorbid conditions, adiposity, medications, and genetic factors. Testosterone treatment of older men with low testosterone levels improves overall sexual activity, sexual desire, and erectile function; improves areal and volumetric bone density, as well as estimated bone strength in the spine and the hip; corrects unexplained anemia of aging; increases skeletal muscle mass, strength and power, self-reported mobility, and some measures of physical function; and modestly improves depressive symptoms. The long-term effects of testosterone on major cardiovascular events and prostate cancer risk remain unclear. The Endocrine Society recommends against testosterone therapy of all older men with low testosterone levels but suggests consideration of treatment on an individualized basis in men who have consistently low testosterone levels and symptoms or conditions suggestive of testosterone deficiency.

INTRODUCTION

Hypogonadism is a syndrome that results from reduced production of testosterone (androgen deficiency) and spermatozoa by the testes due to disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis (1). Testosterone is approved by the US Food and Drug Administration (FDA) for the treatment of classical hypogonadism due to known diseases of the testis, pituitary, and hypothalamus (2). Prior to the advent of radio-immunoassays for the measurement of circulating testosterone levels, the diagnosis of hypogonadism was usually established on the basis of clinical findings, such as delayed or absent pubertal development, absence of secondary sex characteristics, gynecomastia, and small testes. In men with severe hypogonadism, testosterone treatment was associated with clinically apparent benefits, including a marked improvement in sexual function, development or restoration of secondary sex characteristics, and clinically apparent changes in body habitus, with a low frequency of adverse events. Thus, the benefit-to-risk ratio in these patients with severe testosterone deficiency was favorable.

During the past 20 years, testosterone prescription sales in the United States and in many other countries have grown substantially. Today, most testosterone prescriptions in the United States are written for middle-aged and older men, most of whom have low normal or mildly low testosterone levels (2). Neither the clinical benefits nor the long-term safety of testosterone treatment has been fully established in middle-aged and older men with age-related decline in testosterone levels, and testosterone treatment is not currently approved by the FDA for this indication.

EPIDEMIOLOGY OF AGE-RELATED DECLINE IN TESTOSTERONE LEVELS

A number of cross-sectional as well as longitudinal studies are in agreement that after reaching a peak in the second and third decade of life, serum testosterone concentrations decline gradually throughout life at a rate of approximately 1% each year (3, 4). Total as well as free testosterone concentrations are lower in older men than in young men even after accounting for adiposity, time of sampling, comorbid conditions, medications, and lifestyle factors (2–4). In more recent epidemiologic studies that have used accurate liquid chromatography tandem mass spectrometry assays for the measurement of testosterone levels, 10–15% of community-dwelling middle-aged and older men have testosterone levels below the lower limit of the normal range for healthy young men (3). Because sex hormone binding globulin (SHBG) levels increase with advancing age, the age-related decline in free testosterone levels is greater than that in total testosterone levels. The prevalence of total testosterone level <230 ng/dl (8 nmol/L) plus sexual symptoms in the European Male Aging Study was 3.2% for men aged 60–69 years and 5.1% for men aged 70–79 years (4). The term late-onset hypogonadism reflects the view that in some older men, the age-related decline in testosterone concentration is associated with a syndromic clustering of symptoms and signs similar to that observed in men with classical hypogonadism (4).

The trajectory of age-related decline in testosterone levels is affected by adiposity, weight gain, medications, comorbid conditions, and genetic factors (5–7). The rate of age-related decline in testosterone levels is greater in men with chronic illness and adiposity than in healthy nonobese men (5, 7). Comorbidity and adiposity are the major contributors to testosterone deficiency in older men.

PATHOPHYSIOLOGY OF AGE-RELATED DECLINE IN TESTOSTERONE LEVELS

The age-related decline in testosterone levels results from decreased testosterone production by the testes due to abnormalities at all levels of the hypothalamic-pituitary-testicular axis (6). The

plasma clearance of testosterone is lower in older men than in young men (8). Several mechanisms contribute to the age-related decline in testosterone levels; with aging, the secretion of gonadotropin-releasing hormone is attenuated; pituitary luteinizing hormone (LH) secretion becomes more disorderly and asynchronous; and the Leydig cell's response to LH stimulation is diminished (9–13). Aging is associated with a dampening of the diurnal rhythm of testosterone secretion observed more clearly in healthy young men (14).

A vast majority of older men with low testosterone levels have secondary hypogonadism (i.e., they have low or inappropriately normal LH levels in association with low testosterone levels); only a small fraction of these men have primary testicular failure (elevated LH in association with low testosterone) (15). Primary testicular dysfunction in older men is typically accompanied by poor health with multiple comorbidities. Secondary hypogonadism in older men is usually associated with obesity and chronic clinically significant conditions (15).

PHYSIOLOGIC AND CLINICAL SIGNIFICANCE OF AGE-RELATED DECLINE IN TESTOSTERONE LEVELS

Among the various age-related symptoms that middle-aged and older men report, sexual symptoms (decreased sexual desire, poor erections, and diminished early-morning erections) are the most consistently associated with low testosterone levels (16, 17). Low testosterone levels are associated with the age-related loss of skeletal muscle mass, muscle strength, and muscle power; impaired physical performance; frailty; and mobility limitation (18–21). Low total and bioavailable testosterone levels have been associated with low bone mineral density, bone geometry, and bone quality (22, 23), and with an increased risk of osteoporosis and fractures in older men (24, 25). Testosterone exerts direct effects on the bone through the androgen receptor; additionally, testosterone is converted to estradiol by the aromatase enzyme, which exerts its effects on the bone through the estrogen receptor alpha. Estradiol levels are more strongly associated with bone mineral density and fracture risk than are total testosterone levels (22, 24–26).

Testosterone levels are negatively associated with whole-body and abdominal adiposity. Low testosterone levels have been associated with increased risk of diabetes and metabolic syndrome; however, this association is stronger with total testosterone than with free testosterone levels and is attenuated after adjustment for SHBG levels (27–29). Low SHBG levels are independently prospectively associated with increased risk of diabetes (29).

In observational studies, low testosterone levels have been associated with higher all-cause mortality and cardiovascular mortality (30). Although low testosterone levels are associated with greater common carotid artery intima media thickness (31), testosterone levels have not been consistently associated with cardiovascular events.

The aging process is associated with cognitive decline and increased risk of Alzheimer's disease (AD). Testosterone acts as a negative regulator of endogenous Aβ amyloid accumulation in the brain through multiple mechanisms (5–8, 11, 12). Testosterone promotes the conversion of amyloid precursor protein (APP) to soluble APP-α rather than Aβ amyloid. Androgens induce the expression of neprilysin in neuronal cells and thereby decrease Aβ amyloid accumulation (13). Testosterone attenuates AD-like tau pathology by its direct effects on tau phosphorylation as well as indirectly after its aromatization to estradiol (32–34). Androgens promote neuronal viability during neural development and in adult brain following mechanical injury and disease-related toxicity (11). Androgens increase neurite arborization and synapse formation, facilitating intercellular communication. Some (35–39) but not all studies have found an association between low circulating testosterone levels and AD; the relation appears to be stronger with free testosterone levels than with total testosterone (35–37, 40). In the Baltimore Longitudinal Study on Aging (38),

the age-related decline in circulating free testosterone preceded the clinical diagnosis of AD by up to nearly 10 years. The strength of the association between testosterone and AD is affected by apolipoprotein ε4 genotype, a genetic risk factor for AD (36). Low brain levels of testosterone but not estradiol 17β (E_2) were associated with increased risk of AD (39).

Androgens' effects on cognitive function are domain specific. Generally, men with low testosterone levels perform less well than those with normal testosterone levels on tests of verbal fluency, visuospatial abilities (41), verbal memory (37, 42), and executive function (43). Some studies have suggested a curvilinear relation between testosterone levels and cognitive function; both low and high testosterone levels are associated with worse function, suggesting that there may be an intermediate level at which cognitive performance is optimized (43–45).

Neither testosterone nor dihydrotestosterone levels have been associated consistently with an increased risk of prostate cancer (46). Lower urinary tract symptoms are not associated with testosterone levels (47).

Although hypogonadal men often report low mood, testosterone levels have not been consistently associated with major depressive disorder (MDD) (33). Instead, low testosterone levels are more robustly associated with late-onset, low-grade persistent depressive disorder previously referred to as dysthymia (33).

Epidemiologic studies can only suggest an association; the association of low testosterone levels with increased risk of diabetes and all-cause and cardiovascular mortality does not establish a causal role of testosterone in the pathophysiology of these conditions. It is possible that testosterone levels may be a marker of health, and low testosterone levels may be the result of comorbid conditions that are associated with increased risk of death.

MENDELIAN RANDOMIZATION STUDIES

A mendelian randomization study that used data from the United Kingdom Biobank Study found that the effects of genetically determined testosterone levels differ between men and women (48). Higher genetically determined testosterone levels are associated with increased risk of type 2 diabetes and polycystic ovary syndrome in women, but with reduced risk of type 2 diabetes in men. Higher genetically determined testosterone levels were associated with increased risk of prostate cancer in men in this study (48). In another study, higher genetically determined estradiol levels were associated with higher bone mineral density in the spine and the hip (49).

POTENTIAL BENEFITS OF TESTOSTERONE TREATMENT IN OLDER MEN: FINDINGS OF RANDOMIZED TRIALS

Although many open-label trials of testosterone replacement in hypogonadal men have been conducted, only a small number of placebo-controlled randomized trials have evaluated the efficacy of testosterone treatment in older men who had unequivocally low testosterone levels and symptoms of testosterone deficiency (50, 51). No trials have been large enough or long enough to determine the long-term benefits of testosterone treatment in older men on clinically important outcomes such as disability, fractures, progression from prediabetes to diabetes, dysthymia, and progression to AD in men at risk of AD.

The Testosterone Trials (TTrials) comprised seven coordinated placebo-controlled trials of testosterone replacement conducted in 788 community-dwelling older men, 65 years or older, who had an average of two morning fasting total testosterone levels below 275 ng/dl, measured using liquid chromatography tandem mass spectrometry (52–54). Eligible men were required to have one or more sexual or physical symptoms, or fatigue, and were allocated using minimization

to receive either placebo gel or testosterone gel for one year. The dose of testosterone gel was adjusted to achieve and maintain serum testosterone levels in the mid-range for healthy young men. Testosterone treatment was associated with greater improvement in overall sexual activity, sexual desire, erectile function, and satisfaction with sexual experience than placebo (55). A meta-analysis of placebo-controlled trials found that testosterone treatment of hypogonadal men significantly increases sexual desire, erectile function, and sexual satisfaction (56). However, the improvements in erectile function associated with testosterone treatment of older hypogonadal men are substantially smaller than those reported with phosphodiesterase 5 inhibitors, such as sildenafil citrate.

Testosterone deficiency is associated with a decreased frequency of sexual thoughts and lower overall sexual activity (57). However, young hypogonadal men can achieve erections in response to visual erotic stimuli. Testosterone replacement therapy of young testosterone-deficient men improves sexual daydreams, sexual thoughts, spontaneous erections, and attentiveness to erotic stimuli (57). Testosterone treatment also increases the frequency and duration of sleep-entrained penile erections (58). Although hypogonadal men can achieve orgasm and ejaculation, they have decreased ejaculate volume. In healthy young testosterone-deficient men, sexual function is restored by testosterone levels that are at or near the lower limit of the normal male range (59). The effects of testosterone on sexual desire require its aromatization to estradiol (60). In contrast, testosterone treatment does not improve sexual desire or erectile function in middle-aged and older men who have normal testosterone levels and no sexual symptoms (61). Testosterone treatment has not been shown to improve ejaculatory function in hypogonadal men with ejaculatory dysfunction. In men with erectile dysfunction and low testosterone levels, in whom the dose of sildenafil citrate was optimized (62), testosterone treatment did not result in greater improvement in erectile function than placebo.

Testosterone treatment increases skeletal muscle mass, maximal voluntary strength in the large muscle groups of the upper and lower extremities, and leg power in young as well as older men (63, 64). Testosterone increases muscle mass by inducing the hypertrophy of both type 1 and 2 skeletal muscle fibers; it does not increase either the absolute or the relative proportion of type 1 or type 2 muscle fibers (65). Testosterone-induced increase in skeletal muscle mass and maximal voluntary strength are related to the administered dose and the on-treatment testosterone levels. The effects of testosterone treatment on skeletal muscle mass and muscle strength are augmented by resistance exercise training and recombinant growth hormone, but not by increased protein intake (66, 67). Testosterone treatment improves some measures of physical performance, such as stair climbing speed and power in mobility-limited older men with low or low normal testosterone levels (64); the improvements in gait speed have been modest and inconsistent across randomized trials (68). Testosterone treatment of community-dwelling older men with low or low normal testosterone levels is associated with small improvements in aerobic capacity and attenuation of the age-related decline in measures of aerobic capacity (**Figure 1**) (69).

A meta-analysis of randomized trials that included studies in young as well as older hypogonadal men found a greater improvement in vertebral bone mineral density in men randomized to testosterone arms than in those randomized to the placebo arms (70). In the Bone Trial of the TTrials (71), testosterone treatment of older hypogonadal men for 1 year was associated with greater improvements in volumetric bone density and estimated bone strength than placebo; the improvements were greater in the spine than in the hip and greater in the trabecular than the peripheral bone (**Figure 2**). Previous testosterone trials have not been large enough or long enough to determine the effects of testosterone treatment on fracture risk in older hypogonadal men.

Neuroendocrine studies have not found consistently lower testosterone levels in men with MDD compared to healthy controls (72, 73). Randomized controlled trials of testosterone in patients with MDD have failed to demonstrate consistent benefit of testosterone over placebo (74).

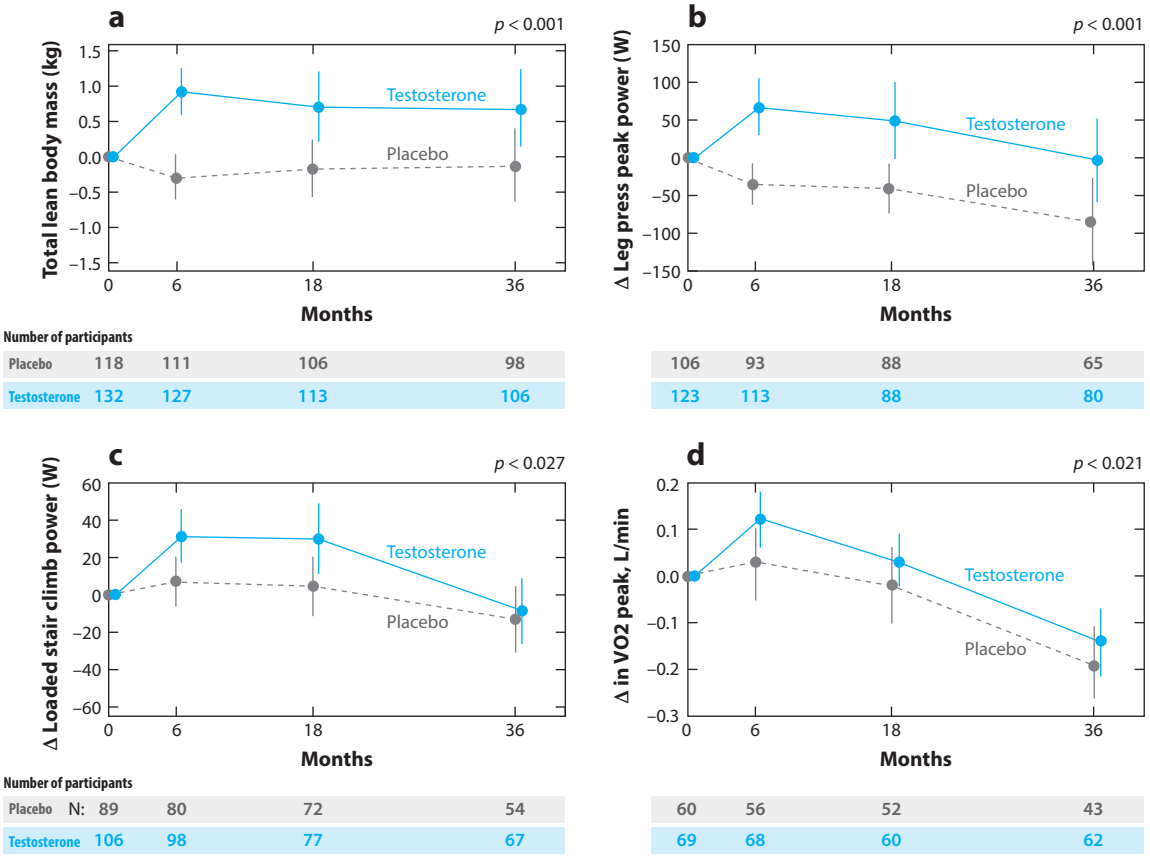

Figure 1

The effects of testosterone treatment for 3 years on lean body mass (*a*), peak leg power (*b*), loaded stair climbing power (a measure of physical function) (*c*), and VO2 peak (maximal oxygen uptake at peak exercise intensity, a measure of aerobic capacity) (*d*) in older men with low or low normal testosterone levels in the Testosterone Effects on Atherosclerosis Progression in Aging Men (TEAAM) Trial. Testosterone treatment was associated with significantly greater improvements in each of these measures, although the effects tended to wane over time. Panels *a–c* adapted with permission from Reference 64; panel *d* adapted with permission from Reference 69.

Similarly, placebo-controlled trials of testosterone replacement in men with refractory MDD have not consistently shown superiority of testosterone treatment relative to placebo (75). Two small randomized trials of testosterone replacement in men with late-onset, low-grade persistent depressive disorder (dysthymia) have reported improvements in depressive symptoms in dysthymic men with low testosterone levels (76, 77). Meta-analyses of randomized testosterone trials in hypogonadal men without a depressive disorder have found significantly greater, though small, improvements in depressive symptoms in testosterone-treated men than in placebo-treated men (78).

Testosterone administration reduces whole-body adipose tissue mass (79); the loss of fat mass during testosterone administration is distributed evenly between the subcutaneous and the visceral adipose tissue compartments (80). The withdrawal of testosterone replacement therapy in hypogonadal men is associated with the development of insulin resistance (81). Although some trials in men with type 2 diabetes or metabolic syndrome have reported greater improvement in measures of insulin resistance with testosterone treatment than with placebo treatment (82), the

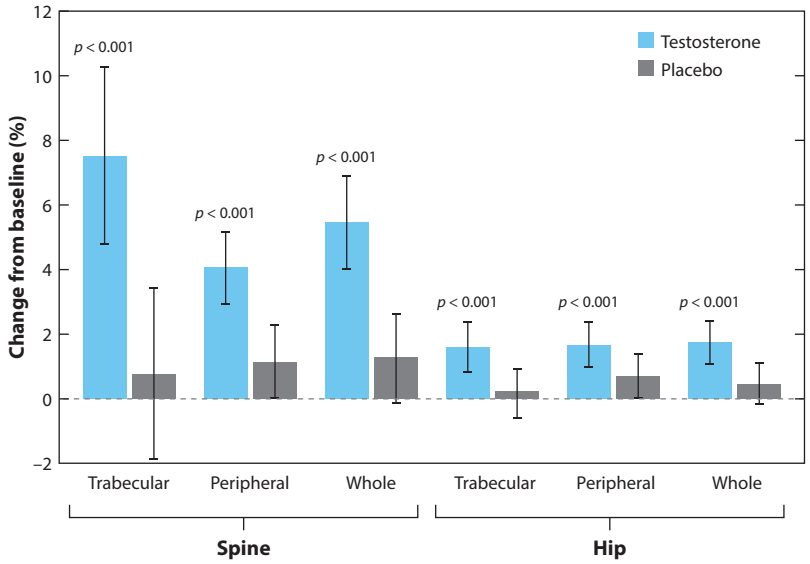

Figure 2

The effects of testosterone treatment relative to placebo on volumetric bone mineral density in older hypogonadal men. The data are derived from the Bone Trial of the Testosterone Trials, a set of placebo-controlled trials in older men with unequivocally low testosterone levels and sexual or physical symptoms or low vitality. Testosterone treatment was associated with greater improvements in vertebral as well as hip bone mineral density compared to placebo. The improvements in volumetric bone density were greater in the spine than in the hip and greater in the trabecular than in the peripheral bone. Figure adapted with permission from Reference 71.

randomized trials of testosterone treatment in older men with type 2 diabetes and low testosterone levels have not found consistent improvement in glycemic control across trials.

Testosterone treatment induces several adaptations that would be expected to improve net oxygen delivery to the tissues, improve aerobic performance, and reduce fatigability. These include an increase in hemoglobin and stimulation of 2, 3-bisphosphoglycerate concentrations, thereby shifting the oxygen–hemoglobin dissociation curve to enhance tissue oxygen delivery, increase muscle capillarity, and improve blood flow to the tissues (including the heart), as well as stimulate mitochondrial biogenesis and mitochondrial quality. However, in the Vitality Trial of the T Trials, testosterone treatment for 1 year did not improve vitality in older men with low vitality measured using the Functional Assessment of Chronic Illness Therapy (FACIT) scale (53). In another large randomized testosterone trial in hypogonadal men, testosterone treatment was associated with greater improvements in energy compared to placebo (50).

No adequately powered randomized placebo-controlled trials of testosterone replacement have been conducted in men wih AD (83). The clinical trials data on the effects of testosterone on cognition are limited and have provided conflicting results. Some studies have reported improvements in verbal memory and visuospatial skill while others found no effect. However, none of the trials has been conducted in men at risk for AD with progression of AD as the primary outcome. The trials have not included any measures of AD pathology, including Aβ amyloid, tau protein, or blood or cerebrospinal fluid markers of AD. A few small testosterone supplementation studies (sample size varying from 11 to 47) of 6 weeks to 6 months duration in men with cognitive impairment associated with AD have reported modest improvements in verbal and spatial memory,

but the interpretability of these data is limited by the small sample sizes, short intervention durations, and variable eligibility criteria (inclusion of men without confirmed AD and inclusion of men with normal testosterone levels) (84, 85). Long-term, adequately powered trials are needed to determine whether testosterone treatment can retard the progression of AD neuropathology in older men at increased risk for AD.

POTENTIAL ADVERSE EFFECTS OF TESTOSTERONE TREATMENT IN OLDER MEN

Testosterone treatment of healthy, young, androgen-deficient men with classical hypogonadism is associated with a low frequency of mild adverse effects such as erythrocytosis, acne, oiliness of skin, and breast tenderness (1). However, the long-term risks of testosterone supplementation in older men are not known. Furthermore, older men with chronic conditions have usually been excluded from randomized testosterone trials.

Older men may be at increased risk of the adverse effects of testosterone treatment for several reasons. The plasma clearance rates of testosterone are lower in older men; consequently, serum testosterone levels are higher in testosterone-treated older hypogonadal men than in young men, after adjusting for age (8). Older men also exhibit greater increments in hemoglobin and hematocrit in response to testosterone administration than young men (43). Older men have higher baseline prevalence of multiple comorbid conditions, such as prostate cancer, benign prostatic hypertrophy, and cardiovascular disease that might be exacerbated by testosterone administration.

In older men, testosterone promotes the growth of metastatic prostate cancer, reduces sperm production leading to infertility, and increases the risk of detection of subclinical prostate cancer (1). Testosterone treatment can cause transient breast tenderness within the first few weeks of starting testosterone treatment. However, the development of gynecomastia is uncommon in randomized testosterone trials. In randomized trials, the incidence of the development or worsening of obstructive sleep apnea has been very low. Liver enzyme elevations, reported with the use of oral, 17-α-alkylated androgens such as methyltestosterone, have not been observed with transdermal testosterone gels or patches, nor with the injectable testosterone esters. There may also be formulation-specific adverse effects. Intramuscular injections of testosterone may be associated with fluctuations in serum testosterone levels during the dosing interval and associated variations in mood and sex drive, as well as pain at the injection site. Intramuscular injection of long-acting testosterone undecanoate has been associated with pulmonary oil microembolism, which manifests as an episode of coughing, difficulty breathing, and chest pain typically within a few minutes after the injection. Infrequently, coughing episodes have also been reported with other injectable esters. Transdermal patches are associated with high rates of skin irritation. Transdermal gels are well tolerated and associated with low frequency of skin irritation. However, transdermal gels are associated with higher variability in on-treatment testosterone levels than injectable esters and with the potential risk of transfer of testosterone to a sexual partner or a child who may come in close contact with the patient.

TESTOSTERONE TREATMENT AND THE RISK OF PROSTATE CANCER AND LOWER URINARY TRACT SYMPTOMS

Several meta-analyses of randomized trials are in agreement that testosterone treatment does not worsen lower urinary tract symptoms in hypogonadal men who do not have severe lower urinary tract symptoms at baseline (86, 87). There is no clear evidence for the association between prostate cancer risk and circulating levels of testosterone, dihydrotestosterone, or estradiol, nor the

polymorphisms in genes that encode proteins involved in steroid hormone action or metabolism (6, 88). A meta-analysis of prospective epidemiologic studies found no significant association between testosterone levels and the risk of prostate cancer (46). Testosterone does not cause prostate cancer (1); however, signaling through the androgen receptor plays an important role in its biology. Testosterone administration promotes the growth of metastatic prostate cancer. The Endocrine Society recommends against testosterone supplementation in men with prostate cancer and advocates individualized consideration of prostate cancer risk prior to treatment initiation.

Testosterone treatment in older men increases the likelihood of prostate biopsy and the detection of subclinical prostate cancers (1). Many middle-aged and older adults harbor small subclinical cancers in the prostate; there is concern that testosterone replacement therapy might cause these foci to grow. Testosterone therapy increases the likelihood of detection of low-grade prostate cancers because of increased surveillance and because of testosterone-induced increase in prostate-specific antigen (PSA) levels, which may prompt a prostate biopsy in some men (30). In a meta-analysis of randomized studies, a greater proportion of men randomized to testosterone treatment were referred for prostate biopsies, had intervention-phase PSA levels exceeding 4 ng/ml, or had prostate cancer diagnoses than those assigned to placebo treatment (89).

TESTOSTERONE TREATMENT AND THE RISK OF CARDIOVASCULAR EVENTS

There is no clear evidence that testosterone treatment increases the risk of major adverse cardiovascular events. No randomized trial to date has been long enough or large enough to determine whether testosterone increases the risk of such events.

Some physiologic effects of testosterone administration could theoretically contribute to increased cardiovascular risk, such as a small increase in low-density-lipoprotein cholesterol a small reduction in high-density-lipoprotein cholesterol, an increase in hematocrit, transient salt and water retention, and induction of vascular cell adhesion molecule expression in the media of blood vessels. Testosterone also exerts other physiologic effects that could reduce cardiovascular risk, such as a reduction of whole-body and abdominal adipose tissue mass, coronary vasodilation and increased coronary blood flow, and a reduction of QTc interval. In two placebo-controlled trials, the rates of atherosclerosis progression did not differ significantly between the testosterone and placebo groups (61, 90) (**Figure 3*a*,*b***). In the Cardiovascular Trial of the TTrials, compared to placebo, testosterone treatment was associated with a greater increase in the volume of the noncalcified plaque, measured using computerized tomography angiography (90) (**Figure 3*c***). The meta-analyses of randomized trials have been inconclusive and limited by the relatively small sample size; short intervention durations; heterogeneity of study populations, doses, and on-treatment testosterone levels; and lack of prospective standardized ascertainment and adjudication of cardiovascular events (91).

Retrospective observational and pharmacovigilance studies also have reported conflicting data on the possible association between testosterone treatment and adverse cardiovascular outcomes in patients treated with testosterone versus matched control groups (92–95); these studies were similarly limited by the heterogeneity of study populations, doses, and on-treatment testosterone levels; confounding by indication; and the lack of prospective standardized ascertainment and adjudication of major cardiovascular events. The FDA conducted an extensive review and concluded that "the studies. . .have significant limitations that weaken their evidentiary value for confirming a causal relationship between testosterone and adverse cardiovascular outcomes" (96). Nevertheless, the FDA directed the pharmaceutical companies to add to the drug label information about a possible increased risk of cardiovascular events with testosterone use. An independent

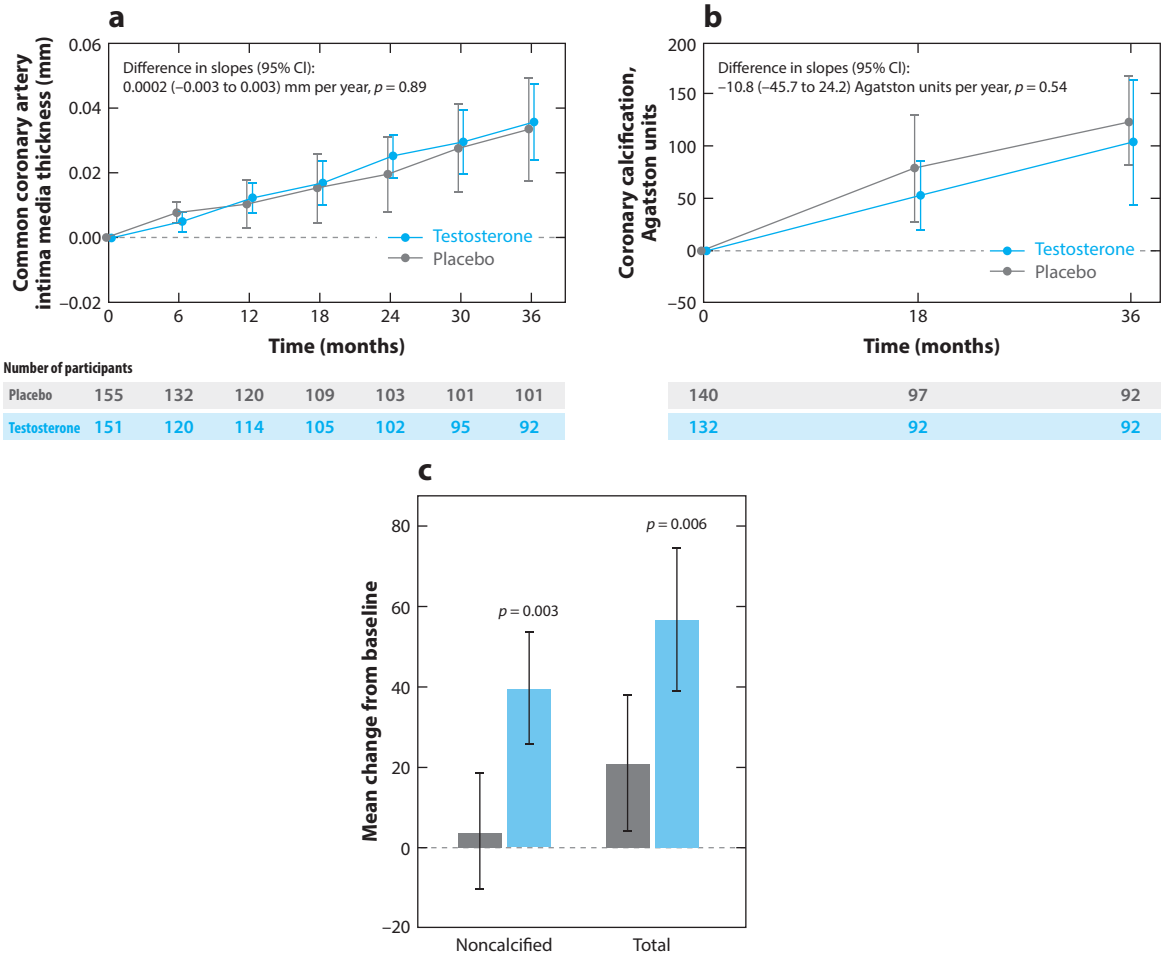

Figure 3

The effect of testosterone treatment on atherosclerosis progression, assessed using common carotid artery intima-media thickness (CCA-IMT) by ultrasound (*a*) and by coronary calcium scores using multidetector computerized tomography (CT) (*b*), and on coronary plaque volume measured using CT angiography (*c*). The rate of atherosclerosis progression, assessed using the CCA-IMT or the coronary calcium score, did not differ between the testosterone and placebo-treated men in the Testosterone Effects on Atherosclerosis Progression in Aging Men (TEAAM) Trial. The change in total plaque volume as well as noncalcified plaque volume was greater in the testosterone-treated men than in the placebo-treated men in the Cardiovascular Trial of the Testosterone Trials (TTrials). Panels *a* and *b* adapted with permission from Reference 61; panel *c* adapted with permission from Reference 90.

review conducted by the European Medicines Agency also found no consistent evidence of an increased risk of coronary heart disease associated with testosterone treatment of hypogonadal men.

There is no evidence of a statistically significant association between testosterone treatment and increased risk of venous thromboembolic events (1, 97). Testosterone increases the levels of both procoagulant and anticoagulant proteins. The number of ascertained venous thromboembolic events in randomized testosterone trials has been too small to enable meaningful inferences.

The risk for venous thromboembolic events may be increased in patients with hypercoagulable states (thrombophilia) (98), especially within the first few months after starting testosterone treatment. The FDA has required manufacturers of testosterone products to include a warning about the risk of venous thromboembolism in the drug labels.

CONTRAINDICATIONS FOR TESTOSTERONE TREATMENT

Metastatic prostate cancer and breast cancer are contraindications for testosterone treatment. Benign prostatic hypertrophy is not a contraindication unless it is associated with severe symptoms, as indicated by an International Prostate Symptom Score higher than 21. Testosterone should not be given to men who have baseline hematocrit greater than 50%; severe untreated sleep apnea; congestive heart failure with Class III or IV symptoms; or myocardial infarction, stroke, or coronary revascularization surgery within the past 4 months. Testosterone should not be prescribed to men who are considering having a child in the near future.

A history of prostate cancer has historically been viewed as a contraindication for testosterone treatment. However, many men with organ-confined, low-grade prostate cancer who have undetectable PSA for at least 2 years after radical prostatectomy have very low 5- and 10-year prostate cancer recurrence rates; some clinicians have suggested considering such patients for testosterone replacement on an individualized basis (99). However, the lack of data from randomized trials precludes a general recommendation.

MONITORING TESTOSTERONE REPLACEMENT THERAPY IN OLDER MEN

Testosterone treatment of older men with testosterone deficiency should be accompanied by a standardized monitoring plan, such as that recommended by an expert panel of the Endocrine Society. The Endocrine Society recommends follow-up at 3 to 6 months and then annually thereafter for assessment of treatment efficacy, on-treatment testosterone levels, detection of any adverse effects, and measurement of hematocrit and PSA levels (1).

Management of PSA Elevations

After initiation of testosterone replacement therapy, PSA levels should be tested at 3 months and annually thereafter. Hypogonadal men have lower PSA levels than eugonadal men, and PSA levels rise after initiation of testosterone replacement therapy. An important question that arises commonly in clinical practice is what level of PSA elevation should prompt a urological referral for consideration of prostate biopsy. The average PSA increase after institution of testosterone replacement therapy is 0.3 ng/ml in young hypogonadal men and 0.44 ng/ml in older men (89). Increases in serum PSA levels of greater than 1.4 ng/ml after starting testosterone treatment are unusual in older men without prostate cancer. PSA levels above 4 ng/ml at any time are associated with increased risk of prostate cancer and should be evaluated. Based on these considerations, the Endocrine Society guideline suggests urological consultation in men receiving testosterone replacement if (*a*) PSA increases more than 1.4 ng/ml in the first 12 months of treatment, (*b*) a PSA above 4 ng/ml is confirmed, or (*c*) a prostatic abnormality is detected on digital rectal examination (1). After 12 months of treatment, prostate monitoring should follow standard guidelines for prostate cancer screening, taking into account the age and race of the patient.

Because of the high test–retest variability in PSA levels, PSA elevations should be confirmed by repeating the test after 4 to 6 weeks. In the TTrials, half of the PSA elevations resolved spontaneously when the test was repeated (100).

Management of Hematocrit Elevations

Hematocrit levels should be measured at baseline and 3 months after institution of testosterone replacement, or after increase in dosage, and every 12 months thereafter. Hematocrit levels above 54% may be associated with increased risk of stroke and neuro-occlusive events (1); men who develop erythrocytosis during testosterone treatment should be evaluated for other causes of polycythemia. The testosterone dose should be reduced if hematocrit rises above 52% and withheld if hematocrit levels rise above 54%. Once hematocrit falls to a safe level, testosterone therapy may be reinitiated at a reduced dose or with a different formulation (1). In some men, therapeutic phlebotomy at regular intervals can be useful in maintaining hematocrit levels in a safe range.

A PATIENT-CENTERED APPROACH TO TREATMENT DECISION IN OLDER MEN WITH TESTOSTERONE DEFICIENCY

Because of the lack of evidence of the long-term safety and limited evidence of long-term efficacy of testosterone therapy in older men with symptomatic androgen deficiency, there still remains some controversy about the indications for treatment in these patients. The expert panel of the Endocrine Society recommended against testosterone therapy of all men 65 years or older with low testosterone levels (1). Instead, the Endocrine Society's guideline suggests that testosterone therapy should be offered on an individualized basis after explicit discussion of the potential risks and benefits "...in men >65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone" (1, p. 1716).

The decision whether to offer testosterone treatment to older men with low testosterone levels should be guided by several considerations. First, evaluate whether the patient has clear evidence of testosterone deficiency. The diagnosis of testosterone deficiency should be made on the basis of two or more early-morning, fasting testosterone levels below the lower limit of normal for healthy young men, plus the presence of symptoms. Consider the imprecision and inaccuracies of the diagnostic assays for total and free testosterone levels, especially in men whose testosterone levels are close to the lower limit of the normal range. Use ancillary data such as testicular volume, secondary sex characteristics, and LH and follicle-stimulating hormone levels, which can reduce the risk of misclassification.

Second, weigh the burden of symptoms/conditions against the known benefits and the uncertainty of long-term harm, recognizing that sexual symptoms are the most robustly associated with testosterone deficiency and are the most consistently improved by testosterone treatment.

Third, ascertain whether the patient has any conditions, such as prostate cancer, severe lower urinary tract symptoms, erythrocytosis, or deep venous thrombosis, that might increase the risk of harm. Older men considering testosterone supplementation should undergo baseline evaluation of risk factors for prostate cancer. Prostate cancer screening has some risks; therefore, initiation of prostate screening and monitoring should be a shared decision. Men with history of prostate cancer should not be given androgen supplementation, and those with palpable abnormalities of the prostate or PSA levels greater than 3 ng/ml should undergo urological evaluation (1).

Fourth, share the burden of decision making with the patient. Physicians should recognize that there is considerable disagreement among experts on this issue due to incomplete evidence.

Nonspecific age-related symptoms and low testosterone concentrations often coexist in older men without a clear causal link. The patient's burden of symptoms, preferences, and risk tolerance should be weighed against the uncertainty of benefits and risks, the burden and risks of monitoring, and the cost. Finally, a shared decision to initiate testosterone treatment should be accompanied by a standardized monitoring plan.

DISCLOSURE STATEMENT

Dr. Bhasin reports receiving research grants from the National Institute on Aging, the National Institute of Nursing Research, the National Institite of Child Health and Human Development, Patient-Centered Outcomes Research Institute, AbbVie, Alivegen, Metro International Biotechnology, and Transition Therapeutics; and personal consulting fees from OPKO and Aditum. These research grants are managed by the Brigham and Women's Hospital, and the conflicts are overseen by the Partners Office of Industry Interaction.

LITERATURE CITED

1. Bhasin S, Brito JP, Cunningham GR, et al. 2018. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 103:1715–44
2. Nguyen CP, Hirsch MS, Moeny D, et al. 2015. Testosterone and "age-related hypogonadism"—FDA concerns. *N. Engl. J. Med.* 373:689–91
3. Bhasin S, Pencina M, Jasuja GK, et al. 2011. Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the Framingham Heart Study and applied to three geographically distinct cohorts. *J. Clin. Endocrinol. Metab.* 96:2430–39
4. Harman SM, Metter EJ, Tobin JD, et al. 2001. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J. Clin. Endocrinol. Metab.* 86:724–31
5. Mohr BA, Bhasin S, Link CL, et al. 2006. The effect of changes in adiposity on testosterone levels in older men: longitudinal results from the Massachusetts Male Aging Study. *Eur. J. Endocrinol.* 155:443–52
6. Spitzer M, Huang G, Basaria S, et al. 2013. Risks and benefits of testosterone therapy in older men. *Nat. Rev. Endocrinol.* 9:414–24
7. Wu FC, Tajar A, Pye SR, et al. 2008. 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.* 93:2737–45
8. Coviello AD, Lakshman K, Mazer NA, Bhasin S. 2006. Differences in the apparent metabolic clearance rate of testosterone in young and older men with gonadotropin suppression receiving graded doses of testosterone. *J. Clin. Endocrinol. Metab.* 91:4669–75
9. Harman SM, Tsitouras PD. 1980. 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.* 51:35–40
10. Harman SM, Tsitouras PD, Costa PT, Blackman MR. 1982. Reproductive hormones in aging men. II. Basal pituitary gonadotropins and gonadotropin responses to luteinizing hormone-releasing hormone. *J. Clin. Endocrinol. Metab.* 54:547–51
11. Mulligan T, Iranmanesh A, Johnson ML, et al. 1997. Aging alters feed-forward and feedback linkages between LH and testosterone in healthy men. *Am. J. Physiol.* 273:R1407–13
12. Pincus SM, Mulligan T, Iranmanesh A, et al. 1996. Older males secrete luteinizing hormone and testosterone more irregularly, and jointly more asynchronously, than younger males. *PNAS* 93:14100–5
13. Winters SJ, Sherins RJ, Troen P. 1984. The gonadotropin-suppressive activity of androgen is increased in elderly men. *Metabolism* 33:1052–59

14. Bremner WJ, Vitiello MV, Prinz PN. 1983. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J. Clin. Endocrinol. Metab.* 56:1278–81
15. Tajar A, Forti G, O'Neill TW, et al. 2010. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *J. Clin. Endocrinol. Metab.* 95:1810–18
16. O'Connor DB, Lee DM, Corona G, et al. 2011. The relationships between sex hormones and sexual function in middle-aged and older European men. *J. Clin. Endocrinol. Metab.* 96:E1577–87
17. Wu FC, Tajar A, Beynon JM, et al. 2010. Identification of late-onset hypogonadism in middle-aged and elderly men. *N. Engl. J. Med.* 363:123–35
18. Baumgartner RN, Waters DL, Gallagher D, et al. 1999. Predictors of skeletal muscle mass in elderly men and women. *Mech. Ageing Dev.* 107:123–36
19. Krasnoff JB, Basaria S, Pencina MJ, et al. 2010. Free testosterone levels are associated with mobility limitation and physical performance in community-dwelling men: the Framingham Offspring Study. *J. Clin. Endocrinol. Metab.* 95:2790–99
20. Roy TA, Blackman MR, Harman SM, et al. 2002. Interrelationships of serum testosterone and free testosterone index with FFM and strength in aging men. *Am. J. Physiol. Endocrinol. Metab.* 283:E284–94
21. Schaap LA, Pluijm SM, Deeg DJ, et al. 2008. Low testosterone levels and decline in physical performance and muscle strength in older men: findings from two prospective cohort studies. *Clin. Endocrinol.* 68:42–50
22. Amin S, Zhang Y, Sawin CT, et al. 2000. Association of hypogonadism and estradiol levels with bone mineral density in elderly men from the Framingham study. *Ann. Intern. Med.* 133:951–63
23. Khosla S, Melton LJ 3rd, Robb RA, et al. 2005. Relationship of volumetric BMD and structural parameters at different skeletal sites to sex steroid levels in men. *J. Bone Miner. Res.* 20:730–40
24. Amin S, Zhang Y, Felson DT, et al. 2006. Estradiol, testosterone, and the risk for hip fractures in elderly men from the Framingham Study. *Am. J. Med.* 119:426–33
25. Mellstrom D, Vandenput L, Mallmin H, et al. 2008. Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. *J. Bone Miner. Res.* 23:1552–60
26. Finkelstein JS, Lee H, Leder BZ, et al. 2016. Gonadal steroid-dependent effects on bone turnover and bone mineral density in men. *J. Clin. Investig.* 126:1114–25
27. Bhasin S, Jasjua GK, Pencina M, et al. 2011. Sex hormone-binding globulin, but not testosterone, is associated prospectively and independently with incident metabolic syndrome in men: the Framingham Heart Study. *Diabetes Care* 34:2464–70
28. Ding EL, Song Y, Malik VS, Liu S. 2006. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 295:1288–99
29. Lakshman KM, Bhasin S, Araujo AB. 2010. Sex hormone-binding globulin as an independent predictor of incident type 2 diabetes mellitus in men. *J. Gerontol. A Biol. Sci. Med. Sci.* 65:503–9
30. Araujo AB, Dixon JM, Suarez EA, et al. 2011. Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J. Clin. Endocrinol. Metab.* 96:3007–19
31. Khazai B, Golden SH, Colangelo LA, et al. 2016. Association of endogenous testosterone with subclinical atherosclerosis in men: the Multi-Ethnic Study of Atherosclerosis. *Clin. Endocrinol.* 84:700–7
32. Liu XA, Zhu LQ, Zhang Q, et al. 2008. Estradiol attenuates tau hyperphosphorylation induced by upregulation of protein kinase-A. *Neurochem. Res.* 33:1811–20
33. Oikawa N, Ogino K, Masumoto T, et al. 2010. Gender effect on the accumulation of hyperphosphorylated tau in the brain of locus-ceruleus-injured APP-transgenic mouse. *Neurosci. Lett.* 468:243–47
34. Rosario ER, Carroll J, Pike CJ. 2010. Testosterone regulation of Alzheimer-like neuropathology in male 3xTg-AD mice involves both estrogen and androgen pathways. *Brain Res.* 1359:281–90
35. Hogervorst E, Combrinck M, Smith AD. 2003. Testosterone and gonadotropin levels in men with dementia. *Neuro Endocrinol. Lett.* 24:203–8
36. Hogervorst E, Lehmann DJ, Warden DR, et al. 2002. Apolipoprotein E epsilon4 and testosterone interact in the risk of Alzheimer's disease in men. *Int. J. Geriatr. Psychiatry* 17:938–40
37. Moffat SD, Zonderman AB, Metter EJ, et al. 2002. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J. Clin. Endocrinol. Metab.* 87:5001–7

38. Moffat SD, Zonderman AB, Metter EJ, et al. 2004. Free testosterone and risk for Alzheimer disease in older men. *Neurology* 62:188–93
39. Rosario ER, Chang L, Stanczyk FZ, Pike CJ. 2004. Age-related testosterone depletion and the development of Alzheimer disease. *JAMA* 292:1431–32
40. Lv W, Du N, Liu Y, et al. 2016. Low testosterone level and risk of Alzheimer's disease in the elderly men: a systematic review and meta-analysis. *Mol. Neurobiol.* 53:2679–84
41. Hier DB, Crowley WF Jr. 1982. Spatial ability in androgen-deficient men. *N. Engl. J. Med.* 306:1202–5
42. Barrett-Connor E, Goodman-Gruen D, Patay B. 1999. Endogenous sex hormones and cognitive function in older men. *J. Clin. Endocrinol. Metab.* 84:3681–85
43. Muller M, Aleman A, Grobbee DE, et al. 2005. Endogenous sex hormone levels and cognitive function in aging men: Is there an optimal level? *Neurology* 64:866–71
44. Martin DM, Wittert G, Burns NR, et al. 2007. Testosterone and cognitive function in ageing men: data from the Florey Adelaide Male Ageing Study (FAMAS). *Maturitas* 57:182–94
45. Matousek RH, Sherwin BB. 2010. Sex steroid hormones and cognitive functioning in healthy, older men. *Horm. Behav.* 57:352–59
46. Roddam AW, Allen NE, Appleby P, Key TJ. 2008. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J. Natl. Cancer Inst.* 100:170–83
47. Lee JH, Kim Y, Park YW, Lee DG. 2014. Relationship between benign prostatic hyperplasia/lower urinary tract symptoms and total serum testosterone level in healthy middle-aged eugonadal men. *J. Sex. Med.* 11:1309–15
48. Ruth KS, Day FR, Tyrrell J, et al. 2020. Using human genetics to understand the disease impacts of testosterone in men and women. *Nat. Med.* 26:252–58
49. Eriksson AL, Perry JRB, Coviello AD, et al. 2018. Genetic determinants of circulating estrogen levels and evidence of a causal effect of estradiol on bone density in men. *J. Clin. Endocrinol. Metab.* 103:991–1004
50. Brock G, Heiselman D, Maggi M, et al. 2016. Effect of testosterone solution 2% on testosterone concentration, sex drive and energy in hypogonadal men: results of a placebo controlled study. *J. Urol.* 195:699–705
51. Steidle C, Schwartz S, Jacoby K, et al. 2003. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J. Clin. Endocrinol. Metab.* 88:2673–81
52. Santos MR, Sayegh AL, Groehs RV, et al. 2015. Testosterone deficiency increases hospital readmission and mortality rates in male patients with heart failure. *Arq. Bras Cardiol.* 105:256–64
53. Snyder PJ, Bhasin S, Cunningham GR, et al. 2016. Effects of testosterone treatment in older men. *N. Engl. J. Med.* 374:611–24
54. Snyder PJ, Bhasin S, Cunningham GR, et al. 2018. Lessons from the testosterone trials. *Endocr. Rev.* 39:369–86
55. Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. 2016. Testosterone treatment and sexual function in older men with low testosterone levels. *J. Clin. Endocrinol. Metab.* 101:3096–104
56. Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, et al. 2018. The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: a systematic review and meta-analysis of randomized, placebo-controlled trials. *J. Clin. Endocrinol. Metab.* 2018:10.1210/jc.2018-00404
57. Kwan M, Greenleaf WJ, Mann J, et al. 1983. The nature of androgen action on male sexuality: a combined laboratory-self-report study on hypogonadal men. *J. Clin. Endocrinol. Metab.* 57:557–62
58. Cunningham GR, Hirshkowitz M, Korenman SG, Karacan I. 1990. Testosterone replacement therapy and sleep-related erections in hypogonadal men. *J. Clin. Endocrinol. Metab.* 70:792–97
59. Buena F, Swerdloff RS, Steiner BS, et al. 1993. Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. *Fertil. Steril.* 59:1118–23
60. Finkelstein JS, Lee H, Burnett-Bowie SA, et al. 2013. Gonadal steroids and body composition, strength, and sexual function in men. *N. Engl. J. Med.* 369:1011–22
61. Basaria S, Harman SM, Travison TG, et al. 2015. 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* 314:570–81

62. Spitzer M, Basaria S, Travison TG, et al. 2012. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. *Ann. Intern. Med.* 157:681–91
63. Bhasin S, Woodhouse L, Casaburi R, et al. 2005. Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. *J. Clin. Endocrinol. Metab.* 90:678–88
64. Storer TW, Basaria S, Traustadottir T, et al. 2017. Effects of testosterone supplementation for 3 years on muscle performance and physical function in older men. *J. Clin. Endocrinol. Metab.* 102:583–93
65. Sinha-Hikim I, Artaza J, Woodhouse L, et al. 2002. Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. *Am. J. Physiol. Endocrinol. Metab.* 283:E154–64
66. Bhasin S, Apovian CM, Travison TG, et al. 2018. Effect of protein intake on lean body mass in functionally limited older men: a randomized clinical trial. *JAMA Intern. Med.* 178:530–41
67. Blackman MR, Sorkin JD, Munzer T, et al. 2002. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. *JAMA* 288:2282–92
68. Bhasin S, Ellenberg SS, Storer TW, et al. 2018. 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.* 6:879–90
69. Traustadottir T, Harman SM, Tsitouras P, et al. 2018. Long-term testosterone supplementation in older men attenuates age-related decline in aerobic capacity. *J. Clin. Endocrinol. Metab.* 103:2861–69
70. Tracz MJ, Sideras K, Bolona ER, et al. 2006. Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. *J. Clin. Endocrinol. Metab.* 91:2011–16
71. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, et al. 2017. Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. *JAMA Intern. Med.* 177:471–79
72. Bhasin S, Seidman S. 2019. Testosterone treatment of depressive disorders in men: too much smoke, not enough high-quality evidence. *JAMA Psychiatry* 76:9–10
73. Seidman SN, Araujo AB, Roose SP, McKinlay JB. 2001. Testosterone level, androgen receptor polymorphism, and depressive symptoms in middle-aged men. *Biol. Psychiatry* 50:371–76
74. Seidman SN, Spatz E, Rizzo C, Roose SP. 2001. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. *J. Clin. Psychiatry* 62:406–12
75. Pope HG Jr., Amiaz R, Brennan BP, et al. 2010. Parallel-group placebo-controlled trial of testosterone gel in men with major depressive disorder displaying an incomplete response to standard antidepressant treatment. *J. Clin. Psychopharmacol.* 30:126–34
76. Seidman SN, Orr G, Raviv G, et al. 2009. Effects of testosterone replacement in middle-aged men with dysthymia: a randomized, placebo-controlled clinical trial. *J. Clin. Psychopharmacol.* 29:216–21
77. Shores MM, Kivlahan DR, Sadak TI, et al. 2009. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with subthreshold depression (dysthymia or minor depression). *J. Clin. Psychiatry* 70:1009–16
78. Walther A, Breidenstein J, Miller R. 2019. Association of testosterone treatment with alleviation of depressive symptoms in men: a systematic review and meta-analysis. *JAMA Psychiatry* 76:31–40
79. Corona G, Giagulli VA, Maseroli E, et al. 2016. Testosterone supplementation and body composition: results from a meta-analysis of observational studies. *J. Endocrinol. Investig.* 39:967–81
80. Woodhouse LJ, Gupta N, Bhasin M, et al. 2004. Dose-dependent effects of testosterone on regional adipose tissue distribution in healthy young men. *J. Clin. Endocrinol. Metab.* 89:718–26
81. Yialamas MA, Dwyer AA, Hanley E, et al. 2007. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. *J. Clin. Endocrinol. Metab.* 92:4254–59
82. Jones TH, Arver S, Behre HM, et al. 2011. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care* 34:828–37
83. Hua JT, Hildreth KL, Pelak VS. 2016. Effects of testosterone therapy on cognitive function in aging: a systematic review. *Cogn. Behav. Neurol.* 29:122–38

84. Cherrier MM, Craft S, Matsumoto AH. 2003. Cognitive changes associated with supplementation of testosterone or dihydrotestosterone in mildly hypogonadal men: a preliminary report. *J. Androl.* 24:568–76
85. Lu PH, Masterman DA, Mulnard R, et al. 2006. Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. *Arch. Neurol.* 63:177–85
86. Kathrins M, Doersch K, Nimeh T, et al. 2016. The relationship between testosterone-replacement therapy and lower urinary tract symptoms: a systematic review. *Urology* 88:22–32
87. Kohn TP, Mata DA, Ramasamy R, Lipshultz LI. 2016. Effects of testosterone replacement therapy on lower urinary tract symptoms: a systematic review and meta-analysis. *Eur. Urol.* 69:1083–90
88. Liverman CT, Blazer DG. 2004. *Testosterone and Aging: Clinical Research Directions*, ed. CT Liverman, DG Blazer. Washington, DC: Inst. Med.
89. Bhasin S, Singh AB, Mac RP, et al. 2003. Managing the risks of prostate disease during testosterone replacement therapy in older men: recommendations for a standardized monitoring plan. *J. Androl.* 24:299–311
90. Budoff MJ, Ellenberg SS, Lewis CE, et al. 2017. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. *JAMA* 317:708–16
91. Corona G, Rastrelli G, Di Pasquale G, et al. 2018. Testosterone and cardiovascular risk: meta-analysis of interventional studies. *J. Sex. Med.* 15:820–38
92. Finkle WD, Greenland S, Ridgeway GK, et al. 2014. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLOS ONE* 9:e85805
93. Onasanya O, Iyer G, Lucas E, et al. 2016. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol.* 4:943–56
94. Shores MM, Smith NL, Forsberg CW, et al. 2012. Testosterone treatment and mortality in men with low testosterone levels. *J. Clin. Endocrinol. Metab.* 97:2050–58
95. Vigen R, O'Donnell CI, Baron AE, et al. 2013. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 310:1829–36
96. FDA (Food Drug Adm.). 2014. Citizen petition denial response from FDA CDER to public citizen. **http://www.regulations.gov/document?D=FDA-2014-P-0258-0003**
97. Houghton DE, Alsawas M, Barrioneuvo P, et al. 2018. Testosterone therapy and venous thromboembolism: a systematic review and meta-analysis. *Thromb. Res.* 172:94–103
98. Glueck CJ, Goldenberg N, Wang P. 2018. Testosterone therapy, thrombophilia, venous thromboembolism, and thrombotic events. *J. Clin. Med.* 8:11
99. Ory J, Flannigan R, Lundeen C, et al. 2016. Testosterone therapy in patients with treated and untreated prostate cancer: impact on oncologic outcomes. *J. Urol.* 196:1082–89
100. Cunningham GR, Ellenberg SS, Bhasin S, et al. 2019. Prostate-specific antigen levels during testosterone treatment of hypogonadal older men: data from a controlled trial. *J. Clin. Endocrinol. Metab.* 104:6238–46