Reviews in Endocrine and Metabolic Disorders
https://doi.org/10.1007/s11154-022-09766-1

The anabolic applications of androgens in older adults with functional limitations

Arijeet K. Gattu[1,1,2] · Anna L. Goldman[1,2] · Ezgi Caliskan Guzelce[1] · Francesca Galbiati[1] · Shalender Bhasin[1,2,3]

Accepted: 20 October 2022

Abstract
Aging is associated with a progressive decrease in skeletal muscle mass, strength and power and impairment of physical function. Serum testosterone concentrations in men decrease with advancing age due to defects at all levels of the hypothalamic-pituitary–testicular axis. Testosterone administration increases skeletal muscle mass, strength and power in older men with low or low normal testosterone levels, but the effects on performance-based measures of physical function have been inconsistent. Adequately powered randomized trials are needed to determine the long-term safety and efficacy of testosterone in improving physical function and quality of life in older adults with functional limitations.

Keywords Androgens · Testosterone and skeletal muscle · Sarcopenia · Anabolic effect of androgens

1 Introduction

The remarkable increase in average life expectancy across the globe from the low 30 s during most of the nineteenth century to 72.6 years in 2019, largely as a result of improved sanitation, clean water supply, immunization, and treatment of infectious diseases, has focused attention on the high prevalence of functional limitations and physical disabilities associated with old age. Advancing age is associated with a slow but progressive loss of skeletal muscle mass and muscle strength, and impairment of physical function [1–3]. Muscle power (the rate of force generation) and muscle endurance also decline after age 50 years [4, 5]. Although the loss of skeletal muscle mass is associated with atrophy and loss of both type I and type II muscle fibers, there is disproportionately greater loss of type II fast-twitch muscle fibers required for the generation of muscle power than type 1 slow-twitch muscle fibers [6–8]. The aerobic capacity declines 3 to 6% per decade in young adults but at a much faster rate in older adults, declining by as much as 20% per decade after age 70. Aging also is associated with a dynamic redistribution of body fat; a loss of subcutaneous fat and accumulation of fat in ectopic locations such as the visceral and the inter and intra-myocellular fat compartments contributes to increased risk of metabolic disorders.

The pathophysiology of age-related loss of skeletal muscle mass and aerobic capacity is multifactorial: a decrease in muscle proteins, including myosin heavy chain and mitochondrial proteins [3], age-related decline in anabolic hormones (testosterone, growth hormone and IGF-1), inflammation and oxidative stress, accumulation of mitochondrial mutations and mitochondrial dysfunction, genomic instability, telomere attrition, loss of proteostasis, altered nutrient sensing, and cellular and stem cell senescence contribute to the loss of muscle mass and strength [9]. The age-related loss of muscle mass, strength and power, and impaired physical function are associated with an increased risk of physical disability, falls, fractures, metabolic disorders, diminished capacity to live independently in the community, and increased health care resource utilization. Thus, the development of interventions to prevent and treat age-related impairment of physical function has emerged as a public health imperative.

Among the anabolic interventions that are being investigated for the prevention and treatment of age-related loss of skeletal muscle mass and physical function, androgens,

✉ Shalender Bhasin
sbhasin@bwh.harvard.edu

[1] Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, RFB-2, Boston, MA 02115, USA

[2] Brigham and Women's Hospital, Research Program in Men's Health: Aging and Metabolism, Boston, MA, USA

[3] Boston Claude D. Pepper Older Americans Independence Center, Boston, MA, USA

Published online: 10 November 2022

especially testosterone, are among the leading candidates. The potential application of testosterone as an anabolic drug to prevent and treat the impairment of muscle performance and physical function associated with aging and chronic diseases is based on the hypotheses that 1, circulating testosterone levels decline with advancing age and contribute to the loss of skeletal muscle mass and performance; 2, that testosterone administration increases muscle mass, strength and physical function in older adults; and 3, that testosterone treatment of older men is safe. This review offers a critical appraisal of each of these hypotheses.

2 Age-related decline in serum testosterone levels

Many cross-sectional as well as longitudinal studies agree that serum total testosterone levels decline with advancing age. As sex hormone binding globulin levels increase with advancing age, the free testosterone levels decline to a greater degree than total testosterone levels. The rate of age-related decline in serum total and free testosterone levels is modulated by genetics, adiposity, weight gain, co-morbid conditions, medications, and physical activity. Weight gain and chronic diseases are associated with an accelerated decline in testosterone levels. Recent studies using liquid chromatography tandem mass spectrometry-based assays find that 10–15% of older men > 65 years have low total testosterone levels [10–13]. In the European male Aging Study [10], 3.2 to 5.1% of men, 40 to 70 years, had serum testosterone level < 231 ng/dL (< 8 nmol/L) as well as one or more sexual symptoms. Age-related decline in testosterone levels is primarily a consequence of decreased rates of testicular testosterone production due to defects at all levels of the hypothalamic-pituitary–testicular axis. In addition, there are disturbances of the feedback and feed-forward relationships between testosterone and LH secretion (See Anawalt & Matsumoto chapter in this issue).

In epidemiologic studies, low bioavailable or free testosterone levels have been associated with low appendicular skeletal muscle mass, reduced strength of the upper as well as lower extremity muscles, impaired performance in self-reported as well as performance-based measures of physical function, and increased risk of mobility limitation and the frailty syndrome. Low testosterone levels are also associated with increased risk of falls and bone fractures in older men; bioavailable and estradiol levels are more robustly associated with fracture risk than total testosterone levels [7, 14]. Low testosterone levels are associated with increased prevalence and progression of the frailty syndrome in older men [15, 16].

3 Evidence of the anabolic effects of testosterone

Administration of testosterone and other androgens increases fat free mass, muscle size, and maximal voluntary muscle strength in men with hypogonadism, healthy young and older men, women, and in adults with chronic diseases such as those associated with chronic obstructive lung disease, HIV-associated weight loss, and end stage renal disease [17–23]. The anabolic effects of testosterone on muscle mass and maximal voluntary strength exhibit a linear dose response [18–20]. Testosterone-induced gains in muscle mass and strength correlate positively with the administered dose and serum testosterone levels both in the physiological and supraphysiological ranges [18–20]. In meta-analyses of randomized trials, replacement doses of testosterone in men with hypogonadism have been associated with an average 1.5 kg increase in lean body mass and an average 2 to 2.5 kg loss of whole-body fat mass. Testosterone-induced increase in fat-free mass was greater in trials that used intramuscular injections of testosterone esters than in those that used transdermal gels likely due to the higher dose and higher serum testosterone levels attained with intramuscular injections of testosterone esters compared with transdermal testosterone formulations. The anabolic effects of testosterone on fat-free mass and maximal voluntary strength are augmented by resistance exercise training and by concomitant administration of recombinant human growth hormone [19, 20]. However, in a randomized trial, increasing the daily protein intake from 0.8 g/kg/day to 1.3 g/kg/day did not augment the testosterone-induced gains in fat-free mass or muscle strength in community-dwelling older adults with mobility limitation [24].

Testosterone effects on muscle performance are domain-specific: testosterone administration increases maximal voluntary strength and leg power but does not affect muscle fatigability or specific force [19]. Thus, the gains in muscle strength during testosterone administration are proportional to the increase in muscle mass and testosterone does not improve the contractile properties of the skeletal muscle, unlike resistance exercise training that increases the specific force of the skeletal muscle.

4 Randomized trials of testosterone in older adults

Randomized trials in community-living, medically stable older men with low or low normal testosterone levels have reported that testosterone treatment improves lean body

mass, muscle strength, stair climbing power and speed compared to placebo [18, 25–32]. Testosterone treatment also attenuates the age-related reduction in aerobic capacity [33]. Similar improvements have also been found with testosterone treatment of older men with mobility limitation and low or low normal testosterone levels. Testosterone treatment has not consistently improved performance-based measures of physical function, such as the 6-min walking distance or sit to stand time (Fig. 1).

The Testosterone Trials (TTrials) were a set of 7 coordinated randomized, placebo-controlled trials that were funded by the National Institute on Aging to determine the efficacy of testosterone treatment, relative to placebo, in older men with sexual dysfunction, mobility limitation, and/ or low vitality and unequivocally low testosterone levels [21]. The participants were older men, 65 years or older, with an average of two early morning, fasting testosterone levels < 275 ng/dL, and sexual dysfunction, physical dysfunction, and/ or low vitality. Eligible men were randomized to receive either placebo gel or 1% testosterone gel for one year to raise serum testosterone levels into the mid-range for healthy young men (400 to 700 ng/dL). The Physical Function Trial (PFT) of the TTrials determined testosterone's effects on mobility, self-reported physical function, falls, and patient global impression-of-change (PGIC) in older men with self-reported mobility limitation and walking speed < 1.2 m/sec [34]. Primary outcome was Increase in 6-min walking distance (6MWD) of ≥ 50 m; secondary outcomes included absolute increase in 6-min walking distance, physical component of Short Form-36 (PF10), and falls. The 6MWD improved significantly more in the testosterone group than in the placebo group among all men in TTrials, but not in those who were enrolled in the PFT [24]. Self-reported function assessed using the Physical Function component of the MOS SF-36 (PF10) improved more in testosterone than in placebo group in all men in TTrials as well as in men enrolled in the Physical Function Trial. Men reporting mobility limitation showed significantly greater improvement in 6MWD and in PF10 than placebo-treated men. A greater proportion of men allocated to the testosterone arm of the trial reported that they felt that their walking ability had improved than that assigned to the placebo arm.

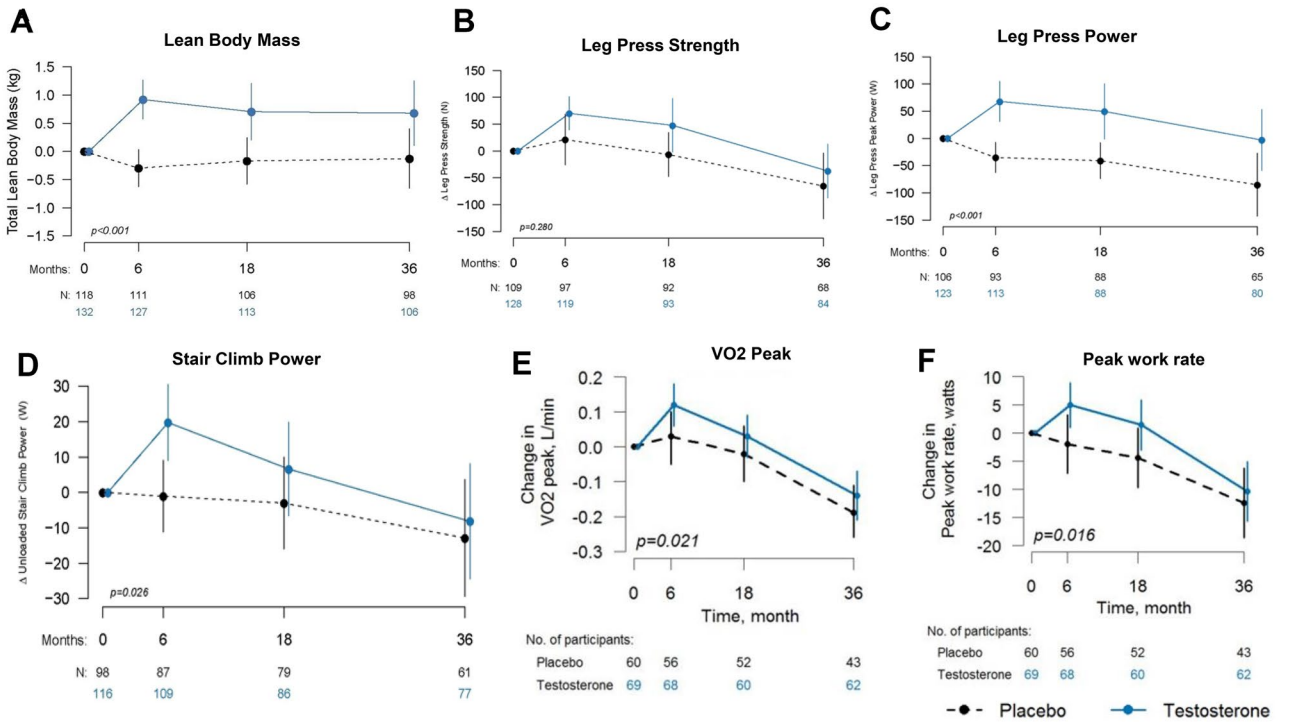


Fig. 1 Panels **A**: Long term effect of testosterone supplementation on lean body mass. Mean changes from baseline for lean body mass in testosterone-treated (blue line) older men compared to placebo(black). Data points represent mean values at each measurement period. Panel **B**, **C** and **D**: Changes in leg press strength, leg press power and stair climb power. Results represent change in mean maximal voluntary strength from baseline for each visit for men randomly assigned to testosterone (blue) or placebo (black) arms. Error bars are 95% CIs. P values are provided from linear mixed-model regression controlling for baseline values and age category. Panels **E** and **F**: Effect of testosterone on aerobic capacity of older men. Data represent mean changes from baseline and error bars are 95% CI in VO2peak (L/min) and in peak work rate in testosterone(blue) and placebo(black). P values indicate the overall effect of the testosterone intervention over time. Reproduced with permission from: Traustadóttir et al., J Clin Endocrinol Metab. 2018;103(8):2861-2869 and Storer et al., J Clin Endocrinol Metab. 2017; 102(2): 583–593

Fall frequency did not differ between groups. Changes in the 6MWD in the testosterone group were associated with changes in circulating testosterone, free testosterone, DHT, and hemoglobin levels (Table 1).

5 Testosterone's effects in adults with chronic diseases

Even with the wide availability of highly active anti-retroviral therapy, the prevalence of low total and free testosterone levels has remained high in men infected with HIV [35–37]. Men with HIV-infection have higher rates of testosterone treatment initiation than non-infected men [37–39]. In randomized, placebo-controlled trials in HIV-infected men with weight loss, testosterone treatment for 3 to 6 months has been associated with greater gains in lean body mass, body weight, and maximal voluntary strength compared with placebo [20, 40–44]. Testosterone treatment also has been reported to improve depression indices and fatigue, but not overall quality of life. Testosterone treatment has no significant effect on CD4 + or CD8 + T lymphocyte counts or HIV copy number and the changes in PSA, HDL cholesterol, and adverse event rates have not differed significantly between the placebo and testosterone groups [38–44]. Thus, short-term [3–6] testosterone treatment in HIV-infected men with low testosterone levels and weight loss is safe and can modestly increase body weight and lean body mass. The heterogeneity of eligibility criteria, testosterone formulations and doses, treatment duration, and outcome ascertainment among trials reduces the strength of the evidentiary base. Testosterone's effects on physical function, risk of disability, and long-term safety in HIV-infected men remain unclear.

Skeletal muscle dysfunction and exercise intolerance are common in patients with chronic obstructive pulmonary disease [22]. The pathophysiologic factors that contribute to skeletal muscle dysfunction in COPD include chronic hypoxia, disuse atrophy, malnutrition, chronic inflammation, corticosteroid use, and low levels of anabolic hormones including testosterone. In a randomized placebo-controlled trial [45], older men with COPD and low testosterone levels were randomly assigned to placebo injections alone, weekly testosterone enanthate 100 mg IM weekly, placebo injections plus resistance training, or testosterone enanthate plus resistance training. Testosterone treatment was associated with an average 2.3 kg gain in lean body mass and 17% increase in leg press strength; the combined regimen of testosterone plus resistance exercise training was associated with greater gains in lean body mass (average gain 3.3 kg) and leg press strength (average gain 27%) than either intervention alone. Other androgenic steroids with and without nutritional supplementation have also been reported to increase lean body mass in patients with COPD [46, 47]. Further studies are needed to determine whether testosterone supplementation can improve physical function, reduce exercise intolerance and promote rehabilitation of adults with COPD.

Glucocorticoid use is common among adults with bronchial asthma, COPD, and in some chronic inflammatory conditions and associated with muscle atrophy and a high frequency of low testosterone levels, muscle atrophy, and bone loss. Testosterone treatment of men receiving glucocorticoid treatment has been shown in randomized trials to increase lean body mass, reduce fat mass, and increase in bone mineral density at the lumbar spine compared with placebo [48, 49].

A paucity of robust evidence of testosterone's efficacy in improving physical function and its long-term prostate and cardiovascular safety precludes a general recommendation to treat functional limitations, sarcopenia or frailty in all older adults with testosterone. An expert panel of the Endocrine Society suggested that clinicians consider short-term testosterone therapy in HIV-infected men with low testosterone levels and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain [50]. In an earlier era, legacy product such as oxandrolone was approved to promote recovery from severe burns [51], and to facilitate growth and development of girls with Turner syndrome. Similarly, nandrolone decanoate was approved for the treatment of anemia in patients with kidney disease. Clinicians may consider offering testosterone on an individualized basis to older men with consistently low testosterone levels, anemia and functional limitations after an explicit discussion of the uncertainty of long-term benefits and risks.

6 Safety of long-term testosterone treatment

Testosterone treatment of medically stable and carefully selected participants in randomized trials of medically stable older adults has been associated with a low frequency of adverse events. Erythrocytosis is the most frequent adverse event associated with testosterone treatment in older adults [50, 52]. Additional adverse events include breast tenderness, acne, suppression of spermatogenesis and infertility, breast tenderness, and leg edema (Table 2).

Whether testosterone increases the risk of prostate cancer and cardiovascular events remains unknown and has been the source of much controversy [53]. In epidemiologic studies, testosterone or DHT levels or polymorphisms in the steroid 5 alpha reductase gene have not been associated with prostate cancer risk. [54]. The frequency of prostate cancer events in randomized trials of testosterone in carefully selected older men has been very low [52]. Testosterone treatment does not worsen lower urinary tract symptoms in men who do not

Table 1 A summary of the findings of major randomized trials of testosterone's effects on lean body mass, muscle performance, and physical function in middle-aged and older men

Trial	Eligibility	Eligibility Testosterone Level	Intervention duration	Main Findings
Snyder et al. The TTrials (n = 790); [21]	65 years or older, low sexual desire, fatigue, and/ or mobility limitation	Average of two total testosterone levels < 275 ng/dL	1 year	Testosterone consistently improved self-reported walking ability, modestly improved 6 min walking distance across all TTtrials participants, but did not affect falls
Storer et al. The TEAAM Trial (n = 308); [25]	60 years and older	Total testosterone < 400 ng/dL and/ or free T < 50 pg/mL	3 years	Testosterone improved lean body mass, leg press power, stair climbing power, and aerobic capacity
Travison et al. The TOM Trial (n = 209); [26]	65 years or older, mobility difficulty, SPPB 4 to 9	Total testosterone < 350 ng/dL or free testosterone < 50 pg/mL	6 months	Testosterone improved lean body mass, leg press strength, stair climbing power, and aerobic capacity
Srinivas-Shankar et al. The Frailty Trial (n = 274); [27]	Men > 65 years; with frailty or intermediate frailty	Total testosterone < 340 ng/L, or free testosterone < 83 pg/mL	6 months	Testosterone improved lean body mass and knee extension strength
Emmelot-Vonk et al. (n = 237); [28]	60 to 80 years	Total testosterone < 395 ng/dL	6 months	Testosterone increased lean body mass, but did not affect muscle strength, or physical function measures
Nair et al. (n = 58); [29]	60 or older	Bioavailable testosterone < 103 ng/dL	2 years	Testosterone increased lean body mass but did not affect muscle strength or VO2max
Sheffield-Moore et al. (n = 24); [30]	60 to 85 years	Total testosterone 280 to 500 ng/dL	5 months	Monthly as well as weekly testosterone treatment increased lean body mass and muscle strength
Page et al. (n = 70); [31]	65 and older;	Total testosterone < 350 ng/dL	3 years	Testosterone increased lean body mass, hand grip strength, and physical function measures
Borst et al. (n = 60); [32]	60 and older	Total testosterone < 300 ng/dL	8 weeks	Testosterone increased fat-free mass and strength in upper and lower extremity muscle groups

Legend: To convert total testosterone from ng/dL to SI units (nmol/L), divide the total testosterone concentration in ng/dL by 28.85. To convert free testosterone concentration from pg/mL to SI units (pmol/L), divide the free testosterone concentration in pg/mL by 0.2885. Please, note the heterogeneity of testosterone thresholds used to determine eligibility, intervention durations, and outcome measures. Most of the randomized trials included healthy older men with no requirement of functional limitations; only the TTrials and the TOM Trial recruited men with mobility limitation, and the Wu trial recruited men with frailty or intermediate frailty

Table 2 Potential adverse events associated with testosterone treatment in middle-aged and older men

Adverse events for which there is evidence of association
1. Erythrocytosis
2. Acne and oily skin
3. Increased risk of detection of subclinical prostate cancer
4. Growth of metastatic prostate cancer
5. Reduced sperm production and fertility
6. Leg edema
Adverse Events for which there is inconclusive evidence of association
1. Induction or worsening of obstructive sleep apnea
2. Gynecomastia
3. Increased risk of major adverse cardiovascular events
4. Increased risk of prostate cancer
Adverse events for which there is evidence of no significant association
1. Worsening of lower urinary tract symptoms in men who do not have severe lower urinary tract symptoms

Adapted with permission from: Bhasin, S., J. P., Cunningham, G. R., Hayes, F. J., Hodis, H. N., Matsumoto, A. M., Snyder, P. J., Swerdloff, R. S., Wu, F. C., Yialamas, M. A. (2018). Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology and Metabolism, 103(5), 1715–1744

have severe symptoms at baseline [55]. None of the trials has been either long enough or large enough to determine the effects of testosterone treatment on the incidence of prostate cancer. Testosterone treatment of older men with hypogonadism increases PSA levels by an average of ~ 0.4 ng/mL and increases the risk of being referred for a prostate biopsy and thereby the risk of detecting prostate cancer [55].

The long-term effects of testosterone treatment on major adverse cardiovascular events (MACE) remain unknown. In the Testosterone's Effects on Atherosclerosis Progression in Aging Men (The TEAAM Trial) [56], the rates of atherosclerosis progression assessed using common carotid artery intima-media thickness and coronary artery calcium scores using multi-detector computerized tomography did not differ over 3 years of treatment with testosterone or placebo. In the Cardiovascular Trial of the TTrials, the men randomized to the testosterone arm had a significantly greater increase in noncalcified coronary plaque volume, assessed using the CT coronary angiography; the clinical significance of these findings is not clear [57]. An Advisory Panel convened by the US Food and Drug Administration concluded that there was insufficient evidence of a causal relationship between testosterone and adverse cardiovascular outcomes. A large, randomized trial to study the effects of testosterone replacement therapy on the incidence of major adverse cardiovascular events in men 45 to 80 years of age with testosterone deficiency and increased risk for cardiovascular events, is underway (The TRAVERSE Trial, NCT03518034) [58]. The TRAVSERSE Trial also will evaluate the efficacy of testosterone treatment in reducing clinical fractures; the progression from pre-diabetes to diabetes; correcting anemia; and improving sexual activity, sexual desire, and erectile function [58].

7 The mechanisms of testosterone's anabolic effects on the skeletal muscle and physical performance

The mechanisms by which testosterone increases skeletal muscle mass and strength are incompletely understood. Testosterone treatment is associated with dose-related increase in the cross-sectional area of both type 1 and 2 muscle fibers; testosterone does not increase either the number or the relative proportion of type 1 and type 2 muscle fibers. Thus, testosterone-induced increase in skeletal muscle mass is due to muscle fiber hypertrophy and not muscle fiber hyperplasia. Testosterone administration increases the numbers of satellite cells (mesenchymal muscle progenitor cells) and myonuclei in the muscle; however, the myonuclear domain does not change. Testosterone promotes the differentiation of mesenchymal muscle progenitor cells into the myogenic lineage, with upregulation of markers of myogenic differentiation, MyoD and myosin heavy chain type II and reciprocally inhibits their differentiation into adipogenic lineage with downregulation of adipogenic differentiation markers (e.g., PPARg) [59] (Table 3).

Testosterone's effects on the skeletal muscle are mediated through the classical androgen receptor. Liganded androgen receptor undergoes a conformational change and binds to its co-activator beta-catenin, translocates to the nucleus and activates a number of Wnt-target genes, including follistatin [60]. Follistatin blocks the actions of myostatin and activins and plays a vital role in mediating testosterone's effects on myogenic differentiation. In addition, testosterone also promotes myoblast proliferation by regulation of polyamine metabolism. Testosterone upregulates key enzymes in the polyamine pathway, including ornithine decarboxylase 1 (ODC1), the rate limiting enzyme in the polyamine pathway, and S-adenosylmethionine decarboxylase.

Testosterone administration in older men is associated with an increase in the fractional synthesis rate (FSR) of proteins measured by stable isotopes [61]. A similar effect on muscle anabolism was noted with the administration of oxandrolone [62]. The effects of testosterone on muscle protein degradation remain unclear.

Testosterone serves as a prohormone and is converted by the catalytic action of steroid 5 alpha reductase enzymes into 5 alpha dihydrotestosterone which can bind to the androgen receptor and act as an agonist and by CYP19 aromatase into estradiol 17beta which serves as a ligand for estrogen receptor

Table 3 Mechanisms by which testosterone increases skeletal muscle mass

1. Testosterone promotes the differentiation of mesenchymal progenitor cells into the myogenic lineage and inhibits their differentiation into adipogenic lineage by activating Wnt-target genes, including follistatin that blocks signaling through the TGF beta pathway
2. Testosterone induces myoblast proliferation by stimulating polyamine biosynthesis
3. Testosterone stimulates mitochondrial biogenesis and quality
4. Testosterone increases net oxygen delivery to the tissue by increasing hemoglobin and red cell mass; blood flow by its vasodilatory effects; and increasing 2, 3 biphosphoglycerate (BPG) levels thereby shifting the oxygen—hemoglobin dissociation curve

Mechanisms for which the evidence is less strong

1. Testosterone may improve neuromuscular transmission and reduce reaction time by upregulating acetyl cholinesterase
2. Testosterone increases muscle protein synthesis and re-utilization of amino acids

Legend: The mechanisms by which testosterone administration increases muscle mass and performance remain incompletely understood. These potential mechanisms should not be viewed as mutually exclusive; multiple mechanisms may be operative. For example, it is possible that testosterone increases muscle mass by promoting differentiation of muscle progenitor cells into the myogenic lineage, stimulating myoblast proliferation, and increasing muscle protein synthesis. These effects may occur non-contemporaneously and be mediated through testosterone's effects on Wnt signaling pathway and on enzymes in polyamine synthesis. Additionally, testosterone could reduce reaction time through its effects on neuromuscular transmission

alpha. Changes in fat-free mass in response to graded testosterone doses did not differ in men in whom DHT was suppressed by administration of dutasteride, a potent inhibitor of both type 1 and type 2 isoforms of steroid 5alpha reductase from those treated with placebo, indicating that testosterone's conversion to DHT is not obligatory for mediating its effects on skeletal muscle mass and strength. [63] The men with benign prostatic hypertrophy who are treated with a 5-alpha reductase inhibitors, finasteride or dutasteride, do not experience muscle loss. Similarly, individuals with congenital steroid 5-alpha-reductase deficiency have normal muscle development at puberty. Testosterone's effects on whole body- fat appear to require its conversion to estradiol by CYP19 (the aromatase enzyme) [64].

Testosterone also exerts nongenomic effects; it promotes the relaxation of vascular smooth muscle by inhibiting the L-type calcium channels [65]. Testosterone increases blood flow in the coronary arteries as well as the penile arteries [66, 67]. Additionally, testosterone as well as DHT promote the relaxation of the smooth muscle in the bronchi, urinary bladder, and the intestine [68–70]. DHT is more potent than testosterone in inducing smooth muscle relaxation.

Testosterone could also improve physical performance through mechanisms that do not directly involve the muscle. For example, testosterone treatment increases hemoglobin [71] which would be expected to improve aerobic performance. In the TTrials, the improvements in 6-min walking distance was related to increases in hemoglobin levels [72]. Testosterone reduces reaction time in frog hind limb model by its effects on neuromuscular transmission.

8 Selective androgen receptor modulators

Selective androgen receptor modulators are ligands that bind to the androgen receptor and induce tissue-specific signaling through the androgen receptor [72, 73]. The development of a large number of steroidal and nonsteroidal SARMs was motivated by concerns about the potential long-term prostate and cardiovascular risks of testosterone treatment in older men as well as by the unmet need to develop more potent anabolic drugs that do not have adverse effects on prostate and cardiovascular outcomes. Guided by an understanding of structure activity relationship within the steroidal structure of testosterone, many steroidal SARMs, such as nandrolone, oxandrolone, oxymetholone, and fluoxymesterone were developed by structural modifications of the testosterone molecule to modify its androgen receptor (AR) binding affinity, AR stabilization, coactivator recruitment, nuclear translocation, DNA binding affinity, presystemic metabolism in the intestine or the liver, specificity as a substrate for the steroid 5**α** reductase and the aromatase enzymes and its tissue specificity, and metabolic clearance (Fig. 2) [73–78].

The addition of a methyl or ethyl group to the 17α carbon position (as in 17α methyltestosterone) inhibits testosterone's presystemic metabolism of testosterone and renders it orally active [75, 76, 79] Oral 17α alkylated androgens are potentially hepatotoxic; their use to treat hypogonadism is not recommended. The removal of the C19 methyl group in C19 increases the anabolic activity; some 19-nortestosterone (nandrolone) series of compounds are approved for the treatment of anemia and osteoporosis and used as anabolic drugs by recreational body builders and athletes. Alkyl substitutions in the 7 position (e.g., in 7α methyl 19-nortestosterone (MENT) reduce susceptibility for 5α reduction and enhance the compound's anabolic activity. The C2 substitution with an oxygen in oxandrolone increases the stability of the 3-keto group and its anabolic activity, and prevents its aromatization.

The esterification of the 17β hydroxyl group increases the molecule's hydrophobicity (e.g., testosterone enanthate, testosterone cypionate), testosterone undecanoate).

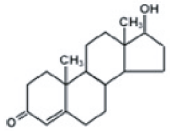
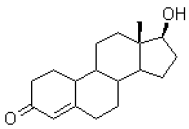
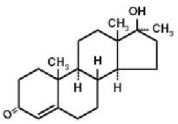
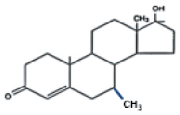
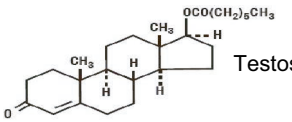
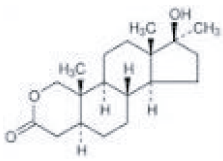
Structural modification	Compound
Unmodified structure of testosterone	 Testosterone
Removing 19 methyl increases anabolic activity.	 19-nortestosterone (nandrolone series)
17-alpha alkyl substitution retards first-pass pre-systemic metabolism: basis of orally active compounds.	 17-alpha methyl testosterone (orally active compounds)
7-alpha alkyl substitutions increase anabolic activity.	 7-alpha alkyl 19-nortestosterone
Esterification of 17-beta hydroxyl group increases hydrophobicity.	 Testosterone enanthate
C2 substitution with oxygen in oxandrolone increases the stability of the 3-keto group and its anabolic activity and prevents its aromatization.	 Oxandrolone

Fig. 2 Structure activity relationship in steroidal selective androgen receptor modulators. Legend. The figure displays the structure of testosterone and modifications of the testosterone molecule that have been used to generate steroidal selective androgen receptor modulators some of which have been approved by the US Food and Drug Administration and used in clinical practice

The longer the side chain, the greater the hydrophobicity of the molecule; these hydrophobic esters when injected intramuscularly in oil are released slowly from the oil depot in the muscle into the aqueous plasma thereby extending the molecule's duration of action. The long duration of action of testosterone esters is almost entirely due to their slow release from the oil depot in the muscle [78].

During the past two decades, many nonsteroidal SARMs have been developed; these compounds do not serve as substrates for CYP19 aromatase or the steroid 5α-reductase, act as full agonists in muscle and bone, but act as partial agonists in prostate and seminal vesicles [73, 74]. The differing interactions of steroidal and nonsteroidal compounds with the AR may at least partially contribute to their unique pharmacologic actions. SARM pharmacophores can be classified into several structural categories including aryl-propionamide, bicyclic hydantoin, quinoline, and tetrahydroquinoline analogs. Structural modifications of aryl propionamide analogs bicalutamide and hydroxyflutamide led to the discovery of the first generation of SARMs [73, 74]. Many nonsteroidal compounds have been shown to bind AR with high affinity and demonstrate tissue selectivity in animal models in terms of greater agonist activity in the muscle vs the prostate. Some of the SARMs in development promote both muscle strength and bone mechanical strength.

Several nonsteroidal SARMs (e.g., enobosarm, ligandrin, OPKO-8044) have undergone phase 2 and some even phase 3 trials [73, 80, 81] but none has been approved by the FDA for any indication. These SARMs increase fat-free mass, muscle strength, but have shown inconsistent improvements in physical function and health outcomes. Oral SARMs, as a class, suppress HDL cholesterol levels and some may increase transaminases at higher doses [82].

9 Synthesis and conclusions

There is compelling evidence that testosterone and other androgens increase skeletal muscle mass and maximal muscle strength. Testosterone treatment has also been shown to improve measures of physical function that are strongly associated with muscle strength, such as the stair climbing speed and power. However, changes in other performance-based measures, such as walking speed, with replacement doses of testosterone have been modest and inconsistent across trials. It is possible that neuromuscular adaptations needed to induce physical functional improvements may require concomitant functional exercise training that includes elements of progressive resistance training, endurance training, gait training to improve mobility and reduce the risk of falls, balance training, task specific training to improve ability to perform activities of daily living, and cognitive behavioral training to increase adherence with exercise regimens. Larger adequately powered randomized trials of longer duration are needed to determine whether testosterone treatment of older men with functional limitations, when administered in conjunction with a multi-dimensional functional exercise training, can safely improve physical function and meaningfully improve how a person *"functions and feels"*.

Author contribution AG, ALG, and SB wrote the first draft; all co-authors reviewed the article and revisions, and provided critical feedback.

Declarations

Financial or non-financial interests SB reports receiving research grants from NIA, NICHD-NCMRR, NINR, PCORI, AbbVie, MIB, FPT, and Transition Therapeutics, and consulting fees from Aditum and OPKO.

Ethical approval Ethical approval was not needed since this is a review article.

Informed consent Not applicable as no human subjects were involved in writing this review article.

Conflict of interest No conflict of interest.

References

1. Jin L, Walters WA, Handelsman J. The effects of chronic high dose androgen or estrogen treatment on the human prostate. J Clin Endocrinol Metab. 1996;81(12):4290–5.
2. Dutta C, Hadley E. The significance of sarcopenia in old age. J Gerontol Series A Biol Sci Med Sci. 1995;50 Spec No(Special), 1–4.
3. Proctor D, Balagopal P, Nair KS. Age-related Sarcopenia in humans is associated with reduced synthetic rates of specific muscle proteins. J Nutr. 1998;128(2):351S–355S.
4. Bassey EJ, Fiatarone M, Oneill E, Kelly M, Evans W, Lipsitz L. Leg extensor power and functional performance in very old men and women. Clin Sci. 1992;82(3):321–7.
5. Rantanen T, Avela J. Leg Extension Power and Walking Speed in Very Old People Living Independently. J Gerontol Series A, Biol Sci Med Sci. 1997;52A(4):M225–31.
6. Frontera WR, Hughes VA, Lutz KJ, Evans WJ. A cross-sectional study of muscle strength and mass in 45- to 78-yr-old men and women. J Appl Physiol. 1991;71(2):644–50.
7. Skelton DS, Greig CA, Davies JM, Young A. Strength, Power and Related Functional Ability of Healthy People Aged 65–89 Years. Age Ageing. 1994;23(5):371–7.
8. Krasnoff BJ, Basaria S, Pencina MJ, Jasuja GK, Vasan RS, Ulloor J, Zhang A, Coviello A, Kelly-Hayes M, D'Agostino RB, Wolf PA, Bhasin S, Murabito JM. Free Testosterone Levels Are Associated with Mobility Limitation and Physical Performance in Community-Dwelling Men: The Framingham Offspring Study. J Clin Endocrinol Metab. 2010;95(6):2790–9.
9. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The Hallmarks of Aging. Cell. 2013;153(6):1194–217.
10. Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Lean ME, Pendleton N, Punab M, Boonen S, Vanderschueren D, Labrie F, Huhtaniemi IT, EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123–35.
11. Bhasin S, Pencina M, Jasuja GK, Travison TG, Coviello A, Orwoll E, Wang PY, Nielson C, Wu F, Tajar A, Labrie F, Vesper H, Zhang A, Ulloor J, Singh R, D'Agostino R, Vasan RS. 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. 2011;96(8):2430–9.
12. Orwoll E, Lambert LC, Marshall LM, Phipps K, Blank J, Barrett-Connor E, Cauley J, Ensrud K, Cummings S. Testosterone and Estradiol among Older Men. J Clin Endocrinol Metab. 2006;91(4):1336–44.
13. Travison TG, Vesper HW, Orwoll E, Wu F, Kaufman JM, Wang Y, Lapauw B, Fiers T, Matsumoto AM, Bhasin S. Harmonized Reference Ranges for Circulating Testosterone Levels in Men of Four Cohort Studies in the United States and Europe. J Clin Endocrinol Metab. 2017;102(4):1161–73.
14. Orwoll E, Lambert LC, Marshall LM, Blank J, Barrett-Connor E, Cauley J, Ensrud K, Cummings SR. Endogenous Testosterone Levels, Physical Performance, and Fall Risk in Older Men. Arch Intern Med. 2006;166(19):2124–31.
15. Travison TG, Nguyen A-H, Naganathan V, Stanaway FF, Blyth FM, Cumming RG, Le Couteur DG, Sambrook PN, Handelsman DJ. Changes in Reproductive Hormone Concentrations Predict the Prevalence and Progression of the Frailty Syndrome in Older Men: The Concord Health and Ageing in Men Project. J Clin Endocrinol Metab. 2011;96(8):2464–74.
16. Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA, Chubb SAP, Yeap BB. Low Free Testosterone Predicts Frailty in Older Men: The Health in Men Study. J Clin Endocrinol Metab. 2010;95(7):3165–72.
17. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Chen X, Yarasheski KE, Magliano L, Dzekov C, Dzekov J, Bross R, Phillips J, Sinha-Hikim I, Shen R, Storer TW. Testosterone dose-response relationships in healthy young men. Am J Physiol - Endocrinol Metab. 2001;281(6):1172–81.
18. Storer TW, Magliano L, Woodhouse L, Lee ML, Dzekov C, Dzekov J, Casaburi R, Bhasin S. Testosterone Dose-Dependently Increases Maximal Voluntary Strength and Leg Power but Does Not Affect Fatigability or Specific Tension. J Clin Endocrinol Metab. 2003;88(4):1478–85.
19. Bhasin S, Storer TW, Berman N, Callegari C, Clevenger B, Phillips J, Bunnell TJ, Tricker R, Shirazi A, Casaburi R. The Effects of Supraphysiologic Doses of Testosterone on Muscle Size and Strength in Normal Men. N Engl J Med. 1996;335(1):1–7.

20. Bhasin S, Storer TW, Javanbakht M, Berman N, Yarasheski KE, Phillips J, Dike M, Sinha-Hikim I, Shen R, Hays RD, Beall G. Testosterone Replacement and Resistance Exercise in HIV-Infected Men With Weight Loss and Low Testosterone Levels. JAMA. 2000;283(6):763–70.
21. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, Gill TM, Barrett-Connor E, Swerdloff RS, Wang C, Ensrud KE, Lewis CE, Farrar JT, Cella D, Rosen RC, Pahor M, Crandall JP, Molitch ME, Cifelli D, Dougar D, Fluharty L, Resnick SM, Storer TW, Anton S, Basaria S, Diem SJ, Hou X, Mohler ER 3rd, Parsons JK, Wenger NK, Zeldow B, Landis JR, Ellenberg SS. Testosterone Trials Investigators. Effects of Testosterone Treatment in Older Men. N Engl J Med. 2016;374(7):611–24.
22. Jaitovich A, Barreiro E. Skeletal Muscle Dysfunction in Chronic Obstructive Pulmonary Disease What We Know and Can Do for Our Patients. Am J Respir Crit Care Med. 2018;198(2):175–86.
23. Johansen KL, Mulligan K, Schambelan M. Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. JAMA. 1999;281(14):1275–81.
24. Bhasin S, Apovian CM, Travison TG, Pencina K, Moore LL, Huang G, Campbell WW, Li Z, Howland AS, Chen R, Knapp PE, Singer MR, Shah M, Secinaro K, Eder RV, Hally K, Schram H, Bearup R, Beleva YM, Basaria S. Effect of Protein Intake on Lean Body Mass in Functionally Limited Older Men: A Randomized Clinical Trial. JAMA Intern Med. 2018;178(4):530–41.
25. Storer T, Basaria S, Traustadottir T, Harman SM, Pencina K, Li Z, Travison TG, Miciek R, Tsitouras P, Hally K, Huang G, Bhasin S. Effects of Testosterone Supplementation for 3-Years on Muscle Performance and Physical Function in Older Men. J Clin Endocrinol Metab. 2017;102(2):583–93.
26. Travison TG, Basaria S, Storer TW, Jette AM, Miciek R, Farwell WR, Choong K, Lakshman K, Mazer NA, Coviello AD, Knapp PE, Ulloor J, Zhang A, Brooks B, Nguyen A-H, Eder R, LeBrasseur N, Elmi A, Appleman E, Brierley L, Bhasin G, Bhatia A, Lazzari A, Davis S, Ni P, Collins L, Bhasin S. Clinical Meaningfulness of the Changes in Muscle Performance and Physical Function Associated With Testosterone Administration in Older Men With Mobility Limitation. J Gerontol Series A Biol Sci Med Sci. 2011;66A(10):1090–9.
27. Srinivas-Shankar U, Roberts SA, Connolly MJ, O'Connell MDL, Adams JE, Oldham JA, Wu FCW. Effects of Testosterone on Muscle Strength, Physical Function, Body Composition, and Quality of Life in Intermediate-Frail and Frail Elderly Men: A Randomized, Double-Blind, Placebo-Controlled Study. J Clin Endocrinol Metab. 2010;95(2):639–50.
28. Emmelot-Vonk MH, Verhaar HJJ, Nakhai Pour HR, Aleman A, Lock TMTW, Bosch JLHR, Grobbee DE, van der Schouw YT. Effect of Testosterone Supplementation on Functional Mobility, Cognition, and Other Parameters in Older Men : A Randomized Controlled Trial. JAMA, J Am Med Assoc. 2008;299(1):39–52.
29. Nair K, Rizza RA, O'Brien P, Dhatariya K, Short KR, Nehra A, Vittone JL, Klee GG, Basu A, Basu R, Cobelli C, Toffolo G, Man CD, Tindall DJ, Melton LJ, Smith GE, Khosla S, Jensen MD. DHEA in Elderly Women and DHEA or Testosterone in Elderly Men. N Engl J Med. 2006;355(16):1647–59.
30. Sheffield-Moore M, Dillon EL, Casperson SL, Gilkison CR, Paddon-Jones D, Durham WJ, Grady JJ, Urban RJ. A Randomized Pilot Study of Monthly Cycled Testosterone Replacement or Continuous Testosterone Replacement Versus Placebo in Older Men. J Clin Endocrinol Metab. 2011;96(11):E1831–7.
31. Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL. Exogenous Testosterone (T) Alone or with Finasteride Increases Physical Performance, Grip Strength, and Lean Body Mass in Older Men with Low Serum T. J Clin Endocrinol Metab. 2005;90(3):1502–10.
32. Borst SE, Yarrow JF, Conover CF, Nseyo U, Meuleman JR, Lipinska JA, Braith RW, Beck DT, Martin JS, Morrow M, Roessner S, Beggs LA, McCoy SC, Cannady DF, Shuster JJ. Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. Am J Physiol Endocrinol Metab. 2014;306(4):E433–42.
33. Traustadóttir T, Harman SM, Tsitouras P, Pencina KM, Li Z, Travison TG, Eder R, Miciek R, McKinnon J, Woodbury E, Basaria S, Bhasin S, Storer TW. Long-Term Testosterone Supplementation in Older Men Attenuates Age-Related Decline in Aerobic Capacity. J Clin Endocrinol Metab. 2018;103(8):2861–9.
34. Bhasin S, Ellenberg SS, Storer TW, Basaria S, Pahor M, Stephens-Shields AJ, Cauley JA, Ensrud KE, Farrar JT, Cella D, Matsumoto AM, Cunningham GR, Swerdloff RS, Wang C, Lewis CE, Molitch ME, Barrett-Connor E, Crandall JP, Hou X, Gill TM. Effect of testosterone replacement on measures of mobility in older men with mobility limitation and low testosterone concentrations: secondary analyses of the Testosterone Trials. Lancet Diabetes Endocrinol. 2018;6(11):879–90.
35. Santi D, Spaggiari G, Vena W, Pizzocaro A, Maggi M, Rochira V, Corona G. The Prevalence of Hypogonadism and the Effectiveness of Androgen Administration on Body Composition in HIV-Infected Men: A Meta-Analysis. Cells (Basel, Switzerland). 2021;10(8):2067.
36. Monroe AK, Dobs AS, Xu X, Palella FJ, Kingsley LA, Witt MD, Brown TT. Sex Hormones, Insulin Resistance, and Diabetes Mellitus Among Men With or at Risk for HIV Infection. JAIDS- J Acquir Immune Defic Syndr. 2011;58(2):173–80.
37. Wunder DM, Bersinger NA, Fux CA, Mueller NJ, Hirschel B, Cavassini M, Elzi L, Schmid P, Bernasconi E, Mueller B, Furrer H. Hypogonadism in HIV-1-infected men is common and does not resolve during antiretroviral therapy. Antivir Ther. 2007;12(2):261–5.
38. Jasuja R, Bhasin S, Rose AJ, Reisman JI, Skolnik A, Berlowitz DR, Gifford AL. Use of testosterone in men infected with human immunodeficiency virus in the veterans healthcare system. AIDS Care. 2018;30(10):1207–14.
39. Haberlen SA, Jacobson L, Palella F, Dobs A, Plankey M, Lake J, Kingsley L, Stall R, Post W, Brown T. To T or not to T: Differences in Testosterone Use and Discontinuation by HIV Serostatus among Men who Have Sex with Men. HIV Med. 2018;19(9):634–44.
40. Kong A, Edmonds P. Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis. Lancet Infect Dis. 2002;2(11):692–9.
41. Choi GPB, Storer TW, Calof OM, Woodhouse L, Singh AB, Padero C, Mac RP, Sinha-Hikim I, Shen R, Dzekov J, Dzekov C, Kushnir MM, Rockwood AL, Meikle AW, Lee ML, Hays RD, Bhasin S. Effects of Testosterone Replacement in Human Immunodeficiency Virus-Infected Women with Weight Loss. J Clin Endocrinol Metab. 2005;90(3):1531–41.
42. Dolan WS, Aliabadi N, Sullivan MP, Basgoz N, Davis B, Grinspoon S. Effects of Testosterone Administration in Human Immunodeficiency Virus-Infected Women With Low Weight: A Randomized Placebo-Controlled Study. Arch Intern Med. 2004;164(8):897–904.
43. Grinspoon S, Corcoran C, Askari H, Schoenfeld D, Wolf L, Burrows B, Walsh M, Hayden D, Parlman K, Anderson E, Basgoz N, Klibanski A. Effects of androgen administration in men with the AIDS wasting syndrome - A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1998;129(1):18–26.
44. Strawford A, Barbieri T, Van Loan M, Parks E, Catlin D, Barton N, Neese R, Christiansen M, King J, Hellerstein MK. Resistance Exercise and Supraphysiologic Androgen Therapy in Eugonadal Men With HIV-Related Weight Loss: A Randomized Controlled Trial. JAMA, J Am Med Assoc. 1999;281(14):1282–90.
45. Casaburi R, Bhasin S, Cosentino L, Porszasz J, Somfay A, Lewis MI, Fournier M, Storer TW. Effects of Testosterone and Resistance Training in Men with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2004;170(8):870–8.

46. Yeh DB, Kramer T. Reversal of COPD-Associated Weight Loss Using the Anabolic Agent Oxandrolone. Chest. 2002;122(2):421–8.
47. Schols AMWJ, Soeters PB, Mostert R, Pluymers RJ, Wounters EFM. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease: a placebo-controlled randomized trial. Am J Respir Crit Care Med. 1995;152(4):1268–74.
48. Crawford LPY, Kean MT, Bleasel JF, Handelsman DJ. Randomized Placebo-Controlled Trial of Androgen Effects on Muscle and Bone in Men Requiring Long-Term Systemic Glucocorticoid Treatment. J Clin Endocrinol Metab. 2003;88(7):3167–76.
49. Reid IR, Wattie DJ, Evans MC, Stapleton JP. Testosterone therapy in glucocorticoid-treated men. Osteoporos Int. 1996;6(S1):274–274.
50. Bhasin BJP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, Snyder PJ, Swerdloff RS, Wu FC, Yialamas MA. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(5):1715–44.
51. Li H, Guo Y, Yang Z, Roy M, Guo Q. The efficacy and safety of oxandrolone treatment for patients with severe burns: A systematic review and meta-analysis. Burns : J Int Soc Burn Injuries. 2016;42(4):717–27.
52. Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, Serrano V, Singh-Ospina N, Rodriguez-Gutierrez R, Salcido-Montenegro A, Benkhadra R, Prokop LJ, Bhasin S, Brito JP. 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;103(5):1745–54.
53. Bhasin S, Valderrábano RJ, Gagliano-Jucá T. Age-Related Changes in the Male Reproductive System. In KR Feingold (Eds.) et. al., Endotext. 2022. MDText.com, Inc.
54. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst. 2008;100(3):170–83.
55. Bhasin S, Singh AB, Mac RP, Carter B, Lee MI, Cunningham GR. Managing the Risks of Prostate Disease During Testosterone Replacement Therapy in Older Men: Recommendations for a Standardized Monitoring Plan. J Androl. 2003;24(3):299–311.
56. Basaria S, Harman SM, Travison TG, Hodis H, Tsitouras P, Budoff M, Pencina KM, Vita J, Dzekov C, Mazer NA, Coviello AD, Knapp PE, Hally K, Pinjic E, Yan M, Storer TW, Bhasin S. 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, J Am Med Assoc. 2015;314(6):570–81.
57. Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER 3rd, Wenger NK, Bhasin S, Barrett-Connor E, Swerdloff RS, Stephens-Shields A, Cauley JA, Crandall JP, Cunningham GR, Ensrud KE, Gill TM, Matsumoto AM, Molitch ME, Nakanishi R, Nezarat N, Matsumoto S, Hou X, Basaria S, Diem SJ, Wang C, Cifelli D, Snyder PJ. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone. JAMA. 2017;317(7):708–16.
58. Bhasin S, Lincoff AM, Basaria S, Bauer DC, Boden WE, Cunningham GR, Davey D, Dubcenco E, Fukumoto S, Garcia M, Granger CB, Kalahasti V, Khera M, Miller MG, Mitchell LM, O'Leary MP, Pencina KM, Snyder PJ, Thompson IM Jr, Travison TG, Wolski K, Nissen SE, TRAVERSE Study Investigators. Effects of long-term testosterone treatment on cardiovascular outcomes in men with hypogonadism: Rationale and design of the TRAVERSE study. Am Heart J. 2022;245:41–50.
59. Singh R, Artaza JN, Taylor WE, Gonzalez-Cadavid NF, Bhasin S. Androgens Stimulate Myogenic Differentiation and Inhibit Adipogenesis in C3H 10T1/2 Pluripotent Cells through an Androgen Receptor-Mediated Pathway. Endocrinology (Philadelphia). 2003;144(11):5081–8.
60. Singh R, Artaza JN, Taylor WE, Braga M, Yuan X, Gonzalez-Cadavid NF, Bhasin S. Testosterone Inhibits Adipogenic Differentiation in 3T3-L1 Cells: Nuclear Translocation of Androgen Receptor Complex with β-Catenin and T-Cell Factor 4 May Bypass Canonical Wnt Signaling to Down-Regulate Adipogenic Transcription Factors. Endocrinology (Philadelphia). 2006;147(1):141–54.
61. Ferrando AA, Sheffield-Moore M, Yeckel CW, Gilkison C, Jiang J, Achacosa A, Lieberman SA, Tipton K, Wolfe RR, Urban RJ. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. Am J Physiol - Endocrinol Metab. 2002;282(3):601–7.
62. Sheffield-Moore M, Urban R, Wolf S, Jiang J, Catlin D, Herndon D, Wolfe R, Ferrando A. Short-term oxandrolone administration stimulates net muscle protein synthesis in young men. J Clin Endocrinol Metab. 1999;84(8):2705–11.
63. Bhasin S, Travison TG, Storer TW, Lakshman K, Kaushik M, Mazer NA, Ngyuen A-H, Davda MN, Jara H, Aakil A, Anderson S, Knapp PE, Hanka S, Mohammed N, Daou P, Miciek R, Ulloor J, Zhang A, Brooks B, Brooks B, Orwoll K, Hede-Brierley L, Eder R, Elmi A, Bhasin G, Collins L, Singh R, Basaria S. Effect of Testosterone Supplementation With and Without a Dual 5α-Reductase Inhibitor on Fat-Free Mass in Men With Suppressed Testosterone Production: A Randomized Controlled Trial. JAMA, J Am Med Assoc. 2012;307(9):931–9.
64. Finkelstein LH, Burnett-Bowie S-AM, Pallais JC, Yu EW, Borges LF, Jones BF, Barry CV, Wulczyn KE, Thomas BJ, Leder BZ. Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men. N Engl J Med. 2013;369(11):1011–22.
65. Scragg JRD, Channer KS, Jones TH, Peers C. Testosterone is a potent inhibitor of L-type Ca(2+) channels. Biochem Biophys Res Commun. 2004;318(2):503–6.
66. English KM, Jones R, Jones T, Morice A, Channer K. Testosterone acts as a coronary vasodilator by a calcium antagonistic action. J Endocrinol Invest. 2002;25(5):455–8.
67. Mills SV, Wiedmeier V. Effects of castration and androgen replacement on the hemodynamics of penile erection in the rat. Biol Reprod. 1994;51(2):234–8.
68. Fernandes VS, Barahona MV, Recio P, Martínez-Sáenz A, Ribeiro AS, Contreras C, Martínez AC, Bustamante S, Carballido J, García-Sacristán A, Prieto D, Hernández M. Mechanisms involved in testosterone-induced relaxation to the pig urinary bladder neck. Steroids. 2012;77(5):394–402.
69. Perusquia M, Stallone JN. Do androgens play a beneficial role in the regulation of vascular tone? Nongenomic vascular effects of testosterone metabolites. Am J Physiol - Heart Circ Physiol. 2010;298(5):1301–7.
70. Montaño LM, Espinoza J, Flores-Soto E, Chávez J, Perusquía M. Androgens are bronchoactive drugs that act by relaxing airway smooth muscle and preventing bronchospasm. J Endocrinol. 2014;222(1):1–13.
71. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of Graded Doses of Testosterone on Erythropoiesis in Healthy Young and Older Men. J Clin Endocrinol Metab. 2008;93(3):914–9.
72. Bhasin S, Ellenberg SS, Storer TW, Basaria S, Pahor M, Cauley JA, Ensrud KE, Farrar JT, Cella D, Matsumoto AM, Cunningham GR, Swerdloff RS, Wang C, Lewis CE, Molitch ME, Barrett-Connor E, Crandall JP, Stephens-Shields AJ, Hou X, Preston P, Cifelli D, Snyder PJ, Gill TM. The Effects of Testosterone Replacement on Self-reported and Performance-based Measures of Mobility in Older Men with Mobility Limitation and Low Testosterone Levels: A Placebo-Controlled Trial. Lancet Diabetes Endocrinol. 2018;6(11):879–90.

73. Bhasin S, Jasuja R. Selective androgen receptor modulators as function promoting therapies. Curr Opin Clin Nutr Metab Care. 2009;12(3):232–40.
74. Narayanan R, Coss CC, Dalton JT. Development of selective androgen receptor modulators (SARMs). Mol Cell Endocrinol. 2018;465(C):134–42.
75. Kicman AT. Pharmacology of anabolic steroids. Br J Pharmacol. 2008;154(3):502–21.
76. Bhasin S, Calof OM, Storer TW, Lee ML, Mazer NA, Jasuja R, Montori VM, Gao W, Dalton JT. Drug Insight: testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. Nat Clin Pract Endocrinol Metab. 2006;2(3):146–59.
77. Fragkaki AG, Angelis YS, Koupparis M, Tsantili-Kakoulidou A, Kokotos G, Georgakopoulos C. Structural characteristics of anabolic androgenic steroids contributing to binding to the androgen receptor and to their anabolic and androgenic activities Applied modifications in the steroidal structure. Steroids. 2009;74(2):172–97.
78. Sokol RZ, Palacios A, Campfield LA, Saul C, Swerdloff RS. Comparison of the kinetics of injectable testosterone in eugonadal and hypogonadal men. Fertil Steril. 1982;37(3):425–30.
79. Hoffman JR, Kraemer WJ, Bhasin S, Storer T, Ratamess NA, Haff GG, Willoughby DS, Rogol AD. Position Stand on Androgen and Human Growth Hormone Use. J Strength Cond Res. 2009;23(5 Suppl):S1–59.
80. Pencina KM, Burnett AL, Storer TW, Guo W, Li Z, Kibel AS, Huang G, Blouin M, Berry DL, Basaria S, Bhasin S. A Selective Androgen Receptor Modulator (OPK-88004) in Prostate Cancer Survivors: A Randomized Trial. J Clin Endocrinol Metab. 2021;106(8):2171–86.
81. Dobs S, Prof Boccia RV, Croot CC, Gabrail NY, Dalton JT, Hancock ML, Johnston MA, Steiner MS. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. Lancet Oncol. 2013;14(4):335–45.
82. Guo W, Pencina KM, Furtado JD, Sacks FM, Vaisar T, Cheng M, Sniderman AD, Page S, Bhasin S. Effect of Selective Androgen Receptor Modulator on Cholesterol Efflux Capacity, Size, and Subspecies of HDL Particles. J Endocrine Soc. 2022;6(8). (In press).