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Supplement Article: Function-Promoting Therapies

Androgens and Selective Androgen Receptor Modulators to Treat Functional Limitations Associated With Aging and Chronic Disease

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Abstract

Testosterone, many steroidal androgens, and nonsteroidal ligands that bind to androgen receptor and exert tissue-specific transcriptional activity (selective androgen receptor modulators [SARMs]) are being developed as function-promoting therapies to treat functional limitations associated with aging and chronic diseases. This narrative review describes preclinical studies, mechanisms, and randomized trials of testosterone, other androgens, and nonsteroidal SARMs. Sex differences in muscle mass and strength and empiric use of anabolic steroids by athletes to increase muscularity and athletic performance provide supportive evidence of testosterone's anabolic effects. In randomized trials, testosterone treatment increases lean body mass, muscle strength, leg power, aerobic capacity, and self-reported mobility. These anabolic effects have been reported in healthy men, hypogonadal men, older men with mobility limitation and chronic diseases, menopausal women, and HIV-infected women with weight loss. Testosterone has not consistently improved walking speed. Testosterone treatment increases volumetric and areal bone mineral density, and estimated bone strength; improves sexual desire, erectile function, and sexual activity; modestly improves depressive symptoms; and corrects unexplained anemia in older men with low testosterone levels. Prior studies have not been of sufficient size or duration to determine testosterone's cardiovascular and prostate safety. The efficacy of testosterone in reducing physical limitations, fractures, falls, progression to diabetes, and correcting late-onset persistent depressive disorder remains to be established. Strategies to translate androgen-induced muscle mass and strength gains into functional improvements are needed. Future studies should evaluate the efficacy of combined administration of testosterone (or a SARM) plus multidimensional functional exercise to induce neuromuscular adaptations required for meaningful functional improvements.

Keywords: Bone mineral density, Depressive symptoms, Functional exercise training, Testosterone

Androgens are 19 carbon steroidal compounds that bind to the androgen receptor (AR) and regulate the development and maintenance of male characteristics in vertebrate animals. Testosterone, 5α dihydrotestosterone, and 11-keto testosterone are potent naturally occurring androgens in humans, whereas δ4 androstenedione and Dehydroepiandrosterone are weak androgens. 11-Keto testosterone is less potent than testosterone and 5α dihydrotestosterone and its role in human physiology, especially in women in whom its concentrations exceed those of 5α dihydrotestosterone, requires further investigation (1). In addition to serving as a potent ligand for AR, testosterone is converted by the catalytic action of CYP19 (aromatase) to 17β estradiol, a ligand for the estrogen receptor.

Testosterone also serves as a precursor for another potent AR ligand, 5α dihydrotestosterone, that can be further reduced in some cell types to 5α-androstane-3α,17β-diol, a modulator of $GABA_A$ receptors and 5α-androstane-3β,17β-diol, a ligand for ERβ (2–7); these metabolites play an important role in mediating testosterone's effects on mood and behavior and Alzheimer's disease neuropathology (2,3).

Selective androgen receptor modulators (SARMs) are ligands that bind to AR and display tissue-specific activation of its transcriptional activity. SARMs fall into 2 broad structural categories—steroidal and nonsteroidal—and can act as AR agonists, partial agonists, or antagonists. Steroidal SARMs are produced by structural modifications of the testosterone molecule that modify their AR binding affinity, coactivator recruitment, nuclear translocation, DNA binding affinity, metabolism, susceptibility to the action of steroid 5α reductase and the aromatase enzymes, tissue specificity, and metabolic clearance (8,9). The understanding of structure–activity relationship in the steroidal structure of the testosterone molecule has enabled the synthesis of a large number of steroidal SARMs, some of which were approved for various indications.

The esterification of the 17β hydroxyl group increases the hydrophobicity of the molecule; these hydrophobic esters when injected in oil are released slowly from the hydrophobic oil depot in the muscle into the aqueous plasma (10). The half-life of testosterone esters in the human plasma is short; their long duration of action is largely due to their slow release from the oil depot in the muscle rather than from slower hydrolysis in plasma. Examples of testosterone esters used in clinical practice include testosterone enanthate, cypionate, and undecanoate.

The addition of an alkyl group (eg, 17α methyltestosterone) to the 17α position inhibits the presystemic metabolism of testosterone, extends its half-life, and renders it orally active (8,9,11). However, orally administered 17α alkylated androgens are potentially hepatotoxic and markedly suppress plasma high density lipoprotein cholesterol, and their use to treat hypogonadism is not recommended.

Removal of the methyl group in the C19 position increases the anabolic activity. The 19-nortestosterone (nandrolone) series of compounds are widely used as anabolic drugs by recreational bodybuilders and athletes and are approved for the treatment of anemia and osteoporosis (8,9,11).

Alkyl substitution in the 7 position increases the anabolic activity and reduces the molecule's susceptibility for 5α reduction. 7α methyl 19-nortestosterone is an example of this class of compounds that have undergone human trials.

The substitution of C2 with an oxygen in oxandrolone increases the stability of the 3-keto group and its anabolic activity, and prevents its aromatization; it also does not serve as a substrate for steroid 5α reductase. Oxandrolone also has a 17**α** methyl group that reduces its presystemic metabolism and renders it orally active. In oxymetholone, 2-hydroxymethylene group provides stability to the 3-keto group and enhances its anabolic activity and the 17**α** methyl group prevents its presystemic metabolism to enable its oral administration.

Evidence of the Anabolic Effects of Androgens

In spite of the well-recognized sex differences in skeletal muscle mass and muscle strength, the empiric experience of athletes and recreational bodybuilders who use androgenic–anabolic steroids to increase muscularity, leanness and athletic performance, and compelling epidemiologic data on the association of circulating testosterone levels with muscle mass and strength, the anabolic effects of androgens remained highly controversial in the academic community until the mid-1990s. Randomized trials published since then have provided clear evidence that supraphysiologic doses of testosterone increase fat-free mass, muscle size, and maximal voluntary strength, and that resistance exercise training augments the anabolic effects of testosterone on fat-free mass and muscle strength (12). Subsequent studies reported that replacement doses of testosterone when administered to men with hypogonadism, healthy older men, and older men with chronic diseases increase fat-free mass, maximal voluntary strength and power, and stair-climbing power (13–17). The anabolic effects of testosterone on muscle mass and strength are related to the administered dose and circulating testosterone levels in young and older men (18–20), and in menopausal women (21). The effects of testosterone on muscle performance are domain specific; testosterone increases maximal voluntary strength and power, but it does not change specific force (22). Thus, testosterone does not improve the contractile properties of the skeletal muscle and the increases in muscle mass induced by testosterone administration are proportional to the increase in muscle mass; in contrast, resistance exercise training improves specific force.

The Mechanisms by Which Testosterone Exerts Its Anabolic Effects on the Skeletal Muscle

Testosterone-induced increase in muscle size is associated with the hypertrophy of both type 1 and type 2 skeletal muscle fibers (23); testosterone does not affect the number or the relative proportion of type 1 and 2 muscle fibers. Several mechanisms have been proposed to explain the testosterone-induced muscle fiber hypertrophy; it is possible that several mechanisms may contribute to the observed increases in skeletal muscle mass and strength.

Testosterone treatment is associated with an increase in the number of muscle satellite cells and myonuclei (24); however, the myonuclear domain (the ratio of muscle fiber cross-sectional area to the myonuclear number per fiber) does not change. Testosterone promotes the differentiation of multipotent muscle progenitor cells into the myogenic lineage and inhibits their differentiation into the adipogenic lineage (25). Testosterone's binding to the AR induces a conformational change in the AR and recruitment of beta-catenin that stabilizes beta-catenin, and the translocation of the complex into the nucleus where it binds to the transcription factor TCF-4 and activates a number of Wnt-target genes including follistatin. In turn, follistatin blocks the action of a number of TGF beta family members such as myostatin and activin, thereby promoting myogenic differentiation (26). Additionally, testosterone also stimulates polyamine synthesis and myoblast proliferation by upregulating ornithine decarboxylase 1 and S-adenosyl methionine decarboxylase (27,28).

Testosterone has also been reported to stimulate fractional muscle protein synthesis and the reutilization of amino acids. The effects of testosterone on muscle protein degradation remain unclear.

Testosterone and other agonists that bind AR have been shown to regulate specific genes within muscle satellite cells and facilitate early proliferation through Pax7 upregulation followed by inducing differentiation of these cells through MyoD-mediated myogenesis which underscores the regenerative capacity of skeletal muscle that is induced with testosterone. Accordingly, in a muscle injury model, the removal of androgens resulted in delayed muscle regeneration

due to reduced satellite cell proliferation and increased inflammation (29).

Testosterone stimulates growth hormone and IGF-1 secretion and upregulates muscle IGF-1 expression levels (30). During the pubertal transition, the combined effects of testosterone, dihydrotestosterone, and growth hormone promote substantial muscle mass accretion in boys. However, testosterone increases muscle mass even in men and mice who have undergone hypophysectomy suggesting that circulating growth hormone and IGF-1 are not essential for mediating testosterone's effects on muscle growth (30). IGF-I signaling plays an important role in mediating testosterone's effects on skeletal muscle progenitor cell growth and differentiation in vitro (30).

Randomized Trials of Testosterone in Healthy Older Adults and Older Adults With Chronic Diseases

Several randomized trials have investigated the effects of testosterone treatment on body composition, muscle performance, and physical function in healthy older adults and in middle-aged and older adults with chronic diseases. In community living, healthy older men with low or low normal testosterone levels, testosterone treatment increases lean body mass and maximal voluntary strength and reduces whole body fat mass (16,17,31,32) (Table 1). Depending on the testosterone dose, formulation, treatment duration, and the study population, the increases in lean body mass have averaged about 1.5–2.0 kg and the decreases in fat mass have averaged about 1–2 kg (8). The performance-based measures of physical function have generally not shown consistent improvements in response to testosterone treatment (16,17,31,32). The measures of physical function that are closely related to muscle strength and power, such as stair-climbing speed and power, have shown greater improvements in response to testosterone treatment compared to placebo treatment (17). However, changes in walking speed during testosterone treatment have been relatively small, inconsistent, and highly variable among trials (32). Testosterone also attenuates the age-related decline in aerobic capacity (33,34).

Effects of Testosterone Treatment in Older Men With Functional Limitations

Only a few testosterone trials have been conducted in older men with mobility limitation, frailty, and pre-frailty (35–40). In a randomized trial of men with pre-frailty or frailty (39), the administration of transdermal testosterone gel daily for 6 months was associated with greater improvements in lean body mass, knee extension peak torque, and sexual symptoms compared to placebo gel (39) (Table 1). Performance-based measures of physical function did not differ significantly between groups overall, but these measures showed improvement in the subgroup of older men with frailty (39). In Testosterone in Older Men Trial, men aged 65 years or older with mobility limitation were randomized to receive either placebo gel or 1% transdermal testosterone gel daily for 6 months (36,37). The trial was stopped early due to an increased number of cardiovascular events in the testosterone arm compared to the placebo arm (37). The leg-press strength, chest-press strength and power, and loaded stair-climbing speed and power improved significantly more in men assigned to testosterone gel than in men assigned to the placebo gel. A greater proportion of men randomized to the testosterone arm of the trial improved their leg-press and chest-press strength and stair-climbing speed more than the minimal clinically important difference for these measures than the men randomized to the placebo arm (36).

The Testosterone Trials were a coordinated set of 7 randomized double-blind, placebo-controlled trials designed to determine the efficacy of testosterone treatment in older men 65 years and older with unequivocally low testosterone levels and sexual dysfunction, physical dysfunction, or fatigue (40). To participate in these trials, the men had to be eligible for at least 1 of the 3 main trials (the Sexual Function Trial, the Physical Function Trial [PFT], or the Vitality Trial). The PFT of the TTrials recruited older men with self-reported difficulty walking or climbing stairs and walking speed below 1.2 m/s and an average of 2 morning fasting testosterone levels less than 275 ng/dL (41). The 6-minute walking distance improved significantly more in the testosterone than in the placebo group among all men in the TTrials, but not in those who were enrolled in the PFT (41). The self-reported physical function assessed using the physical component of the Medical Outcomes Study Short Form-36 questionnaire improved more in the testosterone group than in the placebo group in all men in TTrials and in men enrolled in the PFT (41). The men in the testosterone group were more likely to report improvement in their walking ability than men in the placebo group. The changes in the 6-minute walking distance were significantly associated with changes in testosterone and hemoglobin levels (41). The number of falls was similar in the testosterone and placebo arms (41). Thus, testosterone treatment of older men with mobility limitation consistently improved self-reported walking ability and modestly improved 6-minute walking distance (41).

Effects of Testosterone Treatment on Older Adults With Chronic Diseases

Adults with chronic diseases, such as chronic obstructive pulmonary (COPD) disease, human immunodeficiency virus infection, heart failure, end-stage renal disease, advanced liver disease, and many types of cancers suffer from an accelerated loss of skeletal muscle mass and muscle strength which increases their risk of exercise intolerance, functional limitations, physical disability, metabolic disorders, and poor quality of life. Therefore, there has been substantial interest in developing function-promoting therapies that can prevent or reverse the disease-related loss of muscle mass and function.

Casaburi et al. (15) determined the efficacy of testosterone treatment (100 mg testosterone enanthate weekly for 10 weeks) with and without a standardized program of resistance exercise training in men with COPD (mean forced expiratory capacity 40% of predicted) and low or low normal testosterone levels. Testosterone treatment alone was associated with an average 2.3 kg increase in lean body mass and an average 17% increase in leg-press strength; the gains in lean body mass and leg-press strength averaged 3.3 kg and 27%, respectively, with a combined regimen of testosterone plus resistance exercise training. Another placebo-controlled randomized trial of nandrolone decanoate also found greater improvements in fat-free mass in men with COPD compared to placebo (42). Future studies should determine whether testosterone treatment when administered in the setting of standardized pulmonary rehabilitation program can improve physical function and exercise intolerance in patients with COPD.

Prior to the advent of effective antiretroviral therapy, infection with the human immunodeficiency virus was commonly associated

Table 1. Summary of the Main Findings of Randomized Controlled Trials of Testosterone in Healthy Older Adults and in Older Adults with Chronic Diseases

1. Sexual function
Testosterone treatment significantly improves overall sexual activity of all types, sexual desire, and to a lesser extent erectile function in older men with low libido.
Testosterone does not improve sexual function in men with normal testosterone levels who do not have sexual symptoms.
2. Body composition, muscle performance, and physical function
Testosterone treatment increases whole-body and appendicular lean body mass, maximal muscle strength in the chest-press and leg-press exercises, and stair-climbing power and attenuates the age-related decline in aerobic capacity.
Testosterone improves self-reported measures of function and mobility.
Testosterone increases the mass of pelvic floor muscle in men and women.
3. Bone health
Testosterone treatment increases areal and volumetric bone mineral density, and estimated bone strength in older men with hypogonadism.
4. Anemia
Testosterone increases hemoglobin and corrects unexplained anemia of aging.
5. Depressive symptoms
Testosterone treatment is associate with modest improvement in depressive symptoms.

with weight loss which significantly increased the risk of mortality and adverse disease outcome. Patients with HIV-associated weight loss had an increased prevalence of low serum testosterone levels that correlated with the loss of muscle mass, low Karnofsky scores, and disease progression. With the availability of highly active antiretroviral therapy, the prevalence of weight loss has decreased substantially in patients infected with human immunodeficiency virus (HIV) in the United States and in most countries around the world. However, weight loss continues to be a problem in some countries where antiretroviral drugs are not readily available. Because of their relative safety and low cost, androgens have been evaluated for their efficacy in preventing or reversing weight loss and increasing muscle strength, physical function, and quality of life in patients with HIV-associated weight loss (13,43–46) (Table 1). Testosterone treatment of men with HIV-associated weight loss has been associated with greater increases in body weight, lean body mass, and muscle strength. However, improvements in physical function and health-related quality of life have not been demonstrated with testosterone treatment (13,43,44).

A meta-analysis found small improvements in walking distance with testosterone treatment in patients with heart failure (47). Testosterone treatment can cause salt and water retention which may exacerbate pre-existing heart failure in some patients. The patients with end-stage renal disease who are receiving maintenance hemodialysis experience muscle wasting and functional limitations and have a high prevalence of low testosterone levels. However, there are insufficient data to evaluate the efficacy of testosterone treatment in patients on hemodialysis. In 1 randomized trial, the administration of nandrolone decanoate alone compared to a placebo alone was associated with greater gains in fat-free mass in patients on hemodialysis (48); nandrolone decanoate plus resistance exercise training increased muscle strength more than placebo alone. The efficacy of androgen on physical function and health-related quality of life remains to be demonstrated.

Wright et al. evaluated the effects of testosterone treatment in patients with squamous cell carcinoma of the cervix or head and neck undergoing standard-of-care treatment in a small short-term randomized, placebo-controlled trial (49). Testosterone treatment was associated with greater gains in lean body mass, physical activity, and quality of life than placebo. Overall survival was similar in both groups (49).

Safety of Testosterone Treatment

Erythrocytosis is the most frequent adverse event associated with testosterone treatment in randomized trials (50); other adverse effects of testosterone include acne, oiliness of skin, breast tenderness, leg edema, suppression of spermatogenesis, and infertility. The overall frequency of adverse events in randomized trials of testosterone has been low (51). Testosterone does not worsen lower urinary tract symptoms in older men who do not have severe lower urinary tract symptoms at baseline (51). Older men receiving testosterone treatment are at increased risk of being referred for a prostate biopsy and of the detection of a subclinical prostate cancer (8,50). None of the trials has had a large enough sample size or intervention duration to determine the effects of testosterone treatment on the incidence of major adverse cardiovascular events (MACE) or prostate cancer. Testosterone treatment for 3 years did not significantly affect the rate of atherosclerosis progression, measured using common carotid artery intima-media thickness and coronary calcium scores (52). In the Testosterone Trials (53), the volume of noncalcified soft coronary artery plaque measured using computerized tomography angiography increased more in men treated with testosterone than in men treated with placebo (53). An individual patient-level meta-analysis of randomized trials did not find a significant difference in the incidence of cardiovascular events between testosterone and placebo arms (54). A large randomized, placebo-controlled trial to determine the effects of testosterone replacement therapy on the incidence of MACE in middle-aged and older men, 45–80 years, with hypogonadism and at increased risk of coronary artery disease is nearing completion (the TRAVERSE Trial NCT NCT03518034) (55).

Selective Androgen Receptor Modulators

The SARMs are ligands that bind to AR and induce tissue-specific transcriptional activation of AR-dependent genes and tissue-selective activity in various androgen-responsive organ systems (8,56). The development of SARMs was motivated by a desire to avoid the potential adverse effects of androgens in some androgen-responsive tissues, such as the prostate and the cardiovascular system, and to enhance the potential beneficial effects in some tissues, such as the muscle and bone (8,56). Several structural classes of nonsteroidal SARMs have been developed, including aryl propionamide, bicyclic hydantoin, quinoline, and tetrahydroquinoline analogs; the first-generation SARMs were derived by structural modifications of the aryl propionamide analogs bicalutamide and hydroxyflutamide. The nonsteroidal SARMs are orally available, and typically metabolized by amide-bond hydrolysis and A-ring nitro reduction and eliminated largely through hepatic metabolism (57,58).

Table 2. Gaps in Our Knowledge and Opportunities for Future Investigations of Testosterone and Selective Androgen Receptor Modulators as Function-Promoting Therapies

Adequately powered placebo-controlled trials of longer duration are needed to address the following questions:
1. Can testosterone treatment alone induce clinically meaningful improvements in performance-based measures of physical function, such as walking speed? Are testosterone-induced improvements in skeletal muscle mass and maximal voluntary strength associated with downstream improvements in how a person "...functions or feels", assessed using validated patient-reported outcome (PRO) measures?
2. Are testosterone-induced improvements in skeletal muscle mass associated with other health benefits, such as reducing the incidence of type 2 diabetes mellitus; inducing glycemic remission in older adults with type 2 diabetes mellitus; improving stress urinary incontinence; preventing falls and fractures in at-risk older adults?
3. Can testosterone treatment prevent or retard disease progression in older men with preclinical or early Alzheimer's Disease?
4. Is testosterone treatment efficacious in improving depressive symptoms and inducing remission of late-life persistent depressive disorder (dysthymia) in older men with hypogonadism?
5. Can multidimensional functional exercise training augment and translate testosterone-induced muscle mass and strength gains into clinically meaningful improvements in performance-based measures of physical function and in how a person "...functions and feels"?

The molecular mechanisms of the tissue selectivity of SARMs are not fully understood but several mechanisms have been proposed. Various steroidal and nonsteroidal ligands upon binding to AR may induce distinct conformational changes in the AR resulting in the recruitment of a distinct repertoire of coactivators and corepressors in each specific type of tissue and differential activation of downstream signaling pathways. For example, there is some evidence that a steroidal agonist such as dihydrotestosterone upon binding to AR promotes the assumption of a full agonistic conformation in the prostate by the recruitment of coactivators, a SARM, such as enobosarm, promotes a partial agonist conformation by forming a complex with coactivators as well as corepressors. Additionally, unlike testosterone, nonsteroidal SARMs do not undergo aromatization or 5-alpha reduction, and this may differentiate the actions of SARMs in tissues in which testosterone's effects require its conversion to estradiol or dihydrotestosterone.

Several SARMs have undergone Phase 2 trials and some have advanced to Phase 3 trials. Phase 1 and Phase 2 trials have confirmed the increases in lean body mass, muscle size, and relative sparing of the prostate (59–63). In a Phase 2 trial in patients with weight loss associated with cancer, enobosarm increased lean body mass; in Phase 3 trial, enobosarm failed to show consistent improvements in physical function (61). In another Phase 2 trial in prostate cancer survivors with testosterone deficiency, who had undergone radical prostatectomy for low-grade organ-confined prostate cancer, administration of a SARM, OPK-88004, was safe and not associated with PSA recurrence. OPK-88004 increased lean body mass and decreased fat mass but did not improve physical performance. In another trial in older women with sarcopenia, SARM administration improved lean body mass without significant increases in muscle strength or measures of physical function (64). Enobosarm is being evaluated as an anticancer agent that may also improve the quality of life in Phase 3 studies in women with AR positive, estrogen receptor positive, and HER-2 negative metastatic breast cancer.

Potential Reasons Why Previous Trials Have Failed to Show Consistent Improvements in Physical Function in Spite of Substantial Increases in Lean Body Mass and Muscle Strength

Well-conducted, randomized placebo-controlled trials of testosterone have consistently demonstrated that testosterone treatment is safe and improves lean body mass, maximal voluntary strength, stair-climbing power, and self-reported function in healthy older men as well as in older men with some chronic diseases. Yet, testosterone treatment has not been associated with consistent, clinically meaningful improvements in performance-based measures of physical function. Several explanations have been offered. The measures of physical function used in some previous trials typically had low ceilings. Because of the considerable test-to-test variability in tests of physical function, it is possible that previous studies did not have adequate power to detect meaningful differences in measures of physical function between the placebo and testosterone-treated groups. It is also possible that neuromuscular adaptations needed to translate strength gains into functional improvements require a lot longer than the 3- to 6-month duration of most of the previous trials. Other factors, such as nutritional intake, comorbid conditions such as obstructive sleep apnea, alcohol intake and substance use, and physical activity that may also affect response to intervention should also be considered. The measures of physical function that are more robustly related to lower extremity muscle strength per unit of time, such as stair-climbing speed and power, have shown more consistent improvements in testosterone trials than walking speed (36,37,52). Therefore, strategies to translate muscle mass and strength gains induced by testosterone treatment into functional improvements are needed (Table 2). Future studies should evaluate the efficacy of combined administration of testosterone supplementation along with multidimensional functional exercise training that includes strength training to improve strength and power; task-specific training to improve walking ability, stair-climbing ability, and balance and to reduce fall risk; and cognitive and behavioral training in inducing the neuromuscular and behavioral adaptations that are necessary to translate the gains in muscle mass and strength into clinically meaningful functional improvements and to reduce physical disability (65).

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Conflict of Interest

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