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Hormone Treatment and Muscle Anabolism during Aging: Androgens

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Abstract

Aging is associated with a gradual decline in circulating testosterone concentrations and decreased musculature in men. While testosterone administration is often considered when symptoms of hypogonadism are presented, the long-term effects of androgen use on muscle physiology are not yet fully understood.

The definition of hypogonadism in men remains obscure but is generally indicated by total testosterone concentrations less than a threshold value of 300-500 ng/dL. Androgen replacement therapy is generally safe in men and women with low endogenous testosterone concentrations. The development of selective androgen receptor modulators (SARMs) may provide additional options in treatment of hypogonadism while lowering the potential of side effects often associated with long-term androgen use.

Androgen administration, either alone or in combination with other treatments, can be successful in improving muscle mass by increasing protein anabolism and reducing protein catabolism in men and women. Further research is necessary to optimize the anabolic and anticatabolic properties of androgens for treatment and prevention of muscle loss in men and women.

Keywords

Aging; Testosterone; Skeletal Muscle; Men; Women

1. Introduction

A considerable concern with advancing age is the associated declines in muscle mass and strength. Maintenance of muscle during aging is important to maintain quality of life and independent living, reduce the risk of metabolic disorders, lower the risk of falls and injuries, and lower the risk of morbidities and mortalities. Whether skeletal muscle is lost or gained is significantly affected by quality of nutrition, level of activity and hormonal status. While the association between the decline in sex hormones with age and musculoskeletal

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Conflict of Interest

The authors have no conflict of interest to disclose.

losses has been known for some time, the mechanisms governing the underlying processes are still not fully understood and continue to be a vibrant topic in hormone research in young and old.¹⁻⁷

2. Hypogonadism

The definition of true hypogonadism remains controversial. However, morning serum total testosterone concentrations below 300 – 500 ng/dL (10.4 – 12.1 nmol/L) are generally considered diagnostic for male hypogonadism.⁸ Endogenous testosterone production gradually decreases with advancing age in men. By the 8th decade, 30% of men have low total testosterone concentrations and 70% have low free testosterone concentrations.⁹ In elderly men, the biochemical diagnosis of hypogonadism is certain according to most standards if serum total testosterone is less than 200 ng/dL (6.9 nmol/L).^{8, 10, 11} However, many older men suffer clinically significant signs and symptoms of hypogonadism at concentrations well above the arbitrary cutoff of 200 ng/dL.¹² In addition to determinations of serum total testosterone concentrations, measurements of free testosterone, sex hormone binding globulin (SHBG), estrogen, luteinizing hormone (LH), and follicle stimulating hormone (FSH) can add important supplemental data in diagnosing androgen deficiencies.⁸

There are notable similarities between aging and pathology-related hypogonadism, such as decreases in muscle mass and strength, sexual and cognitive function and overall loss of vitality, that suggest the importance of maintaining testosterone availability for optimal health and quality of life.¹³ However, it is not known whether the fall in testosterone availability *per se* is directly responsible for these adverse consequences during aging.

3. Responses to Testosterone Administration in Men

Testosterone therapies are currently widely used to promote retention and gain of muscle mass and strength, bone mineral density, and sexual function in symptomatic hypogonadal men.⁸ Based on research across a wide range of testosterone doses, current Clinical Practice Guidelines recommend treatment with intramuscular testosterone enanthate or testosterone cypionate between 75-100 mg weekly or 150-200 mg every two weeks.⁸ In healthy young males the administration of supraphysiological testosterone doses (200-300 mg/wk) is anabolic to muscle mass, strength, and power.¹⁴ However, continuous testosterone administration has been associated with elevated hematocrit, increased serum PSA and prostate events in men^{15, 16}. The primary goal of androgen therapy during aging is to improve or maintain muscle mass, muscle strength and functional capability.^{17, 18} In the case of hypogonadal elderly men receiving testosterone therapy, the positive benefits on muscle have been clearly demonstrated with significant increases in protein synthesis¹⁹ or decreases in muscle protein breakdown²⁰, enhanced lean body mass²⁰⁻²⁴ and improved muscular strength.^{19-22, 25} Supplementation of testosterone (300-600 mg/wk) to healthy older men for 20 weeks results in skeletal muscle hypertrophy and increases relative area of both type I and II fibers and myogenin expression.²⁶ However, lower doses (25-125 mg/wk) in the same study failed to show the same anabolic effects. The effect of testosterone treatment on expression of myostatin, a negative regulator of muscle growth, remains unclear. While effective in lowering myostatin mRNA expression in castrated rats,²⁷ testosterone administration leads to increased expression of myostatin protein in healthy young and older men with normal endogenous testosterone concentrations.²⁸ Combined, these studies indicate a dose dependent effect of androgen treatment in stimulating muscle anabolism. Additionally, it is possible that repeated spikes in testosterone concentrations are required to reach substantial anabolic effects that are difficult to obtain with low dose administration regimens. While successful in promoting skeletal muscle mass, strength and power, testosterone treatment (125-300 mg/wk) may have little or no effect on fatigability

and physical function in asymptomatic community-dwelling older men.²⁹ In contrast to these results in humans, administration of nandrolone but not dihydrotestosterone improved resistance to fatigue in orchidectomized rats.³⁰

Several investigators have observed that physiological testosterone administration in healthy older men results in a peak increase in muscle protein synthesis within the first month of treatment but that this anabolic effect wanes if treatment is continued over several months.^{20, 31} This has led our group and colleagues to examine alternate testosterone dosing regimens in an attempt to avoid negative feedback of exogenous testosterone to the HPG (hypothalamic pituitary gonadal) axis. We are examining whether weekly administration of testosterone for a month, alternated with a month without treatment for five months will improve muscle mass and strength in healthy men with low normal testosterone concentrations (200-400 ng/dL). If such monthly on-off cycled testosterone treatments retain the acute anabolic effects on skeletal muscle protein over longer periods than continuous administration this would have both physiological and financial benefits by reducing the total amount of drug needed over the length of treatment.

4. Responses to Testosterone Administration in Women

While cross sectional studies have found total serum testosterone concentrations as much as 50 % lower in women over age 65 compared to young women,³² more recent longitudinal data show increases in total testosterone with age before and after menopause.³³ Nevertheless, normal endogenous serum total testosterone concentrations in women are an order of magnitude lower when compared to that found in healthy men. Thus, although changes in endogenous testosterone levels may not be directly responsible for loss of muscle mass in females, the possibility exists that administration of testosterone could be a viable option for treating or preventing loss of muscle mass.^{32, 34} Accordingly, the Endocrine Society Clinical Practice Guideline supports the view that women, not unlike men, may benefit from androgen therapy³⁵, a view supported by the successful use of androgens to stimulate muscle protein anabolism in women.³⁶ However, the literature is not universally supportive of the use of testosterone to increase or maintain muscle mass in females. Despite the gender difference in endogenous testosterone, a recent investigation demonstrated age related declines in mixed muscle fractional synthetic rates (FSR) in both men and women but a consistently higher FSR in women across the lifespan when compared to men³⁷. Furthermore, this report showed no benefit of 1 year of low-dose testosterone or DHEA in men diminishing this gender gap or additional benefit of DHEA in aging women.

While much remains unclear regarding the role of testosterone in women, the importance of the hormone in female physiology is evident as androgen deficiencies have been associated with impaired sexual function, lean body mass and performance, cognitive function, bone loss, and frailty.³⁸⁻⁴² Risk factors for low testosterone concentrations in postmenopausal women include bilateral oophorectomy, low BMI, and the use of estrogen or corticosteroids.³² However, while no causality was demonstrated, *high* endogenous testosterone in early postmenopausal women correlated with insulin resistance and coronary heart disease in a recent study.⁴³ Such correlations warrant further investigations into risk-benefit ratios of this hormone during treatment in female populations.

While testosterone replacement has known undesirable side effects when administered regularly to women, such as hirsutism or virilization⁴⁴, it remains an appealing treatment option in some circumstances. In extreme cases of muscle wasting, such as in patients with cancer cachexia or HIV, the benefits of testosterone on muscle mass appear to justify the potential for such androgenic events. Furthermore, low dose testosterone use in women is deemed safe with respect to cardiovascular health and cancer risk.^{45, 46} Daily application of

testosterone gel for 7 days has been shown to uniformly raise total and free testosterone concentrations in postmenopausal women in a dose-dependent manner, without affecting serum estradiol, FSH, LH, or SHBG concentrations.³⁴ Oxandrolone, a synthetic testosterone derivative thought to produce fewer androgenic side effects, increased skeletal muscle fractional synthetic rate and the expression of skeletal muscle androgen receptors in older women³⁶ when administered orally for fourteen days. While the use of oxandrolone is beneficial during the management of Turner syndrome⁴⁷, or recovery from burns⁴⁸ long-term studies are necessary to show benefits of androgens on muscle mass and function in populations that include females. Our group is currently investigating the effect of weekly testosterone injections (100 mg/wk) to stimulate muscle protein anabolism in recurrent cervical cancer patients. Further research on testosterone and development of synthetic testosterone derivatives or selective androgen receptor modulators (SARMs) that avoid potential side effects are highly desirable.

5. Anticatabolic Properties of Testosterone

Besides promoting skeletal muscle anabolism, testosterone may possess anticatabolic properties. While not as many studies have focused on its role on protecting existing muscle mass as on the role of testosterone on accretion of new mass, this property is gaining increasing attention. Supraphysiologic (50 nM = 50-fold normal) dosing of testosterone for 8 continuous weeks has been shown protective to muscle mass and fatigue resistance in orchietomized mice compared to sham operated animals.⁴⁹ The protective action of testosterone on skeletal muscle may in part be due to its anti-inflammatory actions or through direct modulation of anticatabolic pathways.⁵⁰⁻⁵⁷ Weekly administration of nandrolone decanoate (6mg/kg) for 3 weeks attenuated functional overload induced inflammatory cytokine response in 5 and 25 mo old rat soleus muscle.⁵⁰ In humans, testosterone has been found capable of reducing systemic inflammatory cytokines such as TNF α , IL-6 and IL-1 β ⁵¹⁻⁵³, and stimulating the anti-inflammatory cytokine IL-10.^{54, 55} Protein degradation is regulated through several pathways, involving the action of ligases. The muscle specific ubiquitin ligase muscle atrophy F-box (MAFbx) is upregulated in skeletal muscle through activation of the transcription factor Forkhead box O (FOXO). FOXO is activated in response to glucocorticoids and is blocked via the IGF/Akt pathway. Dexamethasone induced protein degradation is repressed by testosterone administration in C2C12 cells (50 nM testosterone)⁵⁶ and rats (28-50 mg testosterone/kg/day).^{56, 58} Additionally, binding of testosterone with its nuclear target androgen receptor (AR) inhibits MAFbx expression in C2C12 cells without affecting FOXO activity.⁵⁷ These studies are further complimented by findings that show the shift in balance between muscle protein synthesis and breakdown during 6 months of testosterone treatment of hypogonadal men.²⁰ This study demonstrated that, during the first month of androgen therapy, the primary effect of testosterone on skeletal muscle was increased protein synthesis, whereas at 6 months protein synthesis was no longer elevated. Rather, protein breakdown was significantly reduced, nevertheless resulting in a continued positive net balance in muscle mass. Further, androgen receptor and IGF-I protein expression were elevated at 1 month, with IGF-I remaining elevated throughout the treatment period.²⁰ Therefore, the immediate and sustained elevation of IGF-1 with testosterone therapy and the subsequent suppression of muscle protein breakdown support that testosterone has anti-catabolic properties, and may exert these via the IGF-1 signaling pathway, perhaps by blocking MuRF1 and MAFbx/Atrogin-1. More studies utilizing testosterone concentration within the physiological ranges are needed to confirm whether long-term testosterone treatment is beneficial to prevent excesses of muscle degradation in humans.

6. Combination Therapies

Combination therapies that include testosterone administration with drug, nutrition, and/or exercise interventions may be attractive treatment options in populations suffering from muscle loss. Co-administration of testosterone plus growth hormone (GH) results in greater muscle anabolism than administration of either hormone alone.^{59, 60} Physiological doses of transdermal testosterone gel (5-10 g) and subcutaneous rhGH injections (3 µg/kg) increased lean mass, muscle strength and aerobic endurance in older men while lowering total and trunk fat mass.⁶⁰ Undernourished older men and women receiving 1 year of oral testosterone plus nutritional supplementation showed a reduced need for hospital admission, exceeding that accomplished with testosterone or nutritional supplementation alone when compared to standard of care.⁶¹

7. Selective Androgen Receptor Modulators (SARMs)

Recent developments in pharmacology include the search for compounds that selectively produce the beneficial effects of androgens on musculoskeletal mass and strength without the side effects that this class of steroids generally exhibits. Continuous testosterone administration is associated with elevated hematocrit, increased serum PSA and prostate events in men, and virilization in women.^{16, 62} Several potentially effective steroidal and non-steroidal selective androgen receptor modulators (SARMs) are in different stages of clinical development with the intent to treat conditions including sarcopenia, cancer cachexia, and osteoporosis.^{16, 62-65}

8. Conclusions

Reducing the age related decline in muscle mass and strength remains of high clinical importance. While the importance of sex hormones in muscle physiology is undisputable, further research is needed if the anabolic and anticatabolic properties of androgens are to be harnessed, with minimal side effects, for the prevention and/or treatment of muscle loss in men and women.

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